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DANIEL H. SIMMONS

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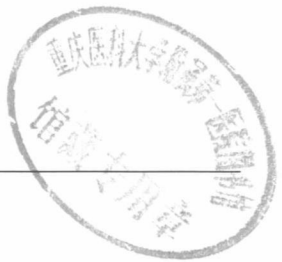

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Preface

This volume of *Current Pulmonology* contains chapters dealing with several aspects of respiratory disease. Emphasis, however, is on core areas of special interest: smoking, COPD, hypoxemia, and respiratory failure.

Considerable thought has been focused on whether treating the various types of COPD early—rather than in late symptomatic stages as we now do—would alter their course. While the only effective therapeutic measure available for treating COPD early is smoking cessation, many other measures are on the horizon. Richard Kanner of the University of Utah discusses the subject.

The critical subject of smoking cessation is covered by David P.L. Sachs of the Smoking Cessation Research Institute in Palo Alto, California. He makes it clear that smoking cessation programs—and their effect on progression of COPD—are often successful, but only with considerable and persistent effort. Perhaps this chapter's main utility is its message to primary care physicians and pulmonologists, who should know what can be done in their offices and how it is best done, but who know also what cannot be accomplished.

Another chapter relevant to COPD is that on protease inhibitors, by Friedrich Kueppers of Temple University. Kueppers points out that production of proteases—enzymes that break down lung proteins and lead to emphysema and bronchitis—is stimulated in the lung by cigarette smoke and other inflammatory agents, but that their effect can be modulated by naturally occurring protease inhibitors. Finally, there is now on the horizon a prophylactic COPD treatment for patients who produce inadequate naturally occurring protease inhibitors.

Two chapters relevant to clinical disorders in which tissue oxygenation is a major problem are presented by David Dantzker of the Albert Einstein College of Medicine and John Reeves of the University of Colorado. Dantzker discusses ef-

fects of abnormal oxygen delivery to tissues. Important to clinicians is his analysis of the phenomenon called "pathological supply dependency," which is increased oxygen consumption when delivering additional oxygen to the systemic circulation. While this poorly understood phenomenon has been recognized in acute conditions such as ARDS, it is becoming clear that it may be a significant problem in chronic disease as well. Progress in monitoring adequacy of cellular oxygenation is discussed.

Reeves outlines many ways that man can and does adapt to hypoxemia, and evaluates their relative importance in the adaptation. In normals, much of the adaptation is respiratory, but respiratory adaptation is impossible in many disease states. Integrating the circulatory and respiratory systems is critical in normals. But, as Dantzker points out, this integration appears to fail in disease, a view that is possibly directly relevant to understanding "pathological supply dependency."

Jeffrey Crowley and Thomas Raffin of Stanford University provide an update on acute lung injury, or ARDS, a very serious cause of hypoxemia. Their comments on mechanisms lead to a discussion of what is a potential new field in pulmonology—drug therapy of ARDS directed toward correcting metabolic abnormalities leading to the syndrome to either prevent or reverse it.

Relevant to maintaining normal carbon dioxide tensions in blood and tissue is the discussion by Apostolos Armaganidis and Charis Roussos from the Evangelismos Hospital of Athens on the work of breathing and the metabolic cost of respiratory muscle function under various conditions. Particularly helpful are their comments on ventilatory work and oxygen cost of breathing while using mechanical ventilators, a subject increasingly important to clinical pulmonology as more and more paraphernalia are added to ventilators (often without full understanding of their functions or effects on the work of breathing).

Predicting ventilatory failure for oxygen or carbon dioxide, one goal of evaluating pulmonary function tests, is discussed by Philip Harber of the University of California at Los Angeles. Harber clarifies what we do when interpreting pulmonary function tests: how we collect and look at data, the limitations of our interpretations, and what the findings imply about function and life-style.

Frederick Moore and others at the University of Colorado point out that, in this era of increasingly common chest trauma, flail chest and severe pulmonary contusion often coexist to create a situation associated with high morbidity and mortality. The pathophysiology of this often overlooked syndrome is discussed and is used as a basis for outlining its management.

A new therapeutic modality—lung transplantation—is discussed by Stuart Jamieson of the University of California at San Diego. While the technique is not yet integral to the practice of pulmonology, it is clearly about to become so. Pulmonologists should now be knowledgeable about indications for the surgery, its outcomes, and technical problems involved.

We appreciate the effort put into this volume by the authors, and we thank them for their excellent and useful work.

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Contents

CHAPTER 1

Oxygen Transport

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THE NEED FOR OXYGEN

For at least half the Earth's existence, oxygen was present in only minute quantities, if at all, and the earliest forms of living matter were created in this anaerobic environment. About 2 billion years ago, the first aerobic life is thought to have evolved. This dramatic change markedly improved the efficiency of metabolic processes, since energy extraction from fuel by oxidation could now be carried to completion using O_2 as the terminal electron acceptor. This remarkable development required the evolution of the cytochrome chain and adenosine triphosphate (ATP), which provided a means for extracting and storing the available energy in easily controllable packets.[1]

These early cells are thought to resemble present-day bacteria in which the components of the cytochrome chain are found in the cytoplasm as well as the cell membrane. In present-day eukaryotic cells, the cytochrome chain is contained within specialized organelles, the mitochondria. Because of structural similarities between mitochondria and bacteria, it has been postulated that mitochondria may have evolved from free living organisms that developed symbiotic relationships with other cells to form the prototype to the present day aerobic cell.[2]

As life forms became more complex, the system for O_2 transport also required modification. Single-cell organisms could extract the necessary O_2 directly from

the environment, but multicellular organisms needed a means of delivering O_2 to the interior cells. Some species continued to use air as a carrier, still seen today in insects. Others developed a true circulatory system and eventually O_2-binding pigments, which could transport far more O_2 than could be dissolved in body water. These are represented today by hemocyanin or more commonly by hemoglobin, which is found circulating in solution or packaged in erythrocytes.

While this complex system markedly improved both the efficiency and capacity of the organism to transport and utilize energy, it also opened the way for malfunctions to occur at many points along the way. This chapter will attempt to review some of these possible points of malfunction.

Proper cell function requires a continuous supply of energy to maintain cellular integrity and allow for important activities such as protein synthesis, muscular contraction, and active transport. Energy is derived from foodstuffs, predominantly through oxidative phosphorylation via the Krebs tricarboxylic acid (TCA) cycle.[3] The TCA cycle is a series of carefully controlled oxidation-reduction reactions during which the energy released from the transfer of electrons is captured. This involves reducing oxidized nicotinamide-adenine dinucleotide (NAD) to NADH, shuttling the electrons from NADH into the mitochondria, transferring the electrons along a series of electron-carrier enzymes, and capturing energy in the high-energy phosphate bonds of ATP. Oxygen is the terminal electron acceptor in this scheme, and sufficient amounts are required if optimal use of substrate for the generation of ATP is to continue. With glucose as substrate, the complete metabolism through the TCA cycle can be represented as follows:

$$\text{Glucose} + 6O_2 + 36\text{ADP} + 36\text{Pi} \rightleftarrows 6CO_2 + 42H_2O + 36\text{ATP}$$

where ADP is adenosine diphosphate and Pi is inorganic phosphate. Most of the O_2 utilization ($\dot{V}O_2$) is for oxidative phosphorylation, although a small amount is used in other synthetic and degradative pathways.

When oxygen is not present in adequate amounts or when demands are excessive, the body must depend on other methods of ATP generation if it is to maintain normal cellular function. Glycolysis utilizes pyruvate as the terminal electron acceptor instead of oxygen and thus produces energy anaerobically. The pyruvate is then reduced to lactate:

$$\text{Glucose} + 2\text{ADP} + 2\text{Pi} \rightleftarrows 2\text{lactate} + 2H_2O + 2\text{ATP}$$

This is a more wasteful method of ATP generation since it produces much less energy per mole of substrate. In addition, the anaerobic environment leads to development of metabolic acidosis due to inability of the tissues to utilize protons produced during ATP hydrolysis, the process by which energy is liberated for utilization:

$$\text{ATP} + H_2O \rightleftarrows \text{ADP} + \text{Pi} + H^+$$

Another alternative to glycolysis, at least in skeletal muscle, heart, and brain, is to make use of the creatine kinase reaction, in which a high-energy phosphate

bond is transferred from a storage compound, phosphocreatine (PCr), to ADP to produce ATP[4]:

$$PCr + ADP + H^+ \rightleftharpoons ATP + creatine$$

While this constitutes a ready source of energy to these organs under conditions of reduced O_2 availability, and in addition consumes protons to spare the tissues the consequences of acidosis, its usefulness is limited by the restricted PCr stores.

The amount of O_2 required for oxidative phosphorylation is substantial. It takes the O_2 found in 650 L of air to burn 1 mole of glucose.[5] Normally O_2 transport ($\dot{T}o_2$) is more than sufficient to maintain adequate cellular bioenergetics by the aerobic TCA pathway. When metabolic requirements are increased as with exercise, $\dot{T}o_2$ is augmented predominantly through an increase in cardiac output, which occurs concomitant with the increase in demands. This increase in $\dot{T}o_2$, which may be as much as three to five times depending on underlying cardiovascular status, is still not enough to satisfy the increased demands, which may exceed ten times or more in highly conditioned athletes at high levels of exercise. An additional source of O_2 is provided through increased O_2 extraction and widening of the arterial-venous O_2 difference. The extraction ratio ($ER = \dot{T}o_2/\dot{V}o_2$),[6] which is about 0.3 at rest, may approach 0.8 or even higher at maximal exercise.

If the level of energy needs is high enough, increase in neither $\dot{T}o_2$ nor ER are sufficient and the body invokes anaerobic means of additional energy production. In normal sedentary individuals this anaerobic threshold (AT) may occur at metabolic demands as low as 40% of maximal $\dot{T}o_2$.[7] The AT is higher in better-conditioned individuals and lower in poorly conditioned people or those with cardiopulmonary or peripheral vascular disease, which interferes with normal augmentation of $\dot{T}o_2$. Regardless of the degree of conditioning or the presence of $\dot{T}o_2$ limitation, the ER at the AT is usually found to be about 0.6.[8]

If $\dot{T}o_2$ is experimentally reduced in various animal models ($\dot{V}o_2$) is maintained until a very low level, the critical $\dot{T}o_2$ ($\dot{T}o_2$crit), is reached[9] (Fig 1). In different studies, the $\dot{T}o_2$crit in healthy animals has varied from about 7 to 10 mL/kg/min. Initially, compensation for the falling $\dot{T}o_2$ is provided by increasing the ER, much as is seen during increasing O_2 requirements. Below the critical $\dot{T}o_2$, $\dot{V}o_2$ falls despite the fact that ER continues to increase. In animal studies, this fall in $\dot{V}o_2$ correlates with the utilization of PCr and elevation of lactate levels.[10] The ER at $\dot{T}o_2$crit (ERcrit) in the different animal studies has varied from about 0.45 to 0.80.

As one might expect, there are no similar data on the effect of experimentally reducing $\dot{T}o_2$ in normal humans. The only data available in relatively healthy individuals were obtained in a group of patients undergoing coronary bypass surgery in whom random measurements of $\dot{T}o_2$-$\dot{V}o_2$ pairs were made following induction of anesthesia.[11] In these patients, it appeared as if $\dot{V}o_2$ remained constant from a $\dot{T}o_2$ of about 19 to 9 mL/kg/min, below which $\dot{V}o_2$ fell. This apparent $\dot{T}o_2$crit of about 9 mL/kg/min was not different from that reported in the animal studies, although the ERcrit in these patients was only 0.30 as compared with the much higher value at the AT in humans and in the animal studies at $\dot{T}o_2$crit.

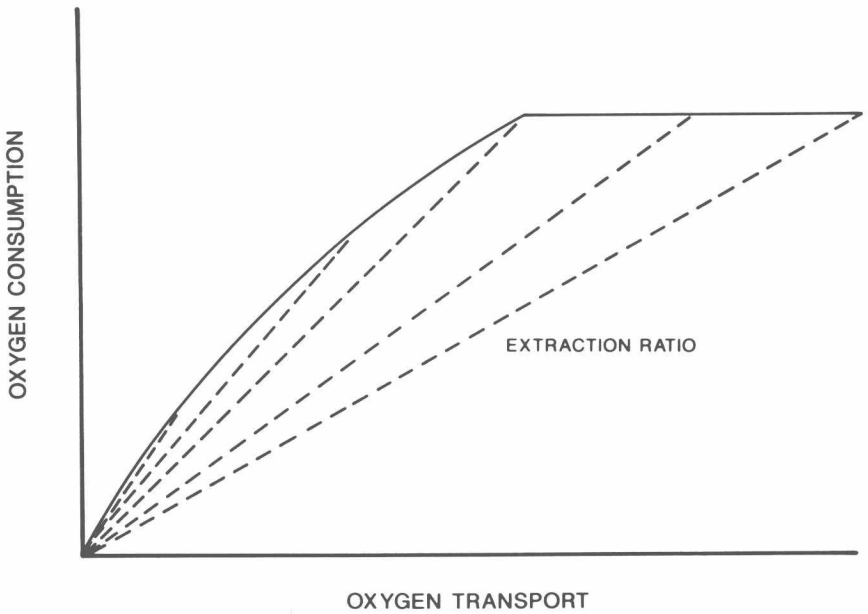

FIG 1.
The relationship between oxygen transport, oxygen consumption, and the oxygen extraction ratio. As oxygen transport falls, oxygen consumption can be maintained by a progressive increase in the extraction ratio (as indicated by the increasing slope of the extraction ratio isopleths). At some point, the critical oxygen transport, baseline oxygen consumption, can no longer be maintained despite continued increase in the oxygen extraction. The level of critical oxygen transport divides the relationship into supply-independent and supply-dependent portions.

The biphasic relationship between $\dot{T}o_2$ and $\dot{V}o_2$ differs from that found in patients suffering from a variety of acute and chronic illnesses.[12–18] In many of these patients, $\dot{V}o_2$ and $\dot{T}o_2$ vary in concert over a much wider range of $\dot{T}o_2$, and a $\dot{T}o_2$crit cannot be identified. In these patients, the assumption is made that $\dot{V}o_2$ is dependent on $\dot{T}o_2$ even at presumed normal levels of $\dot{T}o_2$. This has been termed *pathologic supply dependency*. Increasing $\dot{T}o_2$ to a supply-independent plateau has been suggested, intuitively, as a reasonable therapeutic approach to prevent the onset of multiorgan failure in patients with sepsis and the adult respiratory distress syndrome (ARDS). Unfortunately, our understanding of $\dot{T}o_2$ and $\dot{V}o_2$ at the tissue level is not yet well enough developed to be certain of the reasonableness or achievability of that goal.

In the mitochondrion, very low levels of O_2 are required to maintain cellular respiration at maximal levels. In isolated mitochondria, cytochrome C oxidation, a useful marker of oxidative phosphorylation, is complete at a Po_2 of 0.5 mm Hg.[19] In an isolated perfused lung preparation, in which cellular Po_2 was estimated by perfusing and ventilating the lung with mixtures containing identical Po_2, de-

creased ATP in alveolar cells was not seen until the estimated cellular P_{O_2} fell to 0.7 mm Hg.[20] The similarity of the very low P_{O_2} requirement by both the intact cell and the isolated organelle suggests a negligible resistance to O_2 diffusion within the cell. This has been corroborated, at least in muscle cells, by actual measurements of intracellular P_{O_2}, where cellular P_{O_2} of less than 4 mm Hg was seen in fully aerobic working muscle.[21] Studies in both experimental animals and healthy humans suggest that relatively normal tissue function is present with a P_{aO_2} as low as 28 mm Hg.[22] This high affinity for oxygen would appear to suggest that severe reductions in $\dot{T}_{O_2}$ are necessary before hypoxic tissue damage occurs; yet, in critically ill patients, evidence of tissue hypoxia is seen with much less drastic reductions in $\dot{T}_{O_2}$. Either this is due to a failure of important oxygen-dependent extramitochondrial processes, which have a much lower affinity for O_2, or the levels of tissue oxygenation are markedly underestimated by present monitoring techniques.

$\dot{T}_{O_2}$

Oxygen is transported from the environment to the cell by a series of diffusion and convection steps (Fig 2). These processes in the lung are well understood and will not be covered here. Oxygen convection to the tissues, $\dot{T}_{O_2}$, can be defined as follows:

$$\dot{T}_{O_2} = \text{arterial } O_2 \text{ content} \times \text{cardiac output}$$

Thus, it depends on variables such as P_{aO_2}, O_2 saturation, hemoglobin concentration, and the factors that regulate overall cardiac output. Each of these, in turn, has its own regulatory mechanisms, adding immeasurably to the complexity of the system and the potential for impact on tissue O_2 availability. Oxygen transfer into the tissues is equally easy to define:

$$\text{Tissue } O_2 \text{ Flux} = D_{O_2} (P_{capO_2} - P_{mitoO_2})$$

when D_{O_2} is the diffusing capacity for O_2 in the tissues and P_{capO_2} and P_{mitoO_2} are the capillary and mitochondrial P_{O_2}, although the individual terms are complex and difficult to measure.

While intrinsic cardiac function sets limits on cardiac output and neural input can result in abrupt alterations, the minute-to-minute regulation of total flow is determined by the peripheral vasculature as it alters venous return and left ventricular afterload. The peripheral vascular bed, in turn, is a collection of individual networks, perfused in parallel and serving organs with widely divergent metabolic requirements, which must be met by individualizing local blood flow.[23]

Local vascular control is usually thought of as occurring at two levels. The small muscular arterioles control overall flow distribution by altering local vascular resistance, and the precapillary sphincters optimize the number of open nutritive capillaries. Evidence for the presence of precapillary sphincters as a general

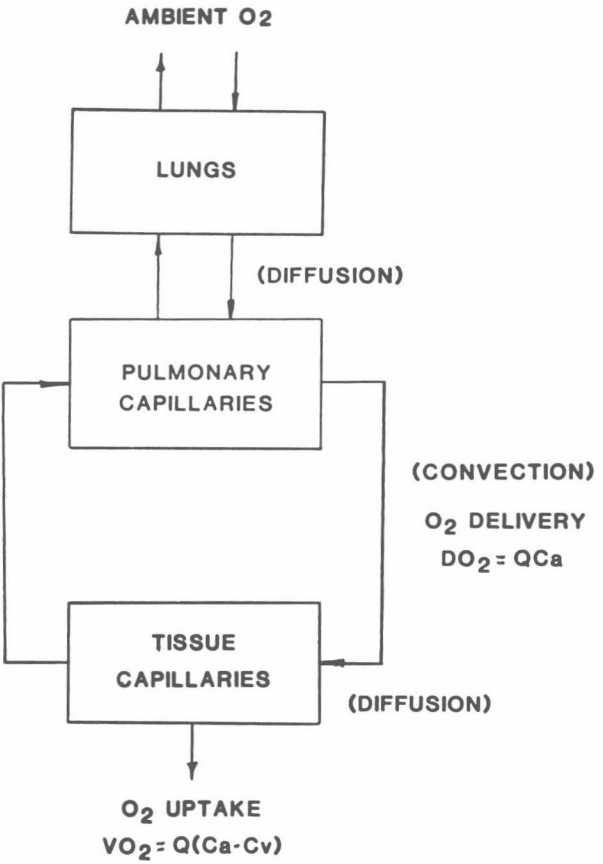

FIG 2.
The oxygen transport pathway. Oxygen is delivered from the environment to the lungs by a series of convection and diffusion steps. Vo_2 = oxygen utilization; Do_2 = oxygen delivery; Q = cardiac output; C_a and C_v are the arterial and venous oxygen contents.

component of microvascular control in humans, however is less certain. While neural innervation of the microvascular bed is present, the most important mechanism for the control of flow distribution appears to be local autoregulation acting through two postulated mechanisms.[24] The first of these, the myogenic mechanism, is responsible for maintaining constant flow in the face of varying intravascular pressures through alterations in smooth-muscle tone. The second, the metabolic controller, alters local $\dot{T}o_2$ to accommodate for continuously varying metabolic demands. While hypoxia dilates the vascular bed and hyperoxia results in vasoconstriction, the actual stimulus for metabolic vasocontrol of the peripheral microvasculature has not been established. Since local blood flow is closely linked to local $\dot{V}o_2$, either tissue Po_2 or some factor released in response to tissue hy-