Pulmonary Function and Tests for Ventilatory Adequacy

Robert A. Mitchell, M.D.

The purpose of this paper is to acquaint the reader with pulmonary physiology and with the tests commonly used to determine pulmonary adequacy in the practice of clinical medicine. It is limited almost entirely to general principles and interpretation of specific pulmonary function tests and is not a comprehensive review of pulmonary physiology or a critical review of methodology. In recent years, numerous, more detailed monographs and reviews on this subject have been written.\(^1\)\(^-\)\(^6\) Excellent reviews of the different processes involved in respiration are cited in this article and recommended to the reader.

Definition of Pulmonary Function

The primary function of the lung is gas exchange, i.e., exchange of oxygen and carbon dioxide between the atmosphere and pulmonary capillary blood. Pulmonary physiologists have divided this function into three main processes—ventilation, diffusion, and pulmonary capillary blood flow. To appreciate these processes and their dependence on other processes, let us consider the sequence of events in the course of a respiratory cycle in a healthy man breathing air.

The respiratory center in the reticular formation of the medulla oblongata initiates a volley of impulses that travel through efferent pathways to the muscles of respiration. The integrated action of these muscles enlarges the thoracic cavity and thus increases the negative intrapleural pressure sufficiently to overcome (1) the elastic resistance of the lung tissue and the alveolar gas-liquid interface, (2) the resistance of nonelastic tissues (i.e., the friction between moving tissues), (3) the resistance to movement of air through the tracheobronchial tree. When the lung expands, alveolar pressure is reduced below atmospheric pressure so that about 500 ml. of air (tidal volume, \(V_T\)) at a partial \(O_2\) pressure of about 149 mm. of mercury flows into the lung. However, only about 350 ml. of the inspired air reaches the alveoli (alveolar volume, \(V_A\)) to be mixed with 2,400 ml. of gas (functional residual capacity, FRC) of alveolar composition (\(P_{CO_2} 40\) mm. of mercury, \(P_{O_2} 100\) mm. of mercury). The partial pressure of \(O_2\) in the alveoli drives \(O_2\) by simple diffusion across the alveolar-capillary membrane into the venous blood entering pulmonary capillaries, thereby raising its \(O_2\) pressure from 40 to 100 mm. of mercury. Likewise, \(CO_2\) diffuses out of the blood into the alveoli, reducing blood \(CO_2\) partial pressure from 40 to 40 mm. of mercury. With cessation of impulses from the central nervous system, the respiratory muscles relax, and elastic forces in the lung overcome frictional and air flow resistance and compress the lung, and alveolar pressure increases. When alveolar pressure exceeds atmospheric pressure, air moves out of the lung. The first 150 ml. exhaled is dead space gas, saturated with water vapor; this is followed by 350 ml. of alveolar gas. A single respiratory cycle would thus move 24.5 ml. of \(O_2\) from the atmosphere to pulmonary capillary blood and 20.0 ml. of \(CO_2\) from capillary blood to the atmosphere. Since arterialized blood reflects the end product of gas exchange, a normal arterial \(CO_2\) and \(O_2\) tension signify adequate exchange. Low \(O_2\) tension and high \(CO_2\) tension separately or together indicate failure of the lung to carry out its primary function.

Conditions Leading to Decreased Arterial Oxygen Tension

Low arterial \(O_2\) tension or high arterial \(CO_2\) tension do not necessarily indicate cardiopulmonary disease and may occur under certain circumstances in a person with normal lungs. The following classification, modified from

Dr. Mitchell is in the Department of Anesthesia, University of California Medical Center, San Francisco, California.
Coombs and Dripps, is a logical approach to the differential diagnosis and therapy of anoxia and hypercapnia.

**Inadequate Gas Exchange in the Normal Lung**

**Decreased Oxygen Tension of Inspired Gas.** A decrease in total gas and therefore in the partial pressure of $O_2$ normally occurs at high altitudes and results in a decrease in arterial $O_2$ tension. Dilution of air at sea level with anesthetic or asphyxial gases has the same effect.

**Hypoventilation in a Normal Lung.** When the volume of inspired air that reaches the functioning alveoli is too small to meet metabolic requirements, arterial tension of $CO_2$ increases and that of $O_2$ decreases. Hypoventilation, then, can be defined as deficient alveolar ventilation ($V_A$). In a normal lung, hypoventilation may result from: central nervous system depression due to disease or anesthetic agents, neuromuscular insufficiency due to disease of the peripheral nerves or to curare-like drugs used for muscle relaxation. Increased work of breathing due to a large external dead space or high air flow resistance in an anesthetic system may reduce alveolar ventilation. Also, because of increased work, hypoventilation occurs in the presence of upper airway obstruction caused by muscle spasm or relaxation of soft tissues, improper intubation, foreign bodies, edema or accumulation of secretions. Each of these results in increased arterial $CO_2$ tension and, during air breathing, decreases arterial $O_2$ tension. Breathing 100 per cent $O_2$ will correct the low $O_2$ tension of hypoventilation. However, it may further depress ventilation by suppressing the hypoxemic stimulus to respiration mediated through the carotid body chemoreceptors. Presuming that the $CO_2$ concentration in the inspired gas is negligible (i.e., competent valves, small dead space), only correction of the hypoventilation will correct the $CO_2$ retention.

**Inadequate Gas Exchange in Cardiopulmonary Disease**

**Hypoventilation** may result from disease processes that reduce the amount of functioning lung tissue so much that compensatory increases in frequency and depth of respiration are insufficient to prevent anoxia and $CO_2$ retention.

**Uneven Distribution of Gas and Blood** is probably the commonest and least appreciated cause of anoxia and $CO_2$ retention. Normally the average ratio of alveolar ventilation to capillary blood flow ($V_A/Q_c$) is 0.8. Even if alveolar ventilation and capillary blood flow are normal, hypoxemia will occur if the distribution of gas, blood, or both is uneven, except for the remote possibility that the ventilation and blood flow to each alveolus are changed proportionally and have retained a normal ratio throughout the lungs. If diffusion is not impaired, the capillary blood reaches equilibrium with the gas tension in the alveoli. Uneven distribution of blood or gas does not alter this process for individual alveoli. However, the net result is the production of a gradient between mean alveolar and mean end-capillary tensions of $CO_2$ and $O_2$. This is illustrated by the two examples shown in figure 1. In A, distribution of ventilation remains normal, but all the blood flow is through one lung. Alveoli in the nonperfused lung do not take part in gas exchange and the composition of alveolar gas is the same as that of the inspired gas. In the perfused lung, where all gas exchange occurs, the increased respiratory minute volume is inadequate to keep the ventilation-perfusion ratio normal. The $CO_2$ tension in the exchanging alveoli increases from a normal of 40 to 46 mm. of mercury and the $O_2$ tension falls from 98 to 91 mm. of mercury. At this tension, ignoring for the moment the diffusion factor, which may cause a small alveolar-capillary $O_2$ gradient, the end-capillary blood would have a $CO_2$ tension of 46 mm. of mercury, an $O_2$ tension of 91 mm. of mercury, or about 98.5 per cent $O_2$ saturation. This relatively high arterial saturation is achieved despite a reduced $O_2$ tension because of the shape of the oxyhemoglobin dissociation curve. However, the mean alveolar gas tensions would suggest hyperventilation since they represent the average in perfused and unperfused lung. In 1B, all of the ventilation is directed to one lung, which has normal ventilation for its capillary blood flow, while the mixed venous blood passes through the other lung unchanged.
ALVEOLAR VENTILATION (L/MIN)  L  R  L&R  L  R  L&R  NORMAL L&R
PULMONARY BLOOD FLOW (L/MIN)  3.5  5.5  7.0  4.0  0  4.0  4.0
MIXED VENOUS O2 TENSION (mmHg)  5.0  5.0  5.0  5.0  1.0  6.0  5.0
MIXED VENOUS CO2 TENSION (mmHg)  42.0  42.0  42.0  42.0  42.0  42.0  42.0
MIXED VENOUS O2 SATURATION (%)  51.0  51.0  45.0  45.0  45.0  45.0  45.0
ALVEOLAR O2 TENSION (mmHg)  146.0  91.0  118.5  98.0  98.0  98.0  74.0
ALVEOLAR CO2 TENSION (mmHg)  0  46.0  25.0  40.0  40.0  40.0  40.0
ARTERIAL O2 TENSION (mmHg)  91.0  91.0  98.0  42.0  72.0  72.0  98.0
ARTERIAL CO2 TENSION (mmHg)  46.0  46.0  40.0  45.0  40.0  40.0  40.0
ARTERIAL O2 SATURATION (%)  96.5  96.5  97.3  74.0  93.3  97.3

Fig. 1. Nonuniform ventilation and perfusion. The normal values are those predicted for a healthy person breathing air at sea level. The following values are assumed: alveolar ventilation of lung L being wasted. Despite the increase of minute ventilation to 9 liters/minute, respiratory quotient of 0.8. The values in A and B are those that might result from the pathologic conditions described.

A. Effect of nonuniform distribution of blood. Gas exchange occurs only in lung R, the ventilation of lung L being wasted. Despite the increase of minute ventilation to 9 liters/minute, effective alveolar ventilation is inadequate to maintain a normal arterial CO2 and O2 tension and O2 saturation. An arterial-to-alveolar O2 and CO2 pressure difference is present. Increasing the ventilation to lung R to 4 liters/minute would restore arterial blood to normal but would not eliminate arterial-to-alveolar gas pressure differences.

B. Effect of nonuniform ventilation and perfusion. Gas exchange occurs only in lung L. The blood passing through lung R is not exposed to alveolar gas and retains the composition of mixed venous blood. Hyperventilation or breathing 100 per cent O2 cannot compensate for the desaturated blood from lung R, restore arterial saturation to normal or eliminate the arterial-to-alveolar O2 pressure difference.

Under these circumstances the CO2 tension in the exchanging alveoli remains normal. The 5 liters of end-capillary blood leaving the ventilated lung has a CO2 tension of 40 mm. of mercury, O2 tension of 98 mm. of mercury (about 97.3 per cent saturated), and is then mixed with one liter of mixed venous blood that has an O2 tension of 42 mm. of mercury and a CO2 tension of 45 mm. of mercury and is 74 per cent saturated. The resulting arterial blood (mean pulmonary capillary blood) has a CO2 tension of 40.8 mm. of mercury, a saturation of 93.3 per cent, and an O2 tension of 72 mm. of mercury. The marked decrease in O2 tension results from the contour of the oxyhemoglobin dissociation curve. A mixture of equal volumes of blood of different O2 tensions does not result in the mean of the two tensions but in the O2 tension at the mean saturation. The mean alveolar CO2 and O2 tensions in expired samples have the O2 and CO2 tensions of the ventilated lung (i.e., Pco2 40 mm. of mercury, PO2 98 mm. of mercury) and are normal.

Certain conclusions from these examples of uncompensated disturbances in ventilation and perfusion, can be applied to less extreme inequalities of distribution and to both unequal distribution of ventilation and perfusion.

(1) Normal minute ventilation (i.e., normal tidal volume and frequency) does not ensure adequate alveolar ventilation.

(2) Normal mean alveolar CO2 tension and O2 tension measured by end-tidal sampling do not indicate adequate gas exchange
since alveolar-arterial gradients are always produced by uneven ventilation and perfusion, the CO₂ tension always being lower and O₂ tension higher in the alveoli than in the arterial blood. Conversely, in the absence of impaired diffusion, alveolar to arterial O₂ and CO₂ gradients indicate an uneven distribution of ventilation and perfusion.

(3) Hyperventilation on air is inadequate to correct arterial desaturation, but will correct CO₂ retention if there are areas with low ventilation-perfusion ratios. An infinite ventilation of some alveoli theoretically could raise the alveolar O₂ tension to about 146 mm. of mercury (tension in saturated air at 38°C) and thus produce a maximum hemoglobin saturation of about 99.5 per cent in the end-capillary blood. Desaturated blood from any remaining underventilated lung would mix with this blood and produce arterial desaturation. Thus, the saturation will be restored to normal only when hyperventilation on air produces normal ventilation in all alveoli. This situation is seen when uneven perfusion is the only defect as in figure 1A, an example of uneven distribution of blood without uneven distribution of gas.

(4) If inspired gas reaches all alveoli, but unevenly, breathing 100 per cent oxygen will correct the O₂ but not correct CO₂ retention if it exists. Failure of 100 per cent O₂ to correct the desaturation indicates shunting either through atelectatic alveoli or through anatomic right-to-left shunts. Figure 1B illustrates this situation. The blood passing through the unventilated lung is in effect a shunt of mixed venous blood to arterial blood. The same effect is produced by extrapulmonary right-to-left shunts in congenital heart disease.

(5) Normally, when compensatory hyperventilation occurs in terms of respiratory minute volume, the arterial PₐCO₂ may be high, low or normal, depending on the distribution of alveolar ventilation-perfusion ratios. However, arterial desaturation will always be present.

Uneven distribution of ventilation usually results from regional alteration of the mechanical forces in the lung, which may favor or impede the flow of air to different regions of the lung. It also may result from extrinsic masses, chest wall deformity or pneumothorax, because each of these restricts expansion. Uneven distribution of pulmonary capillary blood flow may result from anatomic shunts in the lung, occlusion of vessels by emboli or thrombosis, patchy reduction of the vascular bed by fibrosis, gravitation changes and extensive compression of the lung by regional masses or pneumothorax. Usually, disease states that cause uneven ventilation also cause nonuniform blood flow.

Diffusing Capacity is the rate of gas exchange between the alveoli and pulmonary capillary blood per millimeter of mercury partial pressure gradient of the gas between these two compartments. Normally, there is complete equilibration between alveolar gas and end-capillary blood O₂ tensions. Impairment of diffusion across the alveolar-capillary membrane leads to incomplete equilibration and an alveolar-end-capillary gradient, which causes a low arterial O₂ tension and desaturation of arterial blood. However, because CO₂ diffuses 20 times as fast as O₂, patients die of hypoxemia before a gradient for CO₂ develops. Decreased diffusing capacity is frequently misinterpreted as an impairment of diffusion equilibrium brought about solely by thickening or change in character of the tissue between the alveoli and pulmonary capillary blood. The components of diffusion, impairment of which may lead to alveolar-arterial O₂ tension gradients or a reduced diffusing capacity, may be classified in the order of progression of oxygen in the alveoli to its final chemical combination with hemoglobin.

Diffusion Across Pulmonary Membrane. The exchange of gas between blood and alveoli takes place only in areas where capillary blood is in contact with ventilated alveoli. A decrease in the size of the capillary bed or in the number of functioning alveoli decreases the diffusing capacity. Conversely, an increase in blood flow, as in exercise, increases the capillary blood volume and surface area for diffusion and thereby increases the diffusing capacity.

Any disease process which increases the distance for diffusion of O₂ will increase the time required for equilibration of capillary blood with the alveoli.
Since diffusion of a gas depends on the tissue through which it passes, theoretically, changes in the character of the tissue may decrease the rate of transit of a gas through the tissue. Even though the distance of diffusion is not increased, changes in the character of the membrane may have the same effect on diffusion equilibration as increasing the distance for diffusion. Further reduction in arterial $P_{O_2}$ will occur in persons with impaired diffusion if the velocity of the blood passing through the capillaries is increased by exercise.

**Diffusion Within the Blood.** Impedance to diffusion of gas within the blood is rarely of great clinical importance, although this component provides a significant portion of the total impedance to the diffusion of $O_2$. The diffusion through the plasma and red cell membrane and the chemical reaction with hemoglobin are not instantaneous for these gases and are measurable quantities. Since combination with hemoglobin is the final step in diffusion of $O_2$, a reduction in hemoglobin may appreciably reduce the diffusing capacity.

**Clinical Uses of Pulmonary Function Tests**

Diseases of the lungs rarely respect the physiologic segmentation of the functional processes of the lung. Most frequently, more than one process is altered, either as a direct result of the disease or as a compensatory response to impairment of another functional process. For this reason, no single test of pulmonary function can adequately assess abnormally functioning lungs. Instead, a battery of selected tests are necessary to evaluate each functional process and describe objectively a syndrome of pulmonary dysfunction. In the past 15 years, many reasonably specific tests have been developed. By careful selection a few simple tests are usually adequate to characterize the functional derangement in most pulmonary diseases. When these tests prove inadequate, they provide a basis for intelligent selection of further tests. Properly applied and correctly interpreted pulmonary function tests are valuable in the diagnosis, management, evaluation of therapy, preoperative and postoperative evaluation, assessment of disability and epidemiologic survey of industrial diseases of the lung.

The results of pulmonary function tests rarely help in the etiologic diagnosis of a pathologic process in the lungs, because many processes produce similar pathologic changes. Thus, different space-occupying lesions may produce similar functional impairment of the lungs. As more pulmonary function tests are devised, syndromes of pulmonary function are being classified. The syndromes of chronic obstructive emphysema, bronchial asthma, restrictive lung disease, and pulmonary embolism are usually recognizable. Recognition of such a syndrome in a patient then becomes significant in diagnosis. When there is no clinical or radiologic sign of disease, functional tests may provide objective evidence of disease; conversely, they may exclude pulmonary dysfunction in a patient whose dyspnea is psychogenic. Thus pulmonary function tests become an important adjunct for the differential diagnosis of dyspnea.

Pulmonary function tests provide a basis for the rational use of oxygen therapy or assisted respiration. Serial testing of patients with ventilatory insufficiency provides objective evidence of the efficacy of treatment. By these tests the effects of cortisone, ACTH, and bronchodilators on the diseased lung have been evaluated. They have established objectively the best means of artificial respiration.

A knowledge of pulmonary dysfunction will alert the anesthetist to the possible dangers of depression of the respiratory center by preoperative medication, the delay in exchange of anesthetic gases and alveolar hypoventilation due to unequal distribution of gas and blood. By serial determinations of arterial $O_2$ and $CO_2$ tensions and pH throughout operation and the anesthetic recovery period, one can assess ventilatory adequacy and take immediate measures to correct any inadequacy.

Objective evidence of ventilatory insufficiency may preclude or limit the extent of surgical treatment of chest disease. On the other hand, tests may indicate the need of surgical intervention to improve function, for example, the removal of a space-occupying lesion or an isolated anatomic shunt in the lung.

Although pulmonary function tests are often requested for medicolegal purposes, their usefulness in this field is limited. The most fre-
quent questions are: (1) Is the patient disabled? (2) What is the per cent of disability? (3) Is the disability the result of a specified etiologic agent? The third question obviously cannot be answered since the functional syndromes are nonspecific for etiologic agents and the causal relationship of the disability must be established on other grounds. The first and second questions depend on the definition of disability. The claimants usually have excessive dyspnea, a subjective sensation for which we have no objective test. Furthermore, as Comroe has pointed out, the correlation between dyspnea and functional impairment may be very poor. Since disability cannot be equated with functional impairment, questions one and two cannot be answered directly.

Specific Tests in the Diagnosis of Pulmonary Function

The number of tests and modifications of basic tests that can be applied to one person probably number close to 100. Tests of function are classified according to the subdivisions of pulmonary function which they measure. Some tests define a specific process, such as the measurement of airway resistance, and are readily classified. Others are not specific, such as the maximum breathing capacity, and are an index of the function of more than one process and are classified primarily according to the preference of the author. Many of these tests can be performed only in a fully equipped research center by specially trained persons and are not suited to the usual hospital cardiopulmonary laboratory. However, this does not mean that the more complex tests are of value to the clinician, for it is primarily at research centers that a comprehensive and qualitative classification of deranged pulmonary function is being developed with the more complex tests. With such a classification one can assess the value of each test in the diagnosis of the syndrome and develop a group of relatively simple tests that will be suitable for smaller hospital laboratories and that will usually provide a functional diagnosis. The purpose of the following section is to provide a guide to the application of such a group of relatively simple tests.

Lung Volumes. The subdivisions of lung volume, as recently defined, are static measurements and should not be interpreted as being necessarily related to the volume of gas in the functioning alveoli. Vital capacity (VC), functional residual capacity (FRC) and residual volume (RV), and total lung capacity (TLC) help in the diagnosis of a functional syndrome. The VC, for example, is now recognized as a good measure of lung compliance in the absence of obstructive airway disease if the patient is cooperating. Also, once the syndrome of dysfunction is determined, VC, serially measured, may be a useful index of the progress of disease and the efficacy of treatment. When the VC is related to time it is a useful index of the mechanical forces in the lung; this will be discussed later.

The FRC, TLC, and RV are indirectly measured. The FRC is the volume of gas remaining in the lungs in the resting end-expiratory position and is measured by either a gas dilution or gas replacement method. Both methods measure only the volume of gas directly communicating with the trachea. In the normal lung these methods measure the FRC as defined. However, when parts of the lung are underventilated or nonventilated, the estimated FRC is less than the volume of gas in the lungs in the end-expiratory position. This reduction is most often associated with diseases that increase the FRC. This limitation to the usefulness of FRC determinations has been overcome by the pneumometric method of measuring the thoracic gas volume. This method, using the body plethysmograph, not only measures the air in communication with the trachea but also the air in intermittently communicating cysts, pneumothorax and poorly ventilated areas of the lung. The difference between the thoracic gas volume and FRC measured by gas dilution or replacement has been called the trapped gas volume. In emphysema this may amount to over one liter. However, the pneumometric method requires complex equipment and must be classified as a research procedure.

An increased FRC indicates hyperinflation of the lung at the end-expiratory level. Studies of the various components of work of breathing revealed that a person selects an
optimal FRC, as well as rate and depth of ventilation, for minimal work. For this reason the FRC is increased in such diseases as emphysema, asthma and in the normal process of aging.

An increased residual volume indicates the lung is hyperinflated after a maximal expiratory effort. It results from changes in the airways, chest wall, or lung tissue which limit expiration. Residual volume is increased in most conditions that cause an increase in the FRC.

The FRC, TLC, and RV are reduced in diffuse fibrosis of the lung.

Ventilation. Ventilation should always be considered in terms of alveolar ventilation. The measurement of respiratory rate, tidal volume, and respiratory minute volume in the normal lung may provide a good index of alveolar ventilation, since the values for the anatomic dead space are fairly well known and dead space ventilation can be estimated with some confidence. However, in disease, the value of these measurements as an index of alveolar ventilation becomes useful only in the diagnosis of gross hyperventilation. The measurements that most adequately describe the volume of gas that participates in gas exchange are derived from calculation of the alveolar ventilation. This can be assessed from the effectiveness of the ventilation in washing out alveolar CO₂ (normal alveolar or arterial CO₂ tension) or from the calculation of the physiologic dead space. Physiologic dead space represents the ventilation wasted in (1) ventilating the anatomic dead space, (2) ventilating nonperfused alveoli, and (3) the relative hyperventilation of underperfused alveoli. It is determined by the Bohr equation, from the value of arterial PₐCO₂ instead of alveolar PₐCO₂. In a lung that functions normally, the physiologic and anatomic dead spaces are nearly equal. An increased physiologic dead space therefore indicates an abnormality in the distribution of ventilation-perfusion ratios in the lung.

Uneven Distribution of Ventilation. This can be measured by simple tests. The most sensitive test of uniformity of alveolar ventilation is continuous measurement with a nitrogen analyzer of expired nitrogen concentration after a patient has taken a single breath of 100 per cent O₂. In a normal lung, the N₂ concentration in the alveoli, which is approximately equal to that in air, is proportionally diluted in all alveoli, and during expiration the measured alveolar gas concentration of N₂ remains constant. If ventilation is uneven, the N₂ in the underperfused areas is less diluted than in well ventilated areas. Due to sequential emptying, N₂ concentration in the last portion of the expired gas will be higher than that in the first portion of alveolar gas which comes from the well ventilated alveoli. Normally, the alveolar N₂ concentration rises less than 2 per cent between 750 and 1,250 ml of expired gas. A second, less sensitive method of determining uneven ventilation is performed in a maneuver similar to the replacement method of determining FRC. In this test, the inspired gas is suddenly changed from air to 100 per cent O₂ and the end-tidal N₂ concentration is measured continuously for seven minutes. The nitrogen in the lungs is continuously eliminated and replaced by oxygen. Normally, at the end of seven minutes the N₂ concentration in the lung is less than 2.5 per cent. Uneven distribution may not be revealed by this method if the FRC is small in relation to minute ventilation or if there is hyperventilation. Uneven distribution is present in emphysema, asthma, fibrosis, congestive heart failure, chest deformities and in anesthetized patients.

Uneven Distribution of Ventilation-Perfusion Ratios. This abnormality is indicated by a gradient between the mean alveolar and arterial PₐCO₂ and, in the absence of impaired diffusion or venous-to-arterial shunts, by a mean alveolar-arterial O₂ gradient. Quantitation of the ventilation-perfusion ratio for the entire lung has been made possible by the methods described by Riley and Courmand and the graphic solutions of the formulas by Fenn and Rahn. As previously stated, an increase of the physiologic dead space above the estimated anatomic dead space, or an increase in physiologic dead space to tidal volume ratio above normal, results from uneven ventilation-perfusion ratios and gives a quantitative estimate of the extent of the process.
Uneven Perfusion. Uneven perfusion is less readily measured than uneven distribution of ventilation. Since it is closely linked with uneven ventilation and ventilation-perfusion ratios, a derangement in perfusion can be assumed to be present if these processes are abnormal. If ventilation is shown to be uniform, an arterial-alveolar \( CO_2 \) gradient and an increased physiologic dead space indicates unequal distribution of pulmonary capillary flow.

Under most circumstances, breathing 100 per cent \( O_2 \) will increase the \( O_2 \) tension in all alveoli communicating with the trachea. The increased tension will be high enough to saturate the capillary blood even if diffusion is impaired. Thus desaturation of the arterial blood during breathing of 100 per cent \( O_2 \) represents a venous-to-arterial shunt of blood which does not participate in gas exchange. However, this anatomic shunt may be either intrapulmonary or extrapulmonary. To quantify the volume of shunted blood and pulmonary capillary flow, it is necessary to know the mixed venous \( O_2 \) saturation, which can be determined during cardiac catheterization.

Bronchospirometry also provides information on the distribution of blood flow between the two lungs, a reduction in oxygen consumption during breathing of 100 per cent \( O_2 \), indicating a reduction of blood flow in that lung. When one pulmonary artery is temporarily occluded during bronchospirometry and pulmonary artery pressures are measured, the effect of pneumoneectomy on gas exchange can be predicted and the adequacy of the remaining pulmonary capillary bed to handle the total cardiac output without marked elevation in the pulmonary artery pressure can be assessed.

Alveolar Capillary Diffusion. To determine the diffusing capacity of the lung for a gas, it is necessary to know (1) the amount of gas transferred from alveoli to blood per minute, (2) the mean alveolar gas tension, (3) the mean pulmonary capillary gas tension. At present, a number of methods \(^{21-25}\) of estimating the diffusing capacity are in use. All provide useful, although slightly different, information concerning the diffusion of gas across the alveolar-capillary membrane.\(^8\)

The use of \( O_2 \) as the test gas for determining diffusing capacity would appear the most physiologic. However, the method has a number of limitations and requires a number of questionable assumptions in order to calculate the mean pulmonary capillary \( O_2 \) tension. The only other satisfactory test gas is carbon monoxide (CO) and from the laws of diffusion one can theoretically calculate the diffusing capacity of \( O_2 \) (\( D_{CO} \)) from the diffusing capacity of CO (\( D_{CO} \)); the diffusing capacity of the lung for \( O_2 \) is 1.23 times that of CO. Because CO has such a great affinity for hemoglobin, no important degree of CO tension arises in the pulmonary capillary blood and the partial pressure of CO along the whole capillary bed can be assumed to be zero. This advantage as well as simplicity and reproducibility make the methods employing CO the best suited for the cardiopulmonary laboratory. They provide similar values in the normal lungs. However, when there is unequal distribution of ventilation-perfusion ratios, results differ, primarily because of errors in the estimate of the mean alveolar CO concentration. The modified Krogh \( D_{CO} \) is a simple method which does not require arterial blood sampling. This method has been criticized because of the use of an unphysiologic gas, the effect of breath-holding on gas exchange, and the method of estimating the initial and final alveolar CO concentrations. Despite these disadvantages and possible technical errors in estimating the \( D_{CO} \), the method provides a sensitive test of great clinical utility. Diffusing capacity is reduced in diffuse pulmonary fibrosis and granulomatosis, emphysema, pulmonary hypertension, pulmonary embolism and anemia. It is increased in polycythemia, exercise and congenital heart disease with an increased pulmonary blood flow.\(^8\)

Mechanical Factors in Pulmonary Function. The excellent review by Mead \(^{26}\) is recommended for a comprehensive discussion of this subject. In the past ten years many tests have been developed which are specific and provide quantitative information about the forces and resistances involved in respiration. These tests are clinically valuable because abnormalities in these processes (1) correlate well with dyspnea and disability, (2) influence the rate and depth of breathing, (3) are the cause of uneven distribution of ventilation.
The elastic forces in the lung and the lung and chest wall together are a function of the lung volume and increase gradually with the increase in volume of gas within the lung. This relationship between volume and elastic force is called compliance (gas volume in liters/elastic force in cm. of water). In contrast to the elastic forces, which must be measured during static conditions, the resistive forces of the lung are functions of the rate of change of lung volume and must be measured during breathing. The separation of the components of the resistive forces into airway resistance and pulmonary tissue resistance require techniques not applicable in a hospital cardiology-pulmonary laboratory. However, since the airflow resistance comprises most of the resistive force in both normal and diseased lungs, total pulmonary resistance reflects the airway resistance. Pulmonary compliance and total pulmonary resistance can be measured at the same time by simultaneously recording the tidal volume, rate of air flow at the mouth and intrapleural pressure. Intrapleural pressure can be determined by measuring the pressure in the esophagus, which has been shown to parallel it. By measuring esophageal pressure, air flow, and the change in volume, it is possible to determine both the resistance and compliance. The resistance is determined during periods of flow and the compliance at the interval of no flow at end-inspiration and end-expiration.

The resistance is characteristically elevated in emphysema and asthma. It can be increased by aerosols of histamine and acetylcholine and diminished by bronchodilators. Compliance of the lung is reduced in such conditions as fibrosis, heart failure, poliomyelitis, kyphoscoliosis and general anesthesia.

Although tests of the separate mechanical components of pulmonary function are available, they do not replace the overall tests of ventilatory capacity. These tests, such as the maximum breathing capacity (MBC), maximum inspiratory and expiratory flow rates and timed vital capacity (TVC) are simple and sensitive tests of pulmonary function. These tests are affected by changes in airflow and pulmonary resistance, compliance of the lung and chest wall, volume of the lung, and muscular force. With the possible exception of the TVC, they have the disadvantage that they require full cooperation of the patient to be performed correctly. Also, none are pathognomonic of any condition. However, the information from each test is slightly different and when combined with that of other tests may provide an index of specific dysfunction. When tests show improved function after inhalation of bronchodilator aerosol, reversible airway obstruction can be assumed. A reduction in the flow rates, MBC, and percentage of vital capacity expired in one second, when VC is normal, indicates obstructive disease. Restrictive disease reduces VC but TVC remains normal. Neuromuscular weakness reduces the VC and impairs the performance of MBC and reduces flow rates. However, the TVC may be normal if tested at 1 and 3 seconds. If weakness develops on repetitive movements as in myasthenia or myoclema, only the MBC may be significantly reduced. If these tests are normal, it is unlikely dyspnea is due to alteration of mechanical function of the lung.

Characteristic Syndromes of Dysfunction in Specific Diseases

Certain syndromes of deranged gas exchange and mechanics of pulmonary function are characteristic of specific diseases (Table 1).

Emphysema, a disease resulting from loss of elastic tissue, abnormally collapsible airways, and rupture of alveolar septa, results in a syndrome characterized by alterations in the mechanics of pulmonary function. Resistance to air flow, primarily in the expiratory phase, is markedly increased and results in a decreased maximum expiratory flow, MBC, and decrease in TVC. The airway resistance and total pulmonary resistance are increased. The lung is overinflated at end-expiration because the work of breathing is minimal at an increased functional residual capacity. RV is increased. The regional changes in airway resistance and compliance of the lung lead to unequal distribution of ventilation. The destruction of alveolar septa leads to a reduction of surface area for diffusion and of the pulmonary capillary blood volume, which decreases diffusing capacity. Arterial desaturation results from the uneven ventilation and uneven perfusion, which is not corrected by
### Table 1. Pulmonary Function in Specific Conditions

<table>
<thead>
<tr>
<th></th>
<th>Chronic Obstructive Emphysema</th>
<th>Bronchial Asthma</th>
<th>Diffuse Pulmonary Fibrosis</th>
<th>Pulmonary Embolism</th>
<th>Venous-to-Arterial Shunts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung Volumes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital capacity</td>
<td>N or -</td>
<td>N or -</td>
<td>-</td>
<td>N or -</td>
<td>N</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Total lung volume</td>
<td>N or +</td>
<td>N or +</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Residual volume</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Ventilation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory minute volume</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
</tr>
<tr>
<td>Distribution of ventilation</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Physiologic dead space</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Diffusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar-arterial O₂ gradient</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Diffusing capacity</td>
<td>-</td>
<td>N</td>
<td>-</td>
<td>-</td>
<td>N</td>
</tr>
<tr>
<td>Distribution of Blood</td>
<td>N</td>
<td>N</td>
<td>+</td>
<td>N or +</td>
<td>+</td>
</tr>
<tr>
<td>Anatomic shunt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>-</td>
<td>N or -</td>
<td>N or -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CO₂ tension</td>
<td>N or +</td>
<td>N or +</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Mechanics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum breathing capacity</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Maximum flow rates</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Timed vital capacity</td>
<td>-</td>
<td>-</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Compliance of lung</td>
<td>N or -</td>
<td>N</td>
<td>N</td>
<td>N or -</td>
<td>N</td>
</tr>
<tr>
<td>Total pulmonary resistance</td>
<td>+</td>
<td>+</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

N = Normal. A = Abnormal. + = Abnormally increased or tends to increase. − = Abnormally decreased or tends to decrease.

Hyperventilation. However, the arterial CO₂ may be normal or increased, since the CO₂ dissociation curve, unlike the O₂ dissociation curve, is roughly linear, allowing hyperventilation of one area of the lung to compensate for hypventilation in another.

**Bronchial Asthma** presents a syndrome resulting solely from regional obstruction of the airway.32, 34 The findings in the specific and overall tests of the mechanics of pulmonary function may be indistinguishable from those of emphysema. Also as in emphysema, the FRC and the RV are increased. Unequal distribution leads to arterial desaturation as in emphysema. Features of functional disturbance in asthma that may be of assistance in differentiating it from emphysema are a normal diffusing capacity32, 34 and marked improvement in the mechanical properties after inhalation of a bronchodilator. The final differentiation rests on complete return of normal function after adequate therapy.

**Interstitial Disease of the Lung** causes thickening of the alveolar septa, obliteration of alveoli and reduction in the pulmonary capillary bed. The lung volumes are reduced.35 Respiratory rate and often the respiratory minute volume are increased. There is no airway obstruction in most cases, so that the TVC, and airway resistance are normal. The compliance is reduced. Ventilation is uneven as tested by the single-breath test; however, the N₂ elimination rate is normal owing to hyperventilation and reduced functional residual capacity. Diffusing capacity is reduced36 because of thickening of the alveolar membrane and reduction of surface area for diffusion. Uneven ventilation, venous-arterial shunting of blood through fibrotic areas of the lung and reduced diffusing capacity produce arterial desaturation, which is characteristically increased by exercise. Arterial CO₂ tension is usually normal because CO₂ diffuses much more readily than O₂.

**Pulmonary Embolism** causes circulatory obstruction to portions of the lung, resulting in uneven distribution of blood flow. Ventilation in these regions is wasted since it does not contribute to gas exchange. Pulmonary embolism is suggested by an increased physiologic
dead space and CO₂ gradient between mean alveolar gas and arterial blood in the absence of unequal distribution of ventilation. However, because of reduction of ventilation of the nonperfused regions of the lung, one cannot predict the extent of circulatory obstruction from the size of the physiologic dead space. Pulmonary embolism also results in a decreased diffusing capacity because it reduces the surface area for diffusion. Arterial desaturation occurs as the result of (1) relative underventilation of the perfused portion of the lung, which must carry the entire cardiac output, (2) reduced diffusing capacity, and (3) venous-arterial shunting. The site of venous-arterial shunting is unknown but the size of the shunts correlates with the size of the emboli and with the degree of pulmonary hypertension.

Venous-arterial Shunts which carry mixed venous blood into the systemic arterial circulation without exposure to ventilated alveoli lead to arterial desaturation in the presence of normal ventilation, distribution and diffusion. The diagnosis is made by a test in which the patient breathes 100 per cent oxygen until end-tidal N₂ concentration is less than 2 per cent. The O₂ tension at this time would overcome any arterial desaturation due to hypoventilation, uneven distribution, or reduced diffusing capacity. If the O₂ tension does not rise to predicted levels, a right-to-left shunt is present. This may be due to intracardiac shunts, pulmonary atelectasis, or pulmonary hemangiomata.

Summary

The primary function of the lung is gas exchange. This function is performed by a number of integrated processes, each of which can be analyzed by functional tests. Syndromes of pulmonary dysfunction can be detected by a selected battery of simple pulmonary function tests. Properly used and interpreted, these tests add to our knowledge of pulmonary function in health and disease.

Supported in part by United States Public Health Service Grant RG-5851.

References


CHEMORECEPTOR SENSITIVITY By measuring the potential of "Hering's wave" from the carotid sinus of cats, a quantitative assessment of the activity of the sinus to hypoxia and hypoxia plus decreased arterial pH from increased carbon dioxide tensions was made. Sinus activity increased with any decrease in PaO2 below 100 mm. of mercury, indicating that at sea level the sinus may act to drive respiration. An increase in (H)-Pco2 potentiated the response to hypoxia. Below a PaO2 of 40 mm. of mercury the sinus response fell off. (Hornbein, T., Grillo, Z. J., and Roos, A.: Quantitation of Chemoreceptor Activity; Interrelation of Hypoxia and Hypercapnia, J. Neurophysiol. 24: 561 (Nov.) 1961.)