Supersaturation by counterperfusion and diffusion of gases

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HILLS, B. A. *Supersaturation by counterperfusion and diffusion of gases*. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 42(5): 758–760, 1977. – Gaseous supersaturation can be induced under steady-state conditions when two inert gases are transmitted in opposite directions across any system comprising a diffusion barrier adjacent to a zone of limited convective capacity. This has many implications for bubble formation in vivo and can explain the occurrence of symptoms of decompression sickness without decompression.

air embolism; bubble formation; counterdiffusion; decompression sickness; dental anesthesia; gaseous anesthesia

WHEN A SLAB OF A UNIFORM MEDIUM is exposed to one inert gas on one side and to a second inert gas on the other side, all at the ambient pressure, then the tension (partial pressure) gradient of one dissolved gas exactly reciprocates that of the other gas diffusing in the opposite direction. This results in saturation at all points and, moreover, applies under these steady-state conditions whatever the geometry of the system.

However Graves and co-workers (5) have pointed out that if the slab is now a composite of two media of different relative permeabilities to the two gases, then supersaturation can occur under steady-state conditions if they are appropriately orientated with respect to the gases, the total gas tension reaching a peak at the interface. They have then gone on to demonstrate (6) how this can cause bubbles to grow at the interface and have discussed how this phenomenon could give rise to bubble formation at a lipid-aqueous interface likely to be encountered in vivo. Thus they have offered this "counterdiffusion supersaturation" as a possible mechanism for cutaneous (2) and vestibular (10) symptoms of decompression sickness (long associated with bubble formation) yet produced without decompression if the skin or middle ear is exposed to one inert gas (e.g., He) while the subject breathes another (e.g., N_2 as air) at pressure.

However, it is difficult to envisage the relative orientation of lipid and aqueous layers needed to produce counterdiffusion supersaturation in skin and, particularly, in the ear, which is virtually fat-free. Hence it is proposed in this paper that a lipid layer is not necessary, and that supersaturation can occur if there is an appreciable limitation to the countertransfer of the two gases imposed by the circulation.

COUNTERPERFUSION MODEL

Blood perfusion has long been regarded as the dominant factor in controlling blood-tissue exchange of inert solutes in tissue (9). Hence this mode of transfer cannot be ignored in determining gas distributions in vivo and may be considered in combination with diffusion to produce supersaturation by gases in the following manner.

Let us consider a region of tissue being perfused at a rate $\dot{Q}$ with blood saturated only with gas II at the ambient pressure (P). If this zone is surrounded by a diffusion barrier of area A and thickness x whose remote face is continuously flushed with another gas (I) also kept at ambient pressure, then Fick's law can be applied to give the flux of each gas by diffusion ($\dot{q}_1$ and $\dot{q}_2$) which must also equal the transport of each gas by perfusion for steady state to be attained (see Fig. 1).

Thus for gas I

$$\dot{q}_1 = AD_1S_1(P - p_1)/x = \dot{Q}S_1'p_1 \qquad (1)$$

where D_1 is its diffusion coefficient in the static barrier and S_1 and S_1' are its solubilities in that barrier and in blood, respectively. Similarly for gas II

$$\dot{q}_2 = AD_2S_2p_2/x = \dot{Q}S_2'(P - p_2) \qquad (2)$$

where D_2, S_2, and S_2' now refer to gas II. p_1 and p_2 are the tensions of the two gases (I and II) in the stirred pool shown in Fig. 1 to represent the perfused zone and hence they are also the tensions of those gases in the "overflow" corresponding to venous blood.

Rearrangement of these equations with rationalisation by substituting $\alpha = A/x\dot{Q}$, $\beta_1 = D_1S_1/S_1' = D_1\lambda_1$, and $\beta_2 = D_2S_2/S_2' = D_2\lambda_2$, where λ is the tissue-blood partition coefficient, enables the supersaturation to be derived from *Eqs. 1* and *2* as

$$p_1 + p_2 - P = \alpha P(\beta_1 - \beta_2)/(1 + \alpha\beta_1)(1 + \alpha\beta_2) \qquad (3)$$

Thus there will be supersaturation of venous blood ($p_1 + p_2 > P$) if $\beta_1 > \beta_2$. Hence bubbles will grow if

$$D_1\lambda_1 > D_2\lambda_2 \qquad (4)$$

Moreover, if we have a purely aqueous tissue ($\lambda_1 = \lambda_2 = 1$), we can still have supersaturation of venous blood if

$$D_1 > D_2 \qquad (5)$$

This implies that supersaturation by dissolved gases can occur in any system where a diffusional and a

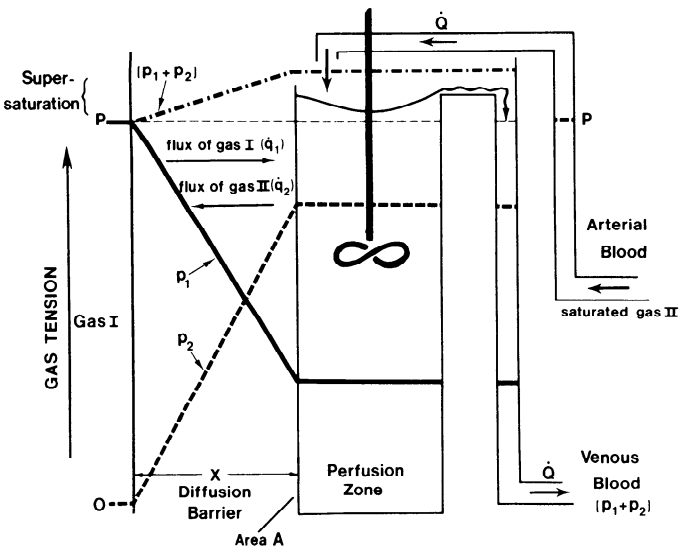

FIG. 1. A readily diffusible gas (I) washes away from the outer surface of the skin or membrane any of a less diffusible gas (II) which has permeated this barrier from the perfused zone supplied with blood free of gas I but saturated with gas II at the ambient pressure (P). By adding gas tensions, it can be seen that the "stirred pool" and hence the overflow (venous blood) becomes supersaturated ($p_1 + p_2 >$ P) as the system reaches steady state.

convective resistance lie in series with respect to the countertransfer of two gases, provided the source of the faster diffusing gas lies adjacent to the diffusion barrier. Numerous transient situations can be envisaged where supersaturation would arise by switching gases, but this result is particularly interesting since it applies to steady-state conditions so that, if there is nucleation of the convection medium, then bubbles can be produced in it continuously.

If we consider the case in vivo, it is likely that the countertransfer of two gases could produce a blood gas tension of those gases well in excess of the level of either gas at the barrier or in arterial blood, particularly under hyperbaric conditions, since ($p_1 + p_2 - P$) increases as P ↑ in *Eq. 3*. Moreover this excess tension could exceed the inherent unsaturation in venous blood arising from the metabolic gases (1) to give a net supersaturation which, if sufficient, would produce bubbles continuously. Hence it is most significant that intravenous bubbles were detected (3) continuously in subjects compressed in an environment of helium all the time that they breathed air. The "counterperfusion" model envisaged here has the advantage that the supersaturation occurs within blood where the bubbles are detected and does not require lipid to be present.

Any failure of blood to equilibrate with inspired gas at the lungs, as occurs to a finite extent (4) by virtue of ventilation:perfusion inequalities, could result in some of the faster diffusing gas (I) being returned to the tissue when it would further increase the degree of supersaturation predicted by *Eq. 3*. This marginal increase should exceed the effect of any failure of the "slower" gas (II) to equilibrate with inspired gas at the lungs, except in the unusual event that this gas is less soluble than I. Hence *Eq. 3* depicts a conservative estimate of the net supersaturation ($p_1 + p_2 - P$) imparted by the inert gases.

However inert gases are never present in vivo in the absence of the metabolic gases, oxygen and carbon dioxide. The conversion of O_2 into a similar number of molecules of a much more soluble gas CO_2, together with the enhancement provided by the shape of the oxyhemoglobin dissociation curve, leads to a net unsaturation of venous blood by these gases. This has been measured as 54 Torr in dogs for air breathing at normal atmospheric pressure (1), while the role of this inherent unsaturation in bubble formation has been emphasized (7) as a major factor in determining the imminence of decompression sickness. Thus, for bubble formation to be possible, the total tension of all gases (metabolic and inert) must exceed the absolute pressure. Hence the inherent unsaturation must be subtracted from the value of ($p_1 + p_2 - P$) calculated in *Eq. 3* to derive the net supersaturation representing the driving force for bubble inception.

EXAMPLE

As an indication of the magnitude of the effects involved, it is interesting to consider the practical case of a normoxic subject exposed to air but breathing an 80:20 N_2O:O_2 mixture by mask at normal pressure during surgical anesthesia induced primarily by other agents. Taking values for a largely aqueous tissue ($S_1 \simeq S_1'$ and $S_2 \simeq S_2'$) of ($\dot{Q}/A$) = 250 ml blood·m^{-2}·min^{-1} (6) and x = 0.3 mm for epidermis, we have $\alpha = (A/x\dot{Q}) \simeq 1.3 \times 10^3$ min·cm^{-2} and $\beta_1 \simeq D_1 = 4 \times 10^{-4}$ $cm^2 \cdot min^{-1}$ for N_2 while, by Graham's law, $\beta_2 \simeq D_2 = 3.15 \times 10^{-4}$ $cm^2 \cdot min^{-1}$ for N_2O. Substituted in *Eq. 3*, these values give a supersaturation of 0.039 ATA (30 Torr) relative to the inert gas partial pressure (P) of 0.8 ATA.

This is less than the inherent unsaturation of 50–60 Torr imparted by the metabolic gases and should therefore still leave venous skin blood with a net unsaturation. However if the volume fraction of oxygen in the inspired gas ($F_{I_{O_2}}$) is reduced to 10%, as once practiced in inducing dental anesthesia with 90:10 N_2O:O_2 alone, then the inherent unsaturation is likely to be reduced at least in proportion to the inspired $P_{I_{O_2}}$, i.e., to 27 Torr or less. This is less than the calculated value of 30 Torr for ($p_1 + p_2 - P$) when there would now be a few Torr of net supersaturation tending to form bubbles.

In the foregoing example it is unlikely this net supersaturation would be sufficient for bubble inception in most cases or would grow these bubbles to any appreciable size in the time available. However, at elevated pressures (P ↑), a poorly perfused tissue ($\dot{Q}$ ↓, α ↑) with a thin epithelium (x ↓, α ↑) and two inert gases of widely differing diffusivities such as N_2 and He ($\beta_1 - \beta_2$) ↑, there could be an appreciable supersaturation, particularly if the inspired P_{O_2} had not been elevated and especially if there were mild hypoxia.

DISCUSSION

Counterperfusion supersaturation has numerous implications. If a diver is breathing a helium-oxygen mixture when he is decompressed and forms extravascular bubbles in his tissues, then these decompression-in-

duced cavities could act as sources of helium gas in close proximity to perfusing blood. If the inert gas in his breathing mix is switched to nitrogen, there are then the basic ingredients for counterperfusion supersaturation, but now, it would result in intravascular bubbles which, although in the venous system, are potentially more dangerous. Several situations can also be envisaged where counterperfusion supersaturation could occur in the lungs, particularly if edema has increased the diffusion barrier or in lungs with poorly ventilated regions following switching of breathing mixes. Any effect would be potentiated by high pressure ($P \uparrow$ in *Eq. 3*) or gases of widely differing permeabilities ($\beta_1 \gg \beta_2$) such as SF_6 and He as widely used together in many respiratory experiments. Any bubbles produced now have the serious potential for becoming arterial gas emboli.

However, the immediate advantage of counterperfusion supersaturation is the convenient explanation it offers for the cutaneous and vestibular forms of decompression sickness which have been observed without decompression (2, 10)! Unless gas-induced osmosis causes these problems as speculated (8), then reversal of the gases (Fig. 1) should produce an unsaturation tending to dissolve bubbles in those organs when, for instance, heliox breathing in an air environment would provide a treatment.

Moreover, the relatively low overall blood perfusion rate of the inner ear ($\dot{Q} \downarrow$, $\alpha \uparrow$ in *Eq. 3*) and the thinness of some of the membranes such as Reissner's ($x \downarrow$, $\alpha \uparrow$ in *Eq. 3*) interposed between blood and middle-ear gas, would predispose the vestibular apparatus to gaseous supersaturation arising by the counterperfusion and diffusion of two inert gases.

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