The Pathophysiology of Respiratory Failure in Chronic Obstructive Pulmonary Disease*

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The most important pathophysiologic aspects of chronic and acute obstructive pulmonary disease involve disturbances in ventilation with resulting derangement of gas exchange in the lung. There is considerable variability in the type of abnormality, the time of its appearance in relationship to the history of the disease, and in the progression of the abnormality in blood gases. The usual sequence, however, is the following: 1) In the earliest stages there is no blood gas abnormality at rest or with exercise, 2) With further progression of the disease the blood gas tensions are normal at rest but on exercise there is a significant decrease in arterial blood P_{O_2}, 3) In a more advanced stage there may be minimal reduction in arterial blood P_{O_2} at rest, while on exercise hypoxemia is accentuated and arterial blood P_{CO_2} rises, 4) In advanced COPD there is decrease in arterial blood P_{O_2} and increase in arterial blood P_{CO_2} at rest, with moderate or marked worsening of these changes on exercise.

Hypoxemia results from one or more of the following factors: disturbance in ventilation/perfusion relationships of lung, hypoventilation, and, to a degree, impaired diffusion. Hypercapnia results from alveolar hypoventilation. Ventilation/perfusion disturbances of the lung may occur because obstruction of bronchi and bronchioles is uneven, resulting in portions of the lung being hypoventilated and other parts being hyperventilated. The mechanism of obstruction can involve several of the following factors, all of which may be unevenly distributed in different areas of the

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lung: tenacious exudate in the bronchi and bronchioles; edema of the bronchial wall and bronchial or bronchiolar wall and mucosa; bronchiolar spasm; loss of the normal radial (outward) traction on the wall of the bronchi and bronchioles, owing to loss of the normal pattern of the pulmonary stroma through departitioning of the lung; and, finally, varying degrees of fibrotic obstruction of the airways. The loss of radial traction from departitioning of the lung, owing to breakdown of alveolar septae, is perhaps the least appreciated of these common mechanisms of obstruction. During expiration, the airways are normally held open, in part, by the outward pull of the various elements in the pulmonary stroma. When this outward pull is diminished or lost, and particularly when the other factors producing obstruction are operative, including loss of integrity of the bronchial and bronchiolar walls, some collapse or closure of the airways after the early phase of expiration is inevitable. As the chest becomes barreled and assumes the position of hyperinflation, the radial traction may be maintained to a greater degree than if the chest had retained its normal contour, although a price is paid in the form of a less efficient performance of the muscles of respiration, including the diaphragm. The accessory muscles of respiration, particularly the scalenes and less importantly the sternomastoids, the upper trapezius, and the pectoral muscles, assume increasing importance in the maintenance of ventilation, particularly in the upright position.

Blood leaving the alveolus, which is underventilated in relation to the amount of blood flow, thus has a low ventilation/perfusion ratio (low $\dot{V}_A/\dot{Q}_C$), both in the oxygen and carbon dioxide exchange. Blood leaving this alveolus will have a lowered oxygen tension and content and an elevated carbon dioxide tension and content. In contrast, certain alveoli are overventilated, since their airways are less obstructed and they feel the effects of the increased respiratory efforts which the patient commonly makes to overcome the overall increase in airway resistance. Blood leaving the hyperventilated alveolus with a high ventilation/perfusion ratio (high $\dot{V}_A/\dot{Q}_C$ ratio) will have an oxygen tension slightly above normal. Owing to the fact that the oxygen dissociation curve is very flat at the arterial end of its normal range, very little additional oxygen content is gained by this increase in oxygen tension. Furthermore, oxygen is relatively insoluble, with only about 0.3 ml of oxygen normally dissolved in 100 ml of arterial blood. The gain in dissolved oxygen from the small increase in oxygen tension is almost negligible. On the other hand, much more carbon dioxide is in solution in the plasma and can be more readily moved under a given diffusion gradient. The CO_2 dissociation curve is steeper than the oxygen dissociation curve. As a result, the blood leaving the hyperventilated alveolus has lost much more carbon dioxide than it has gained oxygen. When these two blood streams, one from an underventilated alveolus and the other from an overventilated alveolus, are united, the stream with low oxygen content, mixing with the stream containing a minimally increased oxygen content, results in blood which has a reduced oxygen content and tension. On the other hand, the mixing of a stream with an elevated CO_2 content with one having a reduced CO_2 content can readily result in blood with normal or near normal carbon dioxide content and tension. Therefore, we commonly observe arterial hypoxia, first during exercise and later at rest, as the initial blood gas abnormality during the progression of chronic obstructive pulmonary disease. The elevation of carbon dioxide tension occurs later as alveolar hypoventilation becomes widespread with further deterioration of respiratory function.

Impairment of diffusion (the third major type of respiratory insufficiency) is usually not marked in COPD unless there is concomitant fibrosis of the lung. In the centrilobular type of emphysema, however, owing to dilatation of terminal airways, diffusion may be impaired because of the longer diffusion path ("distance barrier").

The heart is frequently secondarily involved in emphysema. This introduces another abnormality in the oxygen delivery system. Impairment of cardiac function results primarily from pulmonary hypertension which eventually leads to chronic cor pulmonale. The pulmonary hypertension is due to increased pulmonary vascular resistance which in turn is due to the following factors: 1) loss of vascular bed as a result of destruction of vascular channels, 2) increased intra-alveolar pressure compressing the blood vessels in the lung, 3) vasoconstriction due to the reduced P_{O_2} of the blood, primarily when acidosis is present. This last factor is at present thought to be an important reason for the development of pulmonary hyper-

tension in emphysema, but operates primarily when there is respiratory acidosis. Hypoxic constriction of pulmonary arteries and arterioles is relatively weak when the blood pH is normal. Cardiac function in emphysema may be further impaired as a result of direct harmful effects of the low P_{O_2} and high P_{CO_2} on cardiac muscle and also as a result of increased work of the heart in the high cardiac output stage of the disease. Impairment of cardiac function in emphysema may be more severe if there is associated coronary disease.

Chronic hypoxia of a severe degree in the later stages of chronic obstructive pulmonary disease brings about a deterioration of function of most organs of the body. A patient in late emphysema commonly loses weight, is depressed and often confused, and has little or no tolerance for exertion. Reduction of cardiac output with failure of the right heart further increases tissue hypoxia. The hypoxia does, however, stimulate two types of tissue rather late in the disease: the chemoreceptors of the aortic and carotid bodies (the function of the glomus pulmonale at the bifurcation of the pulmonary artery is still unclear), and the bone marrow. The chemoreceptor stimulation is important in offsetting the narcotic effects of high arterial carbon dioxide tension on the respiratory center complex in the brain stem. Therefore, too rapid or too large a reduction of the hypoxia without adequate respiratory assistance can reduce the drive to respiration and rapidly worsen the elevation of arterial CO_2 tension (hypercapnia).

Physiological Patient Management. In the application of physiology to patient care we seek to use previously accumulated knowledge of physiological processes and mechanisms to plan our therapy, with the aim of shifting abnormal processes and disease toward the normal. We also utilize the physiological approach in evaluating the effect of management in a given patient on a day to day, hour by hour, and, at times, moment to moment basis, as well as in evaluating our past performances so as to plan more effective therapeutic strategies for the future.

The application of cardiovascular and respiratory physiology to the management of a *specific* patient rests upon the adequacy of *quantitative* knowledge of physiological responses and mechanisms. If the information is not quantitative, effective "physiological" management may not be possible. A difficult and ever present problem is the effective application of knowledge of physiological processes and mechanisms obtained from studies on other human beings and animals, both normal and ill, to the care of one particular patient; the physiological responses may differ in important respects, both qualitative and quantitative, from those described in the literature.

As an example of the need for quantitative information, we may cite the pulmonary vascular response to hypoxia. It is not enough to know that pulmonary vessels constrict on the influence of arterial hypoxia and that this constriction is greater during states of acidemia. One needs to know the quantitative relations between hypoxia and acidemia in the studies reported in the literature. From this information, an estimate can then be made of the probable magnitude of the pulmonary vasoconstriction in the patient under treatment, given the data on his arterial blood gas tensions and pH. Certain additional questions must be answered in order to plan effective therapy: Is the magnitude of this patient's hypoxia and of his acidemia by combined effect sufficient to produce a serious increase in pulmonary vascular resistance and an increase in the work load of the right heart? Are the hypoxia, the hypercapnia (if present), and the acidemia acting to impair the ability of the right heart to handle the increased work load? What other important factors, for example, coronary arterial or pulmonary vascular disease, are present and how do they interact with the blood gas and pH abnormalities? Is therapeutic intervention needed, and how urgently? What are the probable favorable and potentially unfavorable physiological effects of the therapeutic options?

If only rough and approximate answers to such questions can be given, which is commonly the case, then some means of continuous or frequent discontinuous monitoring of the physiological state of the patient must be available. Such monitoring can be instrumental, including biochemical, or human. The continuous human monitoring of the patient—the nurse at the bedside of a single patient—is becoming less and less common. The development of intensive care units, providing the nurse with physical proximity to more than one patient, makes possible effective visual and auditory monitoring of two, perhaps three, patients by one nurse. The more seriously

ill the patient, the smaller his physiological reserves and the greater the need for continuous or frequent discontinuous monitoring of basic functions. Such monitoring provides the essential feedback information required for precise adjustment of therapy to the physiological state of the patient and for the early detection and correction of errors in management.

A difficult challenge that must be met is the devising of means of continuous and discontinuous measurement of physiological processes in the individual patient that are sufficiently basic yet *practicable* to provide the data required for effective therapy. At present, variables commonly and readily monitored are: intravascular pressures, the electrocardiogram and the heart rate, the tidal volume and respiratory rate (although this last presents some problems), and rectal temperature. Continuous body weight recording can be done, but these recording scales are at present expensive. Frequent discontinuous information on the blood gas tensions and pH is, of course, readily obtained but continuous recording of these variables still presents problems. Continuous information on other functions, including cardiac output and oxygen delivery to the tissues, is clearly needed in many patients critically ill with cardiorespiratory disorders.

The need is particularly great in relation to the often rapidly changing clinical states of respiratory failure. This is not to say that in every case sophisticated instrumentation is required, or that it will provide all of the information needed for optimal management. Sensitive clinical observation remains essential. For example, the human face, particularly in the elderly in whom physiological reserves are low, is an exceedingly delicate indicator of favorable or unfavorable terms of physiological events. The greatest clinicians of the past, or of today, appear to have an intuitive feeling of the pathophysiology in the patient, even though they are not always able to articulate this feeling. The present day clinician should not abandon efforts to sharpen his own sensitivities toward the subtle summation of physiological processes that result in changes in the appearance of the patient's face, tone of voice, gesture, feel of tissue, in favor of excessive reliance on sophisticated instrumentation. These methods of study of the patient are complementary, not usually exclusive. One can safely predict that, for example, when continuous recording of arterial blood gas tensions, pH, and cardiac output become commonplace in the management of critically ill patients, these same measurements will make it possible to sharpen our bedside observations and the conclusions that we draw from them.