Experimental Alteration of Pulmonary Functions

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Knowledge of the effects of experimental pulmonary disease on pulmonary function has bearing on the effects of various human diseases on pulmonary function. In addition, information about reserves of pulmonary function present in normal animals and the types of functional limitation that occur under various conditions may be related to human disease. For the purpose of this review, pulmonary function will be subdivided into ventilation, diffusion and distribution of blood and gas in the lung.

Ventilation, of which the end result is alveolar ventilation, includes the phenomena responsible for the nervous and chemical control of respiration, the thoracic and diaphragmatic innervation and musculature, the compliance of the lung and chest, the resistance to airflow through the airways and the size of the lung dead space. Diffusion refers to the diffusion of oxygen from the alveoli into the blood circulating through the alveoli. The measurement of this function, the diffusing capacity of the lung, is defined as the volume of oxygen consumed by the lung per minute per mm. mercury pressure difference between the alveolar tension and the mean oxygen tension in the blood flowing through the lung capillaries. Distribution refers to the areas to which blood and gas flow in the lung, particularly in reference to one another. The pulmonary circulation will be considered as a component of the distribution function.

A number of methods are available for producing impairment of one or more of these functions, and the effects of various experimental diseases and procedures on these functions will be reviewed. Limitation of each of the three functions results in distinctly different physiological abnormalities.

Reduction of alveolar ventilation results in elevation of alveolar and arterial carbon dioxide tensions with comparable reductions of alveolar and arterial oxygen tensions. Because of the flat shape of the oxygen dissociation curve above an oxygen tension of 70 mm. Hg., the arterial oxygen tension has to be greatly reduced before arterial unsaturation results. However, slight elevation of the carbon dioxide tension results in acidosis until it is compensated by renal retention of bicarbonate. Impaired diffusion results, eventually, in anoxemia which is greatly aggravated by inspiration of a low oxygen mixture, ascent to high altitude, or by increased oxygen consumption such as occurs during muscular exercise. Because of the relatively great diffusibility of carbon dioxide, \( \text{CO}_2 \) retention would only be expected to be significant when anoxemia were present to an extent incompatible with life. Impaired distribution may take the form of an effective right-to-left shunt which results in anoxemia from the mixture of venous blood with blood arterialized in the lung. Carbon dioxide retention need not occur when reduction of the arterial oxygen saturation

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is present from a shunt because the venous carbon dioxide content is not as different from the arterial carbon dioxide content as the venous oxygen saturation is different from the arterial oxygen saturation. Thus, admixture of a small amount of venous blood containing 55 volumes per cent of CO₂ to pulmonary capillary blood with 51 volumes per cent of CO₂ has an inappreciable effect on the resultant arterial carbon dioxide content whereas the addition of a small amount of venous blood with an oxygen saturation of 75 per cent to pulmonary capillary blood with an oxygen saturation of 98 per cent results in detectable anoxemia. Impaired distribution may also take the form of different ventilation/perfusion ratios in different parts of the lung, in which case carbon dioxide retention does occur, but the anoxemia is more severe. Finally, reduction of the size of the circulatory bed produces impairment of right ventricular function and, as will be discussed, of diffusion in the lung.

General anesthesia. This subject has recently been reviewed by Dripps and Severinghaus.* The physiological effects of anesthetic agents depend largely on the type and strength of anesthetic used, but the common effect of all agents is, eventually, to reduce alveolar ventilation and, thus, to cause retention of carbon dioxide and respiratory acidosis. Additional effects of anesthetic agents include the production of bronchial constriction, pulmonary edema, decreased lung compliance and atelectasis, but the major effect is to reduce alveolar ventilation.

Pulmonary edema may be produced experimentally by means of a variety of agents.³ Alphanaphthylthiourea (ANTU) causes pulmonary edema, apparently, by increasing the permeability of the lung capillaries to protein.⁴ Pulmonary edema produced by ANTU in dogs results, early, in diminished compliance of the lung.⁵ The reduction in compliance, however, is insufficient by itself to reduce alveolar ventilation. Anoxemia develops later because some blood perfuses alveoli which are not ventilated because foam and edema fluid obstruct the airways.⁶ There is no apparent impairment of diffusion through the walls of ventilated alveoli.⁷ Since the anoxemia is due to an effective right-to-left shunt, the administration of oxygen produces little impairment of the arterial oxygen saturation, whereas antifoaming agents or positive inspiratory pressure might be expected to result in better alveolar ventilation through foam-filled airways.

Resection of lung tissue. In acute experiments on anesthetized dogs, pneumonectomy results in a small rise of the pressure in the pulmonary artery, but pulmonary hypertension only becomes severe (with development of right heart failure) after resection of some 70 per cent of the lung.⁸ At this stage, ventilatory function remains adequate, and there is no apparent impairment of distribution of blood and gas in the remaining lung. However, resection of this much pulmonary tissue does cause impaired diffusion of oxygen, resulting in anoxemia which is completely relieved by oxygen. This diffusion limitation apparently results from the fact that the alveolar capillary surface area is so small that the alveolar-mean capillary oxygen tension differences must be large to permit diffusion of the required amount of oxygen from alveoli to the blood. Stated differently,
the entire cardiac output circulates at an accelerated velocity through a reduced number of capillaries so that the blood leaves the lung at an oxygen tension considerably lower than the alveolar oxygen tension. Elevation of the alveolar oxygen tension, by inspiration of oxygen, increases the pressure gradient for diffusion so that more oxygen diffuses into the blood and the anoxemia is completely overcome. Thus, in the dog, functional limitation after resection of pulmonary tissue occurs from inadequate diffusion and from restriction of the pulmonary vascular bed, resulting in right heart failure; there is no significant impairment of the ventilatory or distributive functions.

The chronic effects of pneumonectomy have been studied by Carter et al. who found that, in puppies, pneumonectomy resulted in no apparent impairment of exercise tolerance, as measured by ability to run on a treadmill for two hours and by the arterial oxygen saturation after the run, whereas adult dogs subjected to pneumonectomy demonstrated decreased ability to run on a treadmill and increased anoxemia after the exercise. Phillips et al, resecting pulmonary tissue in stages, found that as much as 85 per cent of the lung could be removed from adult dogs without apparent impairment of health. Although microscopic examination of the tissues of these animals revealed evidence of emphysema, studies of pulmonary function were not reported. It is apparent that the pulmonary reserve is such that extensive resection of lung tissue, particularly if done in stages, can be tolerated by normal animals.

Pulmonary arterio-venous fistula. This abnormality has been created in dogs with the production of anoxemia due to right-to-left shunt of the blood through the abnormal circulatory pathway. Though they were not measured, other pulmonary functions may be presumed to be unaffected by such a lesion.

Lung collapse. In 1931, Moore produced collapse of one lung in closed-chest dogs and found that, 15 to 75 minutes later, the blood flow through the collapsed lung amounted to 0 to 42 per cent of the total blood flow. Similar data were obtained by Andrus. More recently, Peters and Roos found, in open-chest dogs, that collapse of one lung resulted in an immediate (10 min.) reduction of the blood flow to 0 to 34 per cent of the total flow due to a marked increase in pulmonary vascular resistance. Further reduction of the blood flow did not occur up to three hours after collapse. Furthermore, another group of animals was allowed to survive for periods up to six months, and they showed similar reductions in flow through the permanently collapsed lung. Whether the increased vascular resistance in the collapsed lung was due to mechanical collapse or compression of blood vessels or to a neurogenic stimulus remains to be determined. Pertinent to point is the observation that inflation of the lung in dogs, either by positive pressure at the upper airway or by negative pressure around the chest, results in an increase of the pulmonary vascular resistance. It is possible, however, that complete collapse of the lung, not studied by the above authors, also results in increased vascular resistance due to closure of the blood vessels.
Additional data on the chronic effects of unilateral collapse of the lung has been obtained by Rosenberg,\textsuperscript{11} who discovered that chronic collapse of one lung resulted in a reduction of blood flow through that lung and that anoxemia did not develop, even during exercise. In addition, there was no significant rise of the resting pressure in the pulmonary artery, and there was a fall of the mean intrapleural pressure on the side of the collapse.

Apparently, after acute or chronic collapse of part of the lung, anoxemia is prevented by the development of increased vascular resistance in the collapsed lung so that blood is shunted away from the non-ventilated lung. Ventilatory and diffusion limitation would be expected to develop only after collapse of over 70 per cent of the lung (see above: Resection of lung tissue).

When the lungs are allowed to collapse completely at the end of each expiration during positive pressure ventilation in the open-chest dog, anoxemia results.\textsuperscript{18} Study of the alveolar and arterial oxygen tensions at three levels of oxygenation in these animals indicated that the anoxemia is a result of impaired distribution because of the presence of different ventilation/perfusion ratios in various parts of the lungs, rather than the result of right-to-left shunt or impairment of diffusion. Apparently normal lung architecture is important in maintaining blood and gas flows of similar magnitude to various areas of the lung. Anoxemia might be expected to occur in patients with pneumothorax and partial lung collapse and, if so, should be overcome by the administration of oxygen. In connection with the experimental or therapeutic production of pneumothorax, the theoretical analysis of Fenn\textsuperscript{19} is of interest. Normally the intrapleural pressure is as much a result of the elasticity of the chest wall and diaphragm pulling out as to the elasticity of the lungs pulling in. The same is true when air is introduced into the pleural space, except that under these circumstances both chest and lungs approach more closely their equilibrium positions, and the negative pressure in the intrapleural space is less. If sufficient air is introduced to permit both chest and lungs to reach their equilibrium positions, the intrapleural pressure will be atmospheric. Thus, introduction of air into the pleural space will cause both collapse of the lungs and expansion of the chest cage. Because of the pressure volume characteristics of the lungs and chest, introduction of a given volume of air produces approximately half collapse of the lung and half expansion of the chest wall, so that collapse of a given volume of the lung would require the introduction of approximately twice that volume of air.

The observation by Van Allen and collaborators\textsuperscript{20} that there is communication between the peripheral branches of the bronchial tree which permits of gas exchange has important bearing on the problem of atelectasis. Although obstruction of a first order bronchus invariably leads to atelectasis, obstruction of a bronchus beyond the second order does not always lead to atelectasis, and studies of the composition of the gas in the alveoli ventilated by collateral roots indicated approximately 10 per cent efficiency of ventilation of this area.\textsuperscript{21} Additional investigation in Lindskog's labo-
tory led to the discovery that histamine blocked collateral respiration and that a prior injection of an anti-histaminic agent prevented this action of histamine. This observation may have bearing on the pathogenesis and prevention of postoperative atelectasis.

In 1934, Lindskog and Bradshaw demonstrated that reinflation of an atelectatic lung required pressures of from 12 to 16 centimeters of water, and that the pressure required for reinflation of this atelectatic lung did not increase with time. The existence of a threshold pressure which must be reached before reinflation of an atelectatic lung can occur is of obvious clinical significance.

The observation of Radford that surface tension, after lung collapse, tends to make the lung less compliant, has a bearing on the management of patients encased in a respirator. In such patients, deprived of normal cough and sighing movements, atelectasis and decreased compliance of the lungs develop so that large pressures are required to provide adequate alveolar ventilation. Furthermore, the ensuing alteration of ventilation/perfusion relationships may account for the anoxemia often found in these patients. There appears to be ample justification for the therapeutic production of occasional deep breaths in these patients by the application of either positive pressure at the mouth or of negative pressure in the respirator.

*Pulmonary emboli.* A number of observers have produced pulmonary emboli in various species of animals with a variety of materials during the past 50 years. Sufficient embolization of the lungs eventually results in right heart failure and death, and, in the anesthetized dog, this result is attributable to obstruction of pulmonary vessels by the emboli rather than to reflex pulmonary vasoconstriction. In addition, when pulmonary hypertension becomes severe, diffusion limitation develops and anoxemia, relieved by oxygen, results. These findings are similar to those seen after resection of pulmonary tissue, and similar hemodynamic effects have been produced by direct reduction of the pulmonary vascular bed by ligation or compression of the major pulmonary arteries. Fineberg and Wiggers found that, in open-chest dogs, compression of the pulmonary artery to 60 per cent of its normal size resulted in right heart failure, attributed to mechanical obstruction to the flow of blood to the lung. Similar results were obtained by Gibbon and Churchill who also found that over 70 per cent of the lobar arteries had to be ligated before right heart failure developed.

Since evidence of a neurogenic component to the pulmonary hypertension which follows pulmonary embolization is lacking and since the undesirable consequences of embolism are mechanical obstruction to blood flow through the lung and right heart failure, rational therapy should be directed at improving right ventricular function and maintaining blood flow through the lung. Adrenalin is capable of sustaining the blood pressure and cardiac output in the experimental animal and in patients with shock following pulmonary emboli and may be life-saving. Eventually, additional pulmonary blood vessels open and permit adequate circulation through the lung at a reduced pressure in the pulmonary artery. An in-
dication of the extensive pulmonary vascular reserve is the fact that three dogs were each given pulmonary emboli to the point of right heart failure and, two to four weeks later, the pulmonary artery pressure was normal and the same dose of glass beads was needed again to produce heart failure. This sequence was repeated two more times in each animal. Given supportive therapy during the acute episode, the patient with pulmonary emboli may be expected to improve as new blood vessels open in the lung.

**Bronchial collateral circulation.** The existence of a bronchial collateral blood flow to the lung has been found in normal dogs, but its magnitude is not considered to be of physiological importance. After chronic ligation of the pulmonary artery, however, the bronchial collateral flow gradually increases, and, at the end of one year, becomes of great magnitude. The expanded bronchial bed in patients with bronchiectasis and other pulmonary diseases may be a factor in the left ventricular hypertrophy which may develop in such patients.

**Pulmonary emphysema.** Various surgical methods have been reported as capable of producing pulmonary emphysema in dogs. These methods, involving increase of the thoracic cage by rib resection or "reefing" of the diaphragm, or airway obstruction by insertion of valves into the trachea, have resulted in the pathological picture of emphysema. Paine has shown that both types of procedure result, in the dog, in abnormal pulmonary distensibility, manifested by greater intrapleural pressure swings during quiet breathing and, also, in intolerance to exercise. The similarity of these experimental preparations to patients with pulmonary emphysema remains to be demonstrated.

**Bronchiectasis.** Although bronchiectasis has been produced in experimental animals, the effects of the pathology on pulmonary function have not been studied.

**Pneumoperitoneum.** Beecher et al found that the production of pneumoperitoneum in the anesthetized dog resulted in reduction of the functional residual capacity of the dog.

**DISCUSSION AND SUMMARY**

Methods for producing limitation of one or more of the three pulmonary functions have been discussed and are summarized in Table I. Inadequate

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<th>Pulmonary Function</th>
<th>Experimental Procedure</th>
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<td>Ventilation</td>
<td>Depression of respiratory center by anesthesia; muscular paralysis by curare; artificial dead space</td>
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| Diffusion          | Resection of pulmonary tissue  
Pulmonary emboli |
| Distribution       | Pulmonary a-v fistula  
Pulmonary edema  
Atelectasis |
| Uneven vent.-perf. | Partial lung collapse |
ventilatory function may be produced by anesthetic agents and by muscular paralysis. Reduction of alveolar ventilation in the presence of increased total ventilation may be produced by the addition of an artificial dead space. Reduction of lung compliance may be produced by experimental pulmonary edema. Impaired diffusion results from resection of pulmonary tissue and from extensive pulmonary embolization, but pulmonary fibrosis and diffusion limitation from increased thickness of the alveolar-capillary membrane has not been produced in experimental animals. Impaired distribution, in the form of different ventilation/perfusion ratios in different parts of the lung, may be produced by partial collapse of the lung, and effective right-to-left shunt of mixed venous blood may be produced by pulmonary edema or by the surgical construction of a pulmonary arteriovenous fistula. The anoxemia that might be expected to result from complete lung collapse is prevented by effective shunting of blood away from the atelectatic lung, and functional limitation would only be expected to occur when large amounts of pulmonary tissue are collapsed. The functional reserve of the lung, in terms of the circulatory bed and diffusion surface, is obviously large, and mechanisms exist to prevent the development of anoxemia due to impaired distribution under abnormal conditions. Measurements of vital capacity are impossible in the experimental animal, but, by inference from human data, ventilatory reserve is also great, and after resection of pulmonary tissue, inadequate diffusion surface and pulmonary vascular bed prove to be limiting factors before alveolar ventilation becomes inadequate.

DISCUSSION Y RESUMEN

Los métodos para producir la limitación de una o más de las funciones pulmonares se discuten y se resumen en el cuadro 1. Puede producirse una función ventilatoria inadecuada por los agentes anestésicos y por la parálisis muscular. La reducción de la ventilación alveolar en presencia de un aumento de la ventilación total puede producirse por el agregado de un "espacio muerto" artificial. La reducción del rendimiento pulmonar puede ser producida por el edema pulmonar experimental. La difusión reducida resulta de la resección de tejido pulmonar y después de embolización pulmonar extensa pero la fibrosis pulmonar y la difusión limitada a causa de engrosamiento de la membrana alveolo-capilar no se ha producido en los animales de experiencia. La distribución imperfecta en la forma de relación ventilación: perfusión diferente en diversas partes del pulmón puede producirse por el colapso parcial del pulmón, y se puede producir una intercomunicación de derecha a izquierda de sangre venosa mezclada por el edema pulmonar o por el establecimiento quirúrgico de una fistula arteriovenosa pulmonar. La anoxemia que podría esperarse resultara de un colapso completo del pulmón se evita por una intercomunicación efectiva fuera del pulmón atelectásico y sólo son de esperarse limitaciones funcionales cuando grandes volúmenes de ejido pulmonar se colapsan.

La reserva funcional del pulmón en términos de lecho circulatorio y superficie de difusión es evidentemente amplia y existen mecanismos para
evitar el desarrollo de anoxiaemia debida a distribución imperfecta bajo condiciones anormales. Las medidas de la capacidad vital son imposibles en el animal de experiencia por inferencia de los datos en el hombre la reserva ventilatoria es también grande y después de resección de tejido pulmonar la superficie de difusión inadecuada así como del lecho vascular pulmonar demuestran ser los factores limitantes antes que la ventilación alveolar se haga deficiente.

RESUME

Les méthodes capables de réaliser une réduction d'une ou de plusieurs des trois fonctions pulmonaires sont discutées et résumées dans le tableau I. Une fonction ventilatoire insuffisante peut être produite par des agents anesthésiques et par une paralysie musculaire. La réduction de la ventilation alvéolaire, alors que la ventilation totale est augmentée, peut être produite par l'addition d'une zone morte artificielle. La réduction de la capacité pulmonaire peut être réalisée par un oedème pulmonaire expérimental. Des troubles de la diffusion surviennent après résection de tissu pulmonaire et après embolies pulmonaires extensives, mais la fibrose pulmonaire et la réduction de la diffusion provenant de l'augmentation de l'épaisseur de la membrane alvéolo-capillaire n'a pu être réalisée expérimentalement chez l'animal. Les troubles de distribution par altération des rapports qui unissent la ventilation et la perfusion, dans différentes parties du poumon, peuvent être produits par des collapsus pulmonaires limités; un véritable shunt de droite à gauche, avec mélange de sang veineux peut être produit par l'oedème pulmonaire ou par la création chirurgicale d'une fistule pulmonaire artérioveineuse. L'anoxémie qui pourrait résulter d'un collapsus pulmonaire total est supprimée par la dérivation du sang de la partie atélectasée, et on ne doit s'attendre à une diminution fonctionnelle que lorsque de grandes quantités de tissu pulmonaire sont collabées. La réserve fonctionnelle du poumon comprenant le lit circulatoire et la surface de diffusion, est évidemment étendue, et il existe des mécanismes qui empêchent le développement de l'anoxémie qui pourrait survenir à la suite de troubles de la distribution dus à des états pathologiques. La mesure de la capacité vitale est impossible expérimentalement chez l'animal. Toutefois, en se référant à ce qu'on constate chez l'homme, la réserve ventilatoire est également grande; après une résection de tissu pulmonaire, la réduction de la surface de diffusion et du lit vasculaire pulmonaire représentent des facteurs qui agissent avant même que la ventilation alvéolaire ne devienne insuffisante.

ZUSAMMENFASSUNG


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References will appear in reprints.