Pulmonary Disease Reviews Volume 1

Edited by

Roger C. Bone, M.D.

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A Wiley Medical Publication
JOHN WILEY & SONS
New York • Chichester • Brisbane • Toronto

ISBN 0-471-05736-3

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

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Preface

This book is the first of what will be an annual effort to review recent literature in clinical pulmonary disease as well as basic literature with clinical implications. Pulmonary disease intersects many disciplines in general internal medicine. Articles on this subject can be found in many journals not readily available to the clinician.

A different segment of the recent literature is covered in each chapter. Articles have been selected by each chapter author that are felt to have special importance in pulmonary disease. Each article is followed by editorial comments that emphasize its importance. The chapter author introduces related concepts and supplements drawn conclusions with related literature. In essence, each chapter should provide a "journal club" approach with an expert in the area conducting the session.

Major advances are being made with increasing rapidity in pulmonary disease. It is hoped that this volume will provide a way to obtain both recent literature on specific subjects and a critical appraisal of the importance of this literature to pulmonary disease. For readers who desire more detailed information of the various subjects covered, references to the original and related articles are included.

The first volume of *Pulmonary Disease Reviews* has covered literature ranging from late 1977 to mid-1979. Future *Pulmonary Disease Reviews* will be covering a smaller time frame and thus will allow the inclusion of additional excellent contributions that had to be excluded from this review because of space constraints.

Roger C. Bone, M.D.

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Abnormalities of Oxygen Transfer

David R. Dantzker

Introduction

The adequate transfer of oxygen (O_2) from the external environment to the mitrochondria requires a complex network of pumps and pipes, controlled by a number of regulatory mechanisms and modulated by a bewildering array of feedback loops and failsafe systems. It is quite impossible to study any single component in isolation, as these papers indicate. In fact, the clinical realization of just how closely intertwined these systems are and how little we yet understand their coordination has, by itself, been a major step forward. In this review, I have tried to select papers that not only provide new or continuing insights into the basic understanding of the system but also demonstrate findings that may be pertinent to the clinical management of patients.

For ease of presentation I have divided this section into three parts. The first part will concern itself mainly with gas exchange in the lung. The first three papers in this section present data based largely on a multicompartmental model of the lung developed by Wagner et al. (*J Appl Physiol* 36:588, 1975). Despite its complexity, this new approach to the study of lung function has provided major insights into gas exchange not previously available from the classical three-compartment analysis of Riley and Cournand (*J Appl Physiol* 1:825, 1949). The fourth paper presents a new technique for the accurate quantitation of intrapulmonary shunt. The final paper emphasizes the substantial influence on the arterial O_2 tension of nonpulmonary abnormalities such as anemia and heart failure.

The second section deals with O_2 delivery to the tissues and raises some interesting questions concerning the putative role of O_2 affinity. Many theoretical studies of the effects of shifts in the oxyhemoglobin dissocation curve on overall gas exchange have raised questions about the clinical importance of the small changes in P_{50} (P_{O_2} of the blood at 50% saturation) that typically are found in patients. These papers, however, strongly suggest that rightward

shifts in the curve of this magnitude do play a demonstrable physiological role.

The final two papers address the problems of tissue uptake and utilization of oxygen. Despite the fact that this end of the network is the raison d'etre for the whole system, it has not received the attention it undoubtedly deserves. Admittedly, this is due in great part to the uncertainties of quantitating tissue oxygenation. However, information on the peripheral utilization of oxygen in disease states is remarkable for its absence. For those interested in pursuing this topic, a recent volume in Claude Lenfant's series, *Lung Biology in Health and Disease* (Marcel Dekker, Inc., New York) titled *Extrapulmonary Manifestations of Respiratory Disease* (edited by Eugene Robin, 1978), is excellent.

VENTILATION-PERFUSION RELATIONSHIPS

J.B. WEST (University of California San Diego)

Am Rev Respir Dis 116:919, 1977.

In this review, the principles governing gas exchange in a single lung unit are examined first. Next, the clinical assessment of ventilation-perfusion inequality is discussed. The behavior of distributions of ventilation-perfusion ratios, the measurement of these distributions, and typical patterns seen in several types of lung disease are then discussed.

Gas Exchange in a Single Lung Unit

Basic Equation

The partial pressures of oxygen, carbon dioxide, and nitrogen (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: (*1*) the ventilation-perfusion ratio, (*2*) the composition of inspired gas, and (*3*) the composition of mixed venous blood. The reason the ventilation-perfusion ratio is so critical is shown by the ventilation-perfusion ratio equation:

$$\dot{V}_A/\dot{Q} = \frac{C\bar{v}_{CO_2} - Cc'_{CO_2}}{Pa_{CO_2} \cdot K}$$

This equation looks simple, but this simplicity is deceptive, because when the alveolar P_{CO_2} increases as the ventilation-perfusion ratio is decreased, the alveolar P_{O_2} decreases. As a consequence of the decrease in O_2 saturation, the relationship between the P_{CO_2} and the carbon dioxide content (CO_2) in blood is altered. Thus, the alveolar P_{O_2} is an implicit variable in the equation. As a result, it was only possible to solve the equation graphically, using the O_2-CO_2 diagram, until the technique of numerical analysis by computer became available.

O_2-CO_2 Diagram

A useful way of depicting the changed in P_{O_2} and P_{CO_2}, which

occur as the ventilation-perfusion ratio is altered, is by use of the O_2 and CO_2 diagram (Figure 1). Joining the inspired and mixed venous points is the ventilation-perfusion line, which shows all possible combinations of P_{O_2} and P_{CO_2} in a lung that have given values for inspired gas and mixed venous blood. Note that the normal ventilation-perfusion ratio of approximately 1 results in a P_{O_2} of 100 mmHg and a P_{CO_2} of 40 mmHg. As the ventilation-perfusion ratio is increased the P_{O_2} increases and the P_{CO_2} decreases, so that eventually the composition of inspired gas is reached.

Effect of Changing the Ventilation-Perfusion Ratio

The way in which the P_{O_2}, P_{CO_2}, and O_2 content of the effluent blood alters as the ventilation-perfusion ratio is changed in a single unit is shown in Figure 2. The P_{O_2} and P_{CO_2} change relatively little until the ventilation-perfusion ratio increases to approximately 0.2. Also, the P_{O_2} increases little when the ventilation-perfusion ratio exceeds 10. Most of the increase in O_2 content occurs within the ventilation-perfusion ratio range of 0.1 to 1.

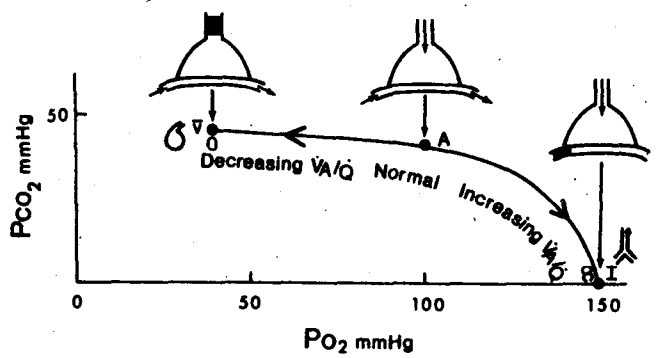

Figure 1. Oxygen-carbon dioxide diagram showing a ventilation-perfusion ratio ($\dot{V}_A/\dot{Q}$) line. The P_{O_2} and P_{CO_2} of a lung unit move along this line from the mixed venous point, $\bar{v}$, to the inspired gas point, I, as it ventilation-perfusion ratio is increased. A = alveolar gas for a lung unit with a normal ventilation-perfusion ratio. (Courtesy of John B. West, M.D. and the American Review of Respiratory Disease.*)*

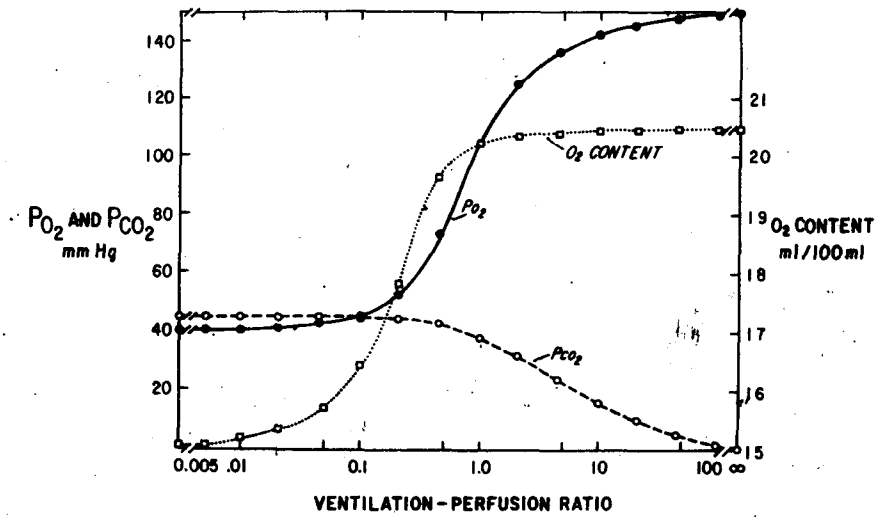

Figure 2. Changes in P_{O_2}, P_{CO_2}, and end-capillary O_2 content of a lung unit as its ventilation-perfusion ratio is increased. The lung is assumed to be breathing air, and the P_{O_2} and P_{CO_2} of mixed venous blood are 40 and 45 mmHg, respectively. The hemoglobin concentration is 14.8 g/100 ml. (Courtesy of John B. West, M.D. and the American Review of Respiratory Disease.)

Effect of Changing Composition of Inspired Gas

Increasing the concentration of inspired O_2 is frequently necessary in the treatment of patients with lung disease. The resulting response of the arterial P_{O_2} depends on the distribution of ventilation-perfusion ratios and, in particular, the amount of blood flow going to units with very low ventilation-perfusion ratios.

Effect of Changing the Composition of the Mixed Venous Blood

The P_{O_2} and P_{CO_2} of the mixed venous blood play a more important role in determining the arterial P_{O_2} and P_{CO_2} than they are usually given credit for. For example, in a patient with myocardial infarction, any decrease in cardiac output results in a decrease in mixed venous P_{O_2}, which exaggerates the arterial hypoxemia.

Effect of Changing the Inspired P_{O_2} on the Ventilation-Perfusion Ratio

At least two mechanisms can alter the ventilation-perfusion ratio of an individual lung unit as the concentration of inspired oxygen is altered, thus changing the distribution of ventilation-perfusion ratios in diseased lungs. One is the hypoxic vasoconstriction that normally restricts the blood flow of poorly ventilated units as their alveolar P_{O_2} decreases. Increasing the inspired oxygen releases this vasoconstriction. The other mechanism that can change the ventilation-perfusion ratio of the lung unit when an enriched oxygen mixture is breathed results from the imbalance between inspired and expired alveolar ventilation. This causes the conversion of poorly

ventilated regions into unventilated areas (shunts). This inherent instability of units with very low ventilation-perfusion ratios during enriched oxygen breathing, has been seen to a small extent in some normal subjects. However, it is particularly evident in patients with acute respiratory failure.

Alveolar-Arterial P_{O_2} Difference

The difference in P_{O2} between alveolar gas and arterial blood is often useful in assessing the degree of ventilation-perfusion inequality. This index has the advantage that it is less sensitive to alterations in the patient's level of ventilation than is the arterial P_{O2} alone.

Physiologic Shunt

Another useful index of ventilation-perfusion inequality is the physiologic shunt (also called venous admixture, or wasted blood flow). In practice, the shunt equation is used in the following form:

$$\frac{\dot{Q}phys}{Qt} = \frac{Ci_{O_2} - Ca_{CO_2}}{Ci_{O_2} - C\bar{v}_{O_2}}$$

where $\dot{Q}phys$ refers to physiologic shunt, Qt = total flow through the lungs, and Ci_{O_2}, Ca_{CO_2}, and $C\bar{v}_{O_2}$ refer, respectively, to the oxygen contents of ideal, arterial, and mixed venous blood. The oxygen content of ideal blood is calculated from the ideal P_{O_2} and the oxygen dissociation curve. The normal value for physiologic shunt is less than 5%.

Physiologic Dead Space

The physiologic dead space is a measure of the amount of ventilation going to lung units with abnormally high ventilation-perfusion ratios. The Bohr equation is used in the following form:

$$\frac{VD_{phys}}{VT} = \frac{Pa_{CO_2} - PE_{CO_2}}{Pa_{CO_2}}$$

where VDphys = physiologic dead space, VT = tidal volume, PE_{CO_2} = expired P_{CO_2}. Again, we use the fact that the P_{CO_2} in ideal gas and arterial blood are virtually the same.

The physiologic dead space as measured in this way includes the anatomic dead space; there is also a contribution from the instrumental dead space of the valve box, which can be subtracted. In normal lungs, the value of the physiologic dead space is in the vicinity of 30% of the tidal volume at rest, is less on exercise, and consists almost completely of anatomic dead space.

Other Two- or Three-Compartment Models

There are other ways on looking at the gas-exchange function of

the diseased lung as if it were composed of two or three compartments. Multibreath nitrogen washouts are used to divide the lung into two (sometimes more) populations of alveoli, one ventilated quickly and the other slowly. These data are then combined with measurements of arterial oxygen saturation and oxygen consumption to determine the perfusion of each ventilated compartment. An emphysematous lung may behave as if nine-tenths of the total ventilation and one-half of the total blood flow went to one-fourth of the volume of the lung, whereas the other three-fourths of the volume received only one-tenth of the ventilation and one-half of the blood flow. Thus, such a lung apparently had a small volume of fast-ventilating alveoli with a high ventilation-perfusion ratio and a large volume of slow-ventilating alveoli with a low ventilation-perfusion ratio. More recently, this approach has been extended to give information about the diffusing capacity per unit of blood flow of each compartment, using the concept of Bohr integral isopleths. This type of analysis is based on calculations of the rate of oxygenation of blood along the pulmonary capillary; it is used to estimate the relative importance of the ventilation-perfusion ratio and the diffusion-perfusion ratio in determining the P_{O_2} and O_2 content of blood draining from each compartment.

Distributions of Ventilation-Perfusion Ratios

One of the most important developments of the past 10 years has been an accelerated interest in the properties of distributions of ventilation-perfusion ratios rather than the behavior of single-lung units or models composed of two or three compartments. The breakthrough was the application of computer methods for analyzing the behavior of distribution.

The measurement includes supplying the distribution of ventilation-perfusion ratios with mixed blood containing a series of inert gases having a large range of solubilities. The gas exchange behavior of the distribution (in this case, the pattern of elimination of the gases) is then measured, and this measurement gives a great deal of information about the distribution.

Distribution in Normal Subjects

In normal subjects, there was no blood flow or ventilation outside the range of approximately 0.3 to 3.0. The log standard deviations of the two distributions were approximately 0.35. There was no shunt. The absence of shunt was a consistent finding in all the normal subjects studied.

Chronic Obstructive Lung Disease

Patients believed to have predominantly emphysema, that is, type A chronic obstructive lung disease, showed a pattern of a large amount of ventilation going to units with high ventilation-perfusion ratios (between 3 and 100). By contrast, there was little blood flow to units with ventilation-perfusion ratios of less than 0.3. There was a small shunt of 3.0%. This pattern is consistent with a large physiologic dead space, but relatively small physiologic shunt. The large ventilation-to-high-ventilation-perfusion-ratio units can presumably be explained by the presence of areas of parenchymal destruction where

the capillary bed is grossly decreased. In a patient with severe chronic bronchitis, that is, type B chronic obstructive lung disease, a substantial amount of blood flow going to lung units has low ventilation-perfusion ratios between 0.03 and 0.1. This explains the more severe hypoxemia in this group of patients and is consistent with a large physiologic shunt. A remarkable finding in patients with chronic obstructive lung disease has been the generally small amount of blood flow to unventilated lung units. The fact that many of these patients had large amounts of blood flow to units with low ventilation-perfusion ratios but very little shunt suggests that collateral ventilation may be important in maintaining some ventilation to units situated behind blocked airways. The low ventilation-perfusion-ratio mode might, therefore, reflect the "parasitic" lung units, which receive all their inspired gas from other alveoli; this is the so-called series inequality of ventilation.

Bronchial Asthma

When bronchial asthma is present, there is a marked bimodal appearance, with some 25% of the total blood flow going to lung units that have ventilation-perfusion ratios in the region of 0.1 in asymptomatic patients with asthma. When these patients are given the bronchodilator isoproterenol by aerosol, the distribution shows a marked increase in the amount of blood flow to low ventilation-perfusion ratio units, which now received approximately one-half the cardiac output. These findings confirm that the decrease in arterial P_{O_2} that is often seen in asthmatics after bronchodilator therapy can be explained by the increase in blood flow to low ventilation-perfusion ratio units.

Myocardial Infarction

Patients who have suffered myocardial infarction often have some arterial hypoxemia, especially if there is evidence of pulmonary edema. Despite relatively mild degrees of ventilation-perfusion inequality, the abnormally low cardiac output in some of these patients can exaggerate the hypoxemia.

Interstitial Lung Disease

Patients with interstitial lung disease form an interesting group because of the possibility that part of their arterial hypoxemia may be caused by impaired diffusion across the thickened blood gas barrier. When a series of patients with interstitial lung disease was studied, their hypoxemia could also be explained by the pattern of ventilation-perfusion inequality when the patients were at rest. When these patients were studied during leg exercise, however, the measured arterial P_{O_2} was systematically lower than the predicted value. The conclusion was that, in these patients during exercise, a component of the hypoxemia must be attributed to some other cause, presumably diffusion impairment. On the average, however, only 19% of the alveolar-arterial P_{O_2} difference in these patients could not be accounted for, so that even in this group, the chief cause of hypoxemia was ventilation-perfusion inequality.