SOME APPLICATIONS OF PULMONARY PHYSIOLOGY TO CLINICAL MEDICINE

During the past ten years a number of techniques and theoretical concepts have been developed for the analysis of various aspects of pulmonary function in health and in disease. An understanding of the principles of modern respiratory physiology enables the physician to provide the proper amount of artificial ventilation to the apneic subject and to assess the nature and the extent of the functional impairment of the lung in patients with pulmonary disease. This paper outlines certain principles of respiratory physiology, the theoretical basis for some tests of pulmonary function, and some ways in which pulmonary function may be impaired in patients with pulmonary disease.

Table 1 is a convenient classification of pulmonary functions. The first function of the lungs is to provide an optimum gaseous environment for the exchange of carbon dioxide and of oxygen between the blood and the air in the alveoli. This ventilatory function is dependent upon the integrity of the thoracic and diaphragmatic muscles and upon the patency of the airways. Ventilation must be adequate to maintain the proper concentration of oxygen and of carbon dioxide in the alveoli. Next, oxygen must diffuse from the alveoli into the blood and carbon dioxide from the blood into the alveoli. This diffusion function is dependent upon the size of alveolar-capillary surface area available for gas exchange and upon the thinness of the barrier between the alveolar space and the red blood cells. Finally, the blood flowing through the lung must be diverted to the alveoli which are ventilated and not to non-ventilated areas or through arteriovenous communications. One or all of these three functions may be disturbed in disease.

Assessment of ventilatory function and of the total ventilation required by the apneic subject requires an understanding of the factors which determine the composition of the air in the alveoli. Carbon dioxide is produced in the tissues and diffuses from the venous blood into the alveoli, and oxygen is taken up by the blood in the alveolar capillaries and carried to the tissues where it is consumed. The concentration of oxygen and of carbon dioxide in the alveolar gas is dependent upon the metabolic rate and upon the volume of air brought in and out of the alveoli. Since, as will be explained later,
precise regulation of the alveolar carbon dioxide tension is of greater importance than is the exact maintenance of a normal alveolar oxygen tension, the factors concerned with the alveolar carbon dioxide tension will be considered first. These factors are illustrated in Figure 1, in which the alveoli are represented as a single large space into which carbon dioxide diffuses continuously and into which fresh air is brought periodically. In reality, the

| Pulmonary function                  | Test                                      | Clinical finding                                      |
|-------------------------------------|------------------------------------------|-------------------------------------------------------|
| Ventilation of alveoli              | Alveolar gas composition                 | Diminished respiratory excursions                      |
|                                     | Spirometry                               | Airway obstruction                                    |
|                                     | A. Maximum breathing capacity            | Respiratory acidosis with or without anoxemia.        |
|                                     | B. Vital capacity                        |                                                       |
|                                     | C. Timed vital capacity                  |                                                       |
| Diffusion of oxygen from alveoli to | Diffusing capacity of lung               | Anoxemia aggravated by exercise, relieved by oxygen   |
| blood                               | A. Low oxygen method                     | breathing                                             |
|                                     | B. Carbon monoxide method                |                                                       |
| Distribution of blood and air in    | Alveolar-arterial oxygen tension         | Anoxemia during oxygen breathing                      |
| lung                                | difference                               |                                                       |
| A. Effective right-to-left shunts   | Per cent venous admixture                | Hyperinflation of lung                                |
|                                     | Lung dead space                          |                                                       |
| B. Uneven ventilation and perfusion | Lung volumes                             | Anoxemia (relieved by oxygen breathing) with CO₂       |
|                                     | Mixing of gases in lung                  | retention                                             |

alveolar space is subdivided into a large number of very small compartments so that the composition of gases in the entire alveolar space is relatively homogeneous. Since fresh air contains less than .1% carbon dioxide, the concentration of carbon dioxide in the alveoli equals the amount of CO₂ produced per minute divided by the volume of air that enters and leaves the alveoli per minute (the alveolar ventilation). The partial pressure or tension of a gas is equal to the barometric pressure (minus the vapor pressure of water) times the per cent of the gas. These relationships may be expressed as follows: \( \dot{V}_A = \frac{\dot{V}_{CO_2} \times (P_B - 47)}{P_{A_{CO_2}}} \) (eq. 1) where \( \dot{V}_A \) is alveolar ventilation (litres/minute), \( \dot{V}_{CO_2} \) is the amount of carbon dioxide produced per minute and \( P_{A_{CO_2}} \) is the alveolar CO₂ tension. Since the \( P_{A_{CO_2}} \) should be
and normally is maintained at 40 mm. Hg, the alveolar ventilation is directly dependent upon the metabolic rate (or, in this instance, the CO₂ produced per minute). One can, then, predict the alveolar ventilatory requirements of an apneic patient simply from a knowledge of the minute carbon dioxide production. The latter may be measured directly or may be estimated from normal standards (based on body surface area), corrected for fever or activity. Knowledge of the desired alveolar ventilation is only part of the requirement, because the total ventilation also includes a fraction of air which merely goes in and out of the air-conducting passages, the dead space. If one assumes a normal value for dead space (the best assumption at the present time appears to be to equate the dead space in cubic centimeters to the weight in pounds), one can compute this dead space ventilation by multiplying the volume of the dead space by the respiratory rate. Addition of the dead space ventilation to the alveolar ventilation gives the total ventilatory requirement, and, if this is divided by the respiratory rate, the tidal volume is computed. Thus, assessment of an individual’s ventilatory requirements is a relatively precise matter for which certain assumptions are made regarding the relationship between physiological dead space and metabolic rate and body weight. This may be done by direct calculation or by means of a nomogram. For a given dead space, the magnitude of the dead space ventilation increases in direct proportion to an increase of the respiratory rate. Thus, an individual has to breathe a larger total volume at fast rates than at slow rates. An individual with psychogenic hyperventilation may breathe very large total volumes at a fast rate, but, since the dead space ventilation is very large, alveolar ventilation may be increased only slightly or not at all. For managing an apneic patient, one does well to select a slow respiratory rate and a large tidal volume so that the dead space occupies a small proportion of the tidal volume. Then, total ventilatory requirements are as small as possible, and if the dead space is not exactly the assumed value, the effect of the error on alveolar ventilation will be minimal.

![Diagram](image-url)
If the alveolar carbon dioxide tension ($P_{ACO_2}$) is kept at a normal value, 40 mm. Hg, the alveolar oxygen tension ($P_{AO_2}$) varies from approximately 96-115 mm. Hg, depending upon the respiratory quotient: (eq. 2) 

$$P_{AO_2} = P_{O_2} - P_{ACO_2} \cdot \frac{.21}{R} + .79 \cdot \frac{P_{ACO_2}}{R}$$

where $P_{O_2}$ is the inspired oxygen tension, normally about 148 mm. Hg at sea level. Since the arterial blood is 90% saturated with oxygen when the oxygen tension is 70 mm. Hg, only a marked reduction of alveolar oxygen tension (in the absence of a significant alveolar-arterial oxygen pressure difference) will result in significant anoxemia. Such a lowering of the oxygen tension would result in a marked elevation of the carbon dioxide tension and, indeed, detrimental hypercapnia would develop long before anoxemia. Furthermore, hyper-ventilation causes elevation of the alveolar oxygen tension which is harmless, whereas it also causes hypocapnia, which may be deleterious.

Proper ventilation of the alveoli is only the first of the three steps involved in the proper oxygenation of the blood. Next, oxygen must diffuse across the alveolar membrane into the capillary blood, and carbon dioxide must diffuse into the alveoli. Since carbon dioxide is approximately 20 times as diffusible as oxygen, impaired diffusion of carbon dioxide is rarely a problem, whereas the diffusion of oxygen may be significantly impaired in disease. The factors concerned in the diffusion of oxygen are best expressed in the formula for calculation of the diffusion capacity of the lung, ($D_{O_2}$), a measure of the area available for diffusion and of the thinness of the diffusion surface: 

$$D_{O_2} = \frac{\dot{V}_{O_2}}{P_{AO_2} - P_{CO_2}}$$

(Eq. 3) where $\dot{V}_{O_2}$ equals oxygen consumption per minute, or metabolic rate, and the denominator equals the difference in oxygen tension between the alveoli ($P_{AO_2}$) and the mean oxygen tension of the blood flowing through the alveoli ($P_{CO_2}$). This expression is a measure of the oxygen consumed per unit pressure head available for diffusion. Normally, the diffusing capacity is so high that there is no difference between the oxygen tension in the alveoli and that in the blood leaving the alveoli. In patients with the loss of the alveolar-capillary surface (pulmonary emphysema) or with pulmonary fibrosis, the diffusing capacity may be greatly reduced and even result in reduction of the arterial oxygen tension. Usually, this reduction is small until the subject exercises. When the oxygen consumption increases, an appreciable difference of oxy-
Oxygen tension may exist between the alveoli and the blood leaving them. Characteristically, patients with pulmonary fibrosis show a lowering of their arterial saturation during exercise. Elevation of the pressure of oxygen in the alveoli by the inspiration of pure oxygen greatly increases the pressure head from the alveolus to the blood entering the alveolus. Such an increase of this pressure head results in the rapid diffusion of oxygen into the mixed venous blood so that the blood leaves the alveoli fully saturated with oxygen. Stated differently, for a given diffusing capacity, elevation of the alveolar oxygen tension from 100 to 700 mg. Hg causes oxygen to diffuse from the alveoli into the venous blood some eight times as fast as it did during the inspiration of room air, with the result that the blood flowing through the alveolar capillaries soon becomes fully saturated. Clinically, patients with diffusion problems may show a marked increase of arterial oxygen saturation during oxygen breathing. For the same reason, inspiration of a low oxygen mixture, or ascent to high altitude, greatly increases the difference in oxygen tension between the alveoli and the blood leaving the alveoli. An individual whose diffusing capacity is moderately reduced may have a normal oxygen saturation at sea level but may suffer from severe anoxemia at 12-15,000 feet. This effect of hypoxia on increasing the alveolar-arterial oxygen tension difference when due to impaired diffusion is the basis for the low-oxygen method of measuring the diffusing capacity of the lung.

The final pulmonary function to be considered concerns the distribution of blood and of gas in the lung. Obviously, if all of the air went to some alveoli and all of the blood went to others, venous blood would pass through the lungs unchanged. Normally, circulation and ventilation are so related
that the blood flows to the ventilated alveoli. If an area of the lung is
diseased, a number of compensatory mechanisms serve to shunt blood away
from that area. However, many diseases cause impaired blood-gas distribu-
tion which results in cyanosis. Indeed, cyanosis is most commonly a result
of impaired distribution. For example, as in Figure 2, a pulmonary arterio-
venous fistula results in the admixture of venous blood to the arterialized
blood such that the saturation of the normally oxygenated blood is reduced
from 98 to 91%. With knowledge of the venous saturation, one can calcu-
late the percentage of blood, \(x\), shunted around normally ventilated
alveoli: \(\frac{S_{CO_2}}{1-x} + \frac{S_{VO_2}}{x} = S_{aO_2}\) (eq. 4), where \(S_{VO_2}\) is the
venous oxygen saturation, \(S_{CO_2}\) is the oxygen saturation in the blood
leaving the ventilated alveoli and \(S_{aO_2}\) is the arterial oxygen saturation.
Similar shunts may occur through atelectatic lung, or, of course, through
cardiac abnormalities, and the same calculation of the per cent of shunt
applies. The low oxygen saturation existing in patients with a shunt of
this sort is only partially improved by the inspiration of pure oxygen.
Oxygen breathing raises the venous saturation and the saturation of the
blood leaving the alveoli so that the arterial saturation may rise as much
as 10%. Solution of equation 4 during oxygen breathing provides a fairly
accurate estimation of the per cent shunt, since other causes of oxygen
unsaturation are eliminated by this procedure. Such a calculation is only
valid if the shunt is over 25% of the total blood flow, since smaller shunts
will not cause appreciable oxygen unsaturation during oxygen breathing.
Because of the relatively steep slope of the carbon dioxide dissociation
curve of blood, elevation of the arterial carbon dioxide tension occurs only
in extensive right-to-left shunts.

Another type of distribution problem, seen particularly in pulmonary
emphysema, occurs when different areas of lung are ventilated at different
rates.\(^1\) For example, as in Figure 3, if one lung is ventilated twice as much
as the other, the alveolar carbon dioxide tension in one lung is 60 mm. Hg,
whereas in the other it is 30 mm. Hg. Assuming equal blood flows to the
two lungs, the mean \(CO_2\) tension in the blood is the average of that of the
blood leaving the two lungs (45 mm. Hg), whereas the average alveolar
\(P_{CO_2}\) is only 40 mm. Hg, because twice as much air containing a smaller
amount of \(CO_2\) contributes to the mean as does air containing the larger
amount of \(CO_2\). This type of situation may result in appreciable retention
of \(CO_2\) in the arterial blood. Uneven ventilation may also cause significant
lowering of the partial pressure of oxygen in the arterial blood. In Figure 3,
the alveolar oxygen tension in one lung is 120 mm. Hg and in the other,
60 mm. Hg. The average alveolar tension is 100 mm. Hg. The bloods
leaving the two lungs have oxygen tensions of 60 and 120 mm. Hg and
saturations of 90 and 100% respectively. Thus, the arterial oxygen saturation is 95% and the arterial oxygen tension is 80 mm. Hg, an alveolar-arterial tension difference of 20 mm. Hg. This form of distribution impairment only results in a pronounced lowering of the arterial oxygen tension when air is breathed since its effect on arterial oxygen tension is largely dependent on the changing slope of the oxygen dissociation curve and can be eliminated by the inspiration of a high or a very low oxygen mixture. A pronounced increase of oxygen saturation during the inspiration of pure oxygen suggests the presence either of impaired diffusion or of uneven ventilation of the lung. Low oxygen saturation during the inspiration of pure oxygen is diagnostic of a shunt or a shunt-like effect in the lung.

Normal respiratory function, then, consists of ventilation of the alveoli with fresh air in sufficient quantity to dilute the carbon dioxide produced per minute to the proper value (40 mm. Hg), diffusion of oxygen and carbon dioxide across the alveolar membrane and even, homogenous distribution of blood and gas flows in the lung. Since the mechanical act of ventilation is dependent upon the integrity of the thoracic muscles and diaphragm.
and the patency of the airways, tests of ventilatory function (maximum breathing capacity, vital capacity, and timed vital capacity) shed light on an individual's ability to ventilate his alveoli. The over-all effectiveness of ventilation can be assessed by measuring the alveolar CO$_2$ and O$_2$ tensions. Since ventilatory needs are directly dependent, as has been developed, upon metabolic requirements, an individual with mild ventilatory insufficiency may have normal alveolar gas composition at rest, but a low oxygen tension and a high CO$_2$ tension during exercise. It is important to bear in mind that ventilatory insufficiency, as opposed to impairment of the other pulmonary functions, results primarily in CO$_2$ retention and, only in advanced cases, in anoxemia.

Precise measurement of the oxygen diffusing capacity of the lung is done, at the present time, by techniques which are difficult to perform and which require special equipment. Evaluation of the diffusing capacity of the lung is important for assessing cyanosis in patients without evidence of ventilatory dysfunction or of shunts, and clinical signs of impaired diffusion are a drop of arterial oxygen saturation during exercise (in the absence of severe emphysema) and a marked rise of oxygen saturation during the inspiration of pure oxygen.

A number of techniques have been developed to assess homogeneity of ventilation and of perfusion. Measurement of the tension of oxygen in alveolar air and arterial blood allows one to calculate the per cent shunt through unventilated lung or through a right-to-left shunt. If the arterial oxygen saturation is less than 100% during the inspiration of oxygen, one can estimate the per cent shunt, assuming a normal venous saturation and a saturation of 110% (which includes dissolved oxygen) of the blood leaving normally ventilated alveoli. Homogeneity of ventilation is assessed by analysis of expired nitrogen or carbon dioxide curves with rapid gas analyzers, measurement of the size of the lung dead space, and of the lung volumes, since increased dead space and residual volume generally indicate the presence of uneven distribution of inspired air.

With the aid of a few equations or a nomogram the physician is able to predict the ventilatory requirements of the apneic subject with a fair degree of accuracy. These techniques are particularly useful to the internist concerned with the management of respirator patients and to the anesthesiologist who is providing the ventilation for an open-chest patient. An understanding of respiratory physiology and a few simple measurements (involving a spirometer and some technique for measurement of the saturation of the arterial blood) enable the physician to assess ventilatory function, the presence or absence of severe impairment of diffusion of
oxygen in the lung, and the presence or absence of marked impairment of blood and gas distribution in the lung.

REFERENCES

1. Comroe, J. H., Jr., Foster, R. E., II, DuBois, A. B., Briscoe, W. A., and Carlsen, E.: The lung. Year Book Publishers, 1955.

2. Donald, K. W., Renzetti, A., Riley, R. L., and Cournand, A.: Analysis of factors affecting oxygen and carbon dioxide in gas and blood of lungs: Results. J. appl. Physiol., 1952, 4, 497.

3. Farhi, L. E. and Rahn, H.: A theoretical analysis of the alveolar-arterial O₂ difference with special reference to the distribution effect. J. appl. Physiol., 1955, 7, 690.

4. Lilienthal, J. L., Jr., Riley, R. L., Proemmel, D. D., and Franke, R. E.: An experimental analysis in man of the oxygen pressure gradient from alveolar air to arterial blood during rest and exercise at sea level and at altitude. Amer. J. Physiol., 1946, 147, 199.

5. Radford, E. P., Jr., Fernis, B. G., Jr., and Kriete, B. C.: Clinical use of a nomogram to estimate proper ventilation during artificial respiration. N. Engl. J. Med., 1954, 251, 877.

6. Riley, R. L. and Cournand, A.: Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs: Theory. J. appl. Physiol., 1951, 4, 77.

7. Williams, M. H., Jr.: Mechanical versus reflex effects of diffuse pulmonary embolism in anesthetized dogs. Circ. Res., 1956, 4, 325.