DIFFUSION IN ANAESTHESIA

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An understanding of the phenomenon of diffusion is important in anaesthesia. It is a process vitally concerned in the transfer of physiological and anaesthetic gases from the alveolus to the plasma and/or red cell. Apart from the fact that diffusion in the normal lung is of interest, an understanding of diffusion also becomes of practical significance to the anaesthetist when dealing with diffusion respiration, diffusion anoxia, and diffusion in the abnormal lung.

The Physics of Gas Diffusion

The molecules of a foreign gas introduced into a mixture of gases at equilibrium will rapidly intermingle with the molecules already present. This rapidity is due to the small molecular volume of a gas, in proportion to the intermolecular space.

Any gas will diffuse much more slowly in a liquid because of the larger molecular volume of a liquid in relation to intermolecular space.[1] Thus diffusion may be defined as "the movement of molecules from a region of high to one of low concentration."[2] Any gas, be it physiological or anaesthetic, in order to enter the body via the lung must be water-soluble, as the pulmonary alveolar membrane is a thin layer of cells with a film of water on its surface.[3] The amount of a gas in millilitres dissolved in a liquid at N.T.P. with the gas as a partial pressure of 760 mm. Hg. is expressed by the Bunsen solubility coefficient d.[4]

The diffusion of gases may be described by the following two physical laws: (1) Graham's Law,[5,1]—"The rate of diffusion of a gas is inversely proportional to the square root of its density." (2) Ficks Law—"The rate of diffusion of a gas is proportional to the gradient of concentration." At the pulmonary membrane, Ficks' law is of paramount importance, as gradients of concentration exist between the alveolus and the blood. The partial pressure of a gas in the alveolus may be expressed by the symbol P_a and that in the plasma on the other side of the alevolar membrane as P_c mm. Hg. Since the Bunsen solubility coefficient and the density of any given gas are constant, these may be combined into a single diffusion coefficient d.[6] If V is the volume of gas in ml. at N.T.P. which flows across a membrane of area S cm.^{2} and x cm. average thickness in time t minutes, the diffusion coefficient d being expressed in ml./min./mm. Hg./cm., then[6]

$$V = [Sd(P_a - P_c)t]/x. \quad (1)$$

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Mass Flow of Gases and Diffusion Respiration

A gas present in the external environment may reach the alveolus by[7]: (1) mass flow down the trachea due to ventilation (ventilatory mass flow); (2) mass flow due to a decrease in barometric pressure in the alveolus (aventilatory mass flow).

During normal breathing, the ventilatory mass flow is predominant. It is possible, however, to maintain adequate oxygenation in the absence of ventilation. This process was termed "diffusion respiration" by Draper and Whitehead, [8-14] "apnoeic diffusion oxygenation" by Holmdahl,[15] and "aventilatory mass flow" by Bartlett *et al.*[7]

Denitrogenation is produced by prior breathing of 100 per cent oxygen, and apnoea is instituted. The subject is then left connected to the source of 100 per cent oxygen. It was originally thought that oxygenation was maintained in the blood by a "haemoglobin oxygen pump"[13] whereby haemoglobin actively pumped oxygen from the alveolus, producing in the alveolus a negative barometric pressure with respect to the external atmosphere. Oxygen thus moves down the trachea by aventilatory mass flow[7] to fill the region of negative pressure.

Subsequent studies[15,7] have established that the negative alveolar pressure is produced solely by diffusion of oxygen across the pulmonary membrane because of the gradient of partial pressure between the alveolus and the pulmonary capillary blood.

The phenomenon of "diffusion respiration" has been investigated in man by Frumin *et al.*[16] In a series of eight subjects, the arterial oxygen saturation was well maintained. The limiting factor to the duration of apnoea is the accumulation of carbon dioxide in equilibrium with arterial blood. Respiratory acidosis results and, in Frumin's series, levels up to 259 mm. PCO_2 with pH to 6.7 following 53 minutes' apnoea were obtained. The rate of rise of PCO_2 was 2.7–4.9 mm. Hg./minute.

The slow rate of rise of PCO_2 emphasizes the body mechanism that makes "diffusion respiration" possible, that is, that only a small amount of the carbon dioxide produced by metabolism enters the alveoli, 90 per cent is equilibrated throughout the body and buffered in the blood.[15]

Urine secretion ceases during diffusion respiration in about 5 minutes The E.E.G. becomes flat in 10 to 15 minutes. The cardiovascular system functions well with the expected rise in carbon dioxide levels producing an increase in systolic and diastolic blood pressure. Occasional cardiac arrhythmias occur.

On termination of apnoea and decreasing carbon dioxide levels by ventilation, moderate hypotension was produced. The occurrence of post-hypercapnia arrhythmias and fibrillation has been described[17] but was not a feature of other studies.[15,16]

Aventilatory mass flow has been shown to occur even during normal breathing. By use of the total body plethysmograph aventilatory mass flow, or "diffusion respiration," has been demonstrated independent of breathing movements.[7] The significance of this in total ventilation is as yet unknown.

Diffusion Respiration in Anaesthesia

1. *During bronchoscopy.* With prior denitrogenation, breathing 100 per cent

oxygen and succinylcholine-induced apnoea, bronchoscopy has been performed with no ventilator by attaching oxygen to the bronchoscope, thus fulfilling the essential facet of keeping the external atmosphere at 100 per cent oxygen. Oxygen passes to the alveoli by "diffusion respiration."

2. *During intubation.* The value of prior ventilation with 100 per cent oxygen in maintaining arterial oxygen saturation during intubation apnoea is well known. This is "diffusion respiration."

Diffusion within the Alveolus

Gases which are brought to the alveolus by ventilation must then travel across the alveolus by diffusion through the gas already present there to reach the pulmonary membrane. This process takes place very rapidly, thus presenting no barrier to gas exchange.

The rate of diffusion may be calculated on the following basis. Since the rate of diffusion of gases in air is approximately 1 million times their diffusion rate in saline solution[2] and, since the thickness of the alveolar membrane is approximately one micron,[3] for the same pressure gradient, the equivalent distance diffused would be one metre in air.

Diffusion in the Normal Lung

All water-soluble gases will diffuse across the pulmonary membrane to the capillary in a similar fashion. The rate of diffusion depends on the physical characteristics of the gas and in general follows equation (1). Rearranging equation (1) gives:

$$V/[P_a - P_c)t] = Sd/x, \tag{2}$$

and if D_M is the diffusing capacity of the whole lung membrane in ml./min./mm. Hg, then

$$D_M = Sd/x. \tag{3}$$

Values for S, the total surface area of the pulmonary membrane, are difficult to measure and have been variously reported at 50–100 sq. m. (quoted in Ref. 18) from anatomical methods and 38 sq. m.[6] and 5–10 sq. m.[18] by physical methods; x has been estimated at 1.4 microns.[6] But

$$D_M = V/[(P_a - P_c)t]. \tag{4}$$

V, the volume of diffused gas, and t, the time, may be precisely measured. $(P_a - P_c)$, which is the difference in partial pressure between the alveolus and the pulmonary capillary for the gas in question, is more difficult to measure. Simultaneous alveolar gas samples and end capillary blood samples are needed; also a reliable means of measuring arterial gas pressures.

Equation (4) above presents the whole picture for the inert gases, N_2, and all anaesthetic gases. The physiologic gases, oxygen and carbon dioxide, and toxic agents such as carbon monoxide, however, present a more complex problem. Equation (4) is still true and expresses diffusion across the membrane but, in addition, these gases must diffuse across the plasma and through the red cell membrane and combine with haemoglobin.

It was originally considered that the barrier to diffusion presented by the plasma and red cells was negligible and that practically instantaneous combination of oxygen with haemoglobin occurred. Using carbon monoxide as a test gas, however, it was found that considerable resistance to diffusion was present in the plasma.[6] An equation has been derived to express this[6]:

$$\frac{1}{D_L(CO)} = \frac{1}{D_M(CO)} + \frac{1}{\theta(CO)V_c},$$

in which D_L = diffusing capacity of the whole lung in ml./min./mm. Hg,
$\theta(CO)$ = number of ml. of carbon monoxide taken up by the red cells in 1 ml. of blood/minute/mm. gradient partial pressure between the plasma and interior of the red cell,
V_c = total volume of blood in the lung capillaries.

V_c has been variously estimated as 60 c.c. at rest and 90 c.c. during exercise[19] and 75 c.c. average.[6]

The third barrier to diffusion is the red cell membrane. It had been formerly thought to present a negligible barrier to diffusion,[20] as haemoglobin suspensions and packed cells, when tested, showed the same relative diffusion rates. Recent work, however, by Forster *et al.*,[21] has established that the resistance of the red cell membrane is 3.6 times that of the cell interior. Whether this materially affects diffusion is unresolved.

The time spent by the red cell in the lung capillary, T_c, is the final factor of importance in the diffusion process. If this time is considerably foreshortened, as it would be by increasing the flow rate, insufficient time for uptake of oxygen would be allowed.[19] The average time spent by the erythrocyte in the lung capillaries has been estimated as 0.75±0.25 seconds[19] and 0.79 seconds[22] at rest and 0.34±0.1 seconds[19] during exercise

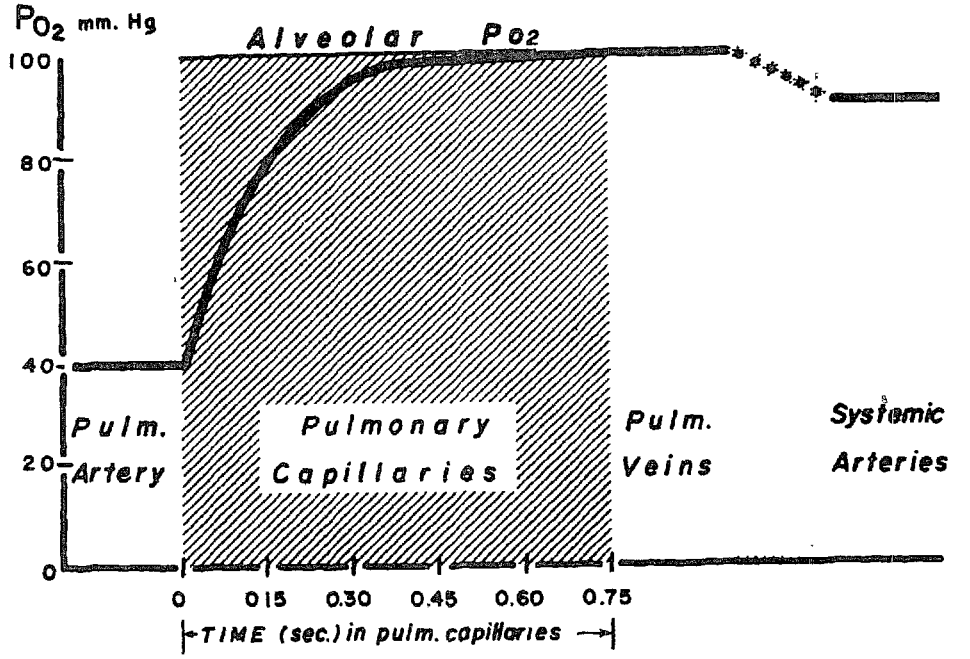

FIGURE 1. Alveolar-capillary diffusion. (From Comroe *et al.* The Lung. Chicago: The Year Book Publishers (1955))

Figure 1 presents a graphical description of the saturation of a red cell during its transit through the pulmonary capillary.[5] In Figure 1 note that 98 per cent saturation occurs in about 0.45 second. If the transit time, T_c, through the capillary is decreased below 0.45 second, the oxygen saturation must fall, and the alveolar–arterial PO_2 difference will increase.

Note (Figure 1) that the PO_2 of systemic arterial blood differs from alveolar and capillary PO_2. This difference in the arterial saturation is termed the alveolar–arterial PO_2 ($AaPO_2$) difference. Values of 0.3 mm.[23] to 9 mm.[24] have been calculated for the $AaPO_2$ difference.

The major components of the $AaPO_2$ difference are listed in Table I.

TABLE I

COMPONENTS OF $AaPO_2$ DIFFERENCE

I. *Membrane component*—preventing the achievement of complete diffusion equilibrium between alveolar gas and end capillary blood
   A. Diffusion across pulmonary membrane
   B. Diffusion within the blood

II. *Venous admixture component*
   A. Shunt component
      Thebesian veins
      Bronchial drainage
   B. Non-uniformity of alveolar gas
      Variation in ventilation
      Perfusion relationships

Normal Values for $D_M(O_2)$ and $D_L(O_2)$

Early calculations of $D_M(O_2)$ using a formula based on equations (1) and (3) gave results up to 250 c.c./min./mm. Hg. This calculated value depends on an accurate anatomical measurement of the area and thickness of the pulmonary membrane. More recently, measurements by Roughton and Forster[6] based on equation (4) have given values of 55 ml./min./mm. Hg. The difference between the two values reflects the difficulty in anatomical measurement of the pulmonary membrane.

Values for $D_L(O_2)$ have been calculated by Lilienthal[24] as 21 ml./min./mm. Hg from measurements of oxygen consumption and alveolar and arterial PO_2. The barrier to diffusion presented by the plasma and red cells is thus of considerable magnitude and has been estimated[2] as 49.5 per cent of the total resistance to diffusion.

Normal Variations in Oxygen Diffusion

1. *Relation to body size.* The mean diffusion of oxygen is probably constant regardless of size in the normal lung.[25] Total D_M and D_L must necessarily increase with body size because of the need for more oxygen. $D_L(O_2)$ increases as a linear function of body surface area, increasing 12 ml./min./mm. Hg/m^2.

2. *Sex.* No variation other than that introduced by body size.[26]

3. *Age.* There is a significant decrease in D_L with age[27] both at rest and on exercise, unaccompanied by a change in other pulmonary parameters. The change

in D_L may be related to an alteration in the pulmonary capillary bed, and a decrease in the cardiac output.

4. *Exercise.* D_L increases in essentially a linear fashion with increased oxygen consumption.[2,22,28] This may be due to: (*a*) an increase in effective capillary blood volume,[29] (*b*) an increase in D_M. An increase in the capillary blood volume occurs via dilatation of the capillary bed, decrease in pulmonary capillary resistance, and increased blood flow.

5. *Alveolar volume.* D_L increases with alveolar volume only after the lung has attained two-thirds of its maximum capacity.[30]

6. *Anoxia.* An increase in D_L occurs probably as a result of an increase in the capillary blood volume and flow at AP_{O_2} levels of 50 mm. Hg. $D_L(O_2)$ appears to be relatively constant over the range AP_{O_2} 50–100 mg. Hg.[31]

7. *Alveolar carbon dioxide tension.* D_L increases with AP_{CO_2}, probably because of increased pulmonary blood flow.[2]

8. *Body temperature.* D_L falls because of the decrease in the specific diffusivity of oxygen[25] and the decrease in the pulmonary blood flow.

Diffusion of Nitrogen and Other Inert Gases

The diffusion of inert gases follows equation (1)[4] and depends on the solubility and molecular weight. As diffusion through the plasma is unnecessary, $D_M = D_L$.

The time taken by diffusion across the membrane is unimportant. For nitrogen, molecular weight 28, aP_{N_2} reaches 99 per cent of AP_{N_2} in 0.01 second. A gas of molecular weight 146 would still require only 0.02 second. Since the blood spends 0.79 second in the pulmonary capillary, it can be clearly seen that no impairment to equilibrium can exist at the membrane; also that a reduction in the transit time of the blood in the pulmonary capillary causes no reduction in equilibration. This is not to say, however, that 100 per cent equilibrium occurs in 0.01–0.02 second when a foreign gas is introduced into a patient's upper airway. Far from it. Two additional factors must be introduced: (1) the initial process of lung washout, that is the dilution of the foreign gas by the residual gas of the lung and its removal by pulmonary blood; (2) the contribution to the aP of the foreign gas by the recirculating mixed venous blood.

The transfer of inert gases has been developed in an equation by Kety[4] (Equation 55) and may be expressed graphically as in Figure 2. With reference to this figure, factor (1) corresponds to the initial rapid rise in the graph, and factor (2), to the slow rise with time. Factor (2) depends on blood flow, diffusion at the tissue level, solubility, and volume of saturable body tissue.

The fraction of complete saturation in the first few minutes determines the rapidity of induction and recovery from anaesthesia.

Normal Variations in the Diffusion of Inert Gases

These occur through variations in alveolar ventilation and pulmonary blood flow. Because of the speed of equilibration, changes in D_M and T_c are of little importance.

Anaesthetic Gases and Diffusion Anoxia

It must be remembered that whenever the concentration of gases in the

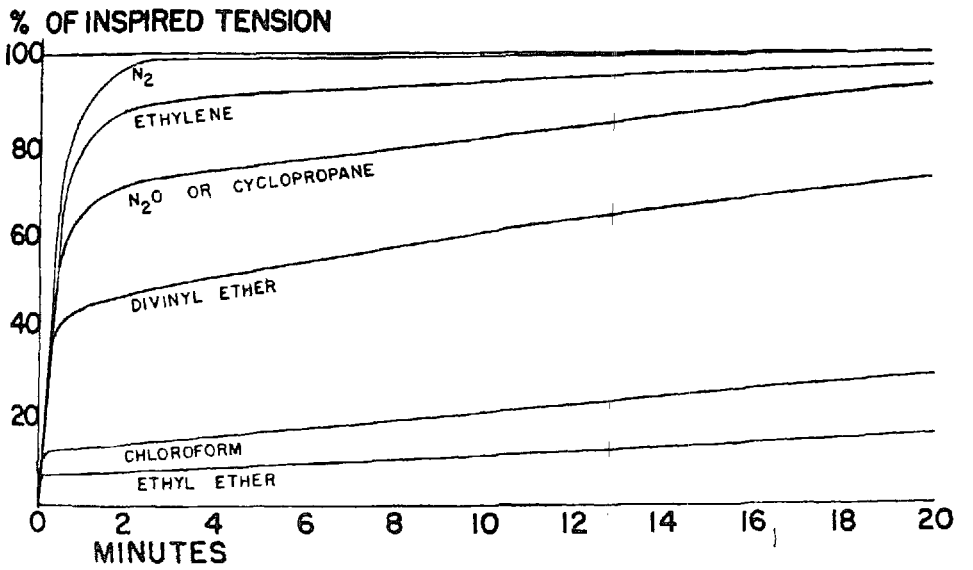

FIGURE 2. Alveolar or arterial tensions of several inert gases (expressed as per cent of a constant inspired tension). (From Kety, S S. Pharmacol. Revs. 3: 1 (1951).)

patient's environment is changed, diffusion gradients are set up. Thus, if 100 per cent oxygen is substituted for air, an outward gradient for nitrogen is set up. If 20 per cent oxygen and 80 per cent N_2O is introduced, an outward gradient for nitrogen and an inward gradient for N_2O is set up. One must always make sure that, in establishing these gradients, adequate oxygen is provided taking into account the partial pressure of the gas undergoing outward diffusion in the system.

Fink, in 1955,[32] emphasized this point in his paper on "Diffusion Anoxia." The decrease in alveolar PO_2 was particularly apparent at the conclusion of a nitrous oxide–cyclopropane anaesthetic as both these gases, which are rapidly diffusable (Fig. 2), will be diffusing outward at the same time. Fink feels that the resultant anoxia may account for cases of emergence excitement seen after cyclopropane anaesthesia.

Security from this state of anoxia is obtained by supplying additional oxygen at the end of anaesthesia.

Diffusion of Carbon Dioxide

Since carbon dioxide is more soluble in water than oxygen, it diffuses about 20 times more rapidly than oxygen. Because of this, carbon dioxide has a 99 per cent equilibration time of 0.072 second, well below the transit time of blood in the lung capillaries. Thus the $AaPCO_2$ difference is negligible, and only changes in D_M of greater degree than ever found clinically would impair the diffusion of carbon dioxide.

The intracellular reaction

$$H_2CO_3 \underset{\longleftarrow}{\xrightarrow{\text{carbonic anhydrase}}} H_2O + CO_2 \uparrow$$

may, however, be quite slow, perhaps slower than the transit time through the capillary. If this is so, equilibration of the blood PCO_2 and the alveolar PCO_2 will take place as long as the blood is in contact with alveolar air. This equilibration ceases when the blood leaves the alveolus, but if the above reaction is not complete, further CO_2 will be added to the plasma and will be reflected as part of the $AaPCO_2$ difference. This, plus the venous admixture component, has been measured as 4.6±2.5 mm. Hg.[33]

Ordinarily, the delay due to carbonic anhydrase can be ignored. By using carbonic anhydrase inhibitors, however, one can interfere considerably with elimination of carbon dioxide.[34] In the presence of an inhibitor such as acetazoleamide (Diamox) the carriage of CO_2 as H_2CO_3 in the red cell decreases and the PCO_2 of plasma increases. More carbon dioxide is carried as carbamino, H^+ increases, and pH decreases.

During anaesthesia the limiting factor in carbon dioxide elimination is the level of alveolar PCO_2. This may become elevated from external sources, such as rebreathing in an anaesthetic system, or because of poor elimination due to intrinsic ventilatory lung disease.[35]

Diffusion in the Abnormal Lung

The term alveolar-capillary block was introduced in 1951 by Austrian *et al.*[36] to describe "an abnormal physiologic state due to increased thickness of the tissue planes which separate air in the alveoli from blood in the capillaries of the alveolar walls."[37] The pathophysiological process comprises deposition of fibrous tissue in the alveolar walls with impairment of D_M, often accompanied by decrease in and obliteration of lung capillaries, thus decreasing V_c. These changes are unaccompanied by change in airway resistance.

The syndrome of pulmonary fibrosis may be produced by various aetiologic factors (Table II). In addition, impairment of the cross-sectional area of the

TABLE II

Causes of Pulmonary Fibrosis

Miliary tuberculosis
Boeck's sarcoidosis
Scleroderma
Radiation fibrosis
Lymphangitic carcinomatosis
Pulmonary berylliosis
Asbestosis
Sulphur dioxide inhalation
Chronic disseminated histiocytosis X

pulmonary capillaries followed by increased pulmonary vascular resistance and decrease in V_c may cause impaired D_L. The causes of this are shown in Table III.

The abnormal physiologic component in the syndrome of alveolar-capillary block comprises the following[36]: (1) reduced lung volumes, (2) maintenance of a large maximum breathing capacity, (3) hyperventilation at rest, (4) normal or nearly normal arterial PO_2 at rest but a marked reduction during exercise,

TABLE III

CAUSES OF DECREASED CAPILLARY BED AREA

Extensive pulmonary resection
Multiple pulmonary emboli
Cor pulmonale
Pneumothorax

(5) normal APO_2, (6) decreased D_M, (7) pulmonary hypertension (decreased V_c?).

The diffusion barrier is limited to oxygen because of its insolubility and the length of time necessary for equilibration. No impairment to diffusion of inert gases or carbon dioxide exists. In the later stages, however, restriction of ventilation by increasing fibrosis may cause carbon dioxide retention.

The relationship of cor pulmonale to diffusion insufficiency has been recognized by Luchsinger *et al.*[38] The rise of pulmonary pressure with increased cardiac output in the face of a fixed vascular resistance implies that the velocity of flow through the pulmonary capillaries must increase. Contact time with alveolar air is shortened to the point of insufficient time for equilibration, particularly during exercise with heavy oxygen demands. Thus the $AaPO_2$ difference increases markedly with exercise and dyspnoea and cyanosis result.

Anaesthetic Considerations

In the early stages of pulmonary fibrosis little problem exists as high concentrations of oxygen may be supplied. Later, when extensive fibrosis occurs, the problems of airway resistance and carbon dioxide removal emerge. There is fortunately never any problem in the diffusion of anaesthetic gases.

SUMMARY

1. Diffusion of gases may be described by the equation

$$V = [Sd(P_a - P_c)t]/x.$$

2. Gas travels from the environment to the blood through the following: (*a*) mass flow down the trachea, (*b*) diffusion across the alveoli, (*c*) diffusion through the lung membrane, (*d*) diffusion through the plasma and into the red cell.

3. Diffusion of oxygen, which is relatively insoluble, depends on a gradient for oxygen between the alveolus and the capillary and on the time of contact of blood and alveolar air.

4. Nitrogen and inert gases equilibrate rapidly and are not affected by diseases affecting the pulmonary membrane.

5. Carbon dioxide diffuses readily because of its high solubility.

6. Alveolar capillary block and diffusion respirations are described and some anaesthetic considerations given.

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