A role for oxygen-induced osmosis in hyperbaric oxygen therapy

Brian A Hills

Key words
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Summary

(Hills BA. A role for oxygen-induced osmosis in hyperbaric oxygen therapy. Medical Hypothesis 1999; 52(3): 259-263) The principles of gas-induced osmosis, demonstrated in the 1970s, have been applied to the very large steady-state gradients of O₂ arising between arterial blood and hypoxic tissue during hyperbaric oxygen (HBO) therapy to produce a fluid ‘pump’ in the desired direction for resolving accompanying oedema. Thus, in soft-tissue injuries, an oxygen-induced fluid pump would break the vicious cycle between ischaemia, hypoxia and oedema at the point of oedema rather than hypoxia, as hitherto assumed. This osmotic mechanism enables the successes of HBO therapy in hypoxic disorders to be reconciled with early failures in such areas as hyperbaric radiotherapy, where substitution of O₂ for N₂ in inspired air was clearly not reflected at the tissue level. This argument also applies to the success of HBO in treating air embolism and decompression sickness over simple compression. The oxygen pump would seem to offer a more plausible explanation for the success of HBO therapy than theories based upon O₂ delivery by the circulation, especially when considering cardiovascular reflexes to elevated PaO₂ and the marginal increase in blood O₂ content upon switching to HBO from normobaric oxygen breathing.

Introduction

In making a ‘careful comeback’,¹ hyperbaric oxygen (HBO) therapy has now become established as a recognized clinical modality with a proven efficacy for a limited number of disorders.² It can no longer be called the ‘Maverick of Modern Medicine’ as it was dubbed in the 1970s, following the disappointing results of hyperbaric radiotherapy³ despite impressive in vitro scientific studies predicting success.⁴ Failure to substantiate a number of extravagant claims made at the time in treating a host of other diseases exacerbated the scepticism. There were also compelling physiological arguments⁵ explaining why large increases in arterial PO₂ do not necessarily elevate tissue PO₂ to any significant degree. In those days, the ‘believers’ emphasized arterial values of PO₂ while ‘disbelievers’, including this investigator,⁵ regarded venous values as offering a better reflection of tissue oxygenation on the grounds that venous blood leaves in gas-equilibration with the tissue. So why does HBO work in some disorders and not in others?

There is no doubt that the use of hyperbaric oxygen is the treatment of choice in resolving air embolism or any disorder related to an unwanted gas phase in tissue.² Not only does the additional hydrostatic pressure reduce the volume of that gas, increasing the tension gradient of the inert gas controlling its rate of resolution, but the substitution of O₂ for N₂ in the breathing mixture is not reflected at the tissue level.⁶ The resulting ‘inherent unsaturation’ of the tissue is transformed into a larger O₂ gradient, later termed an ‘oxygen window’ for removing the inert gas and resolving the gas phase as a whole. The above examples of the application of HBO are consistent with each other in demonstrating the failure of HBO to affect the tissue level of O₂ significantly, so why should it be so successful in disorders related to hypoxia? Typical of these diseases is soft-tissue trauma, for which quite remarkable rates of resolving the resulting compartment syndrome have been claimed.⁸-¹⁰ In these injuries; oedema forms rapidly with rapid onset of ischaemia as blood perfusion is curtailed by the compartment effect with extravascular tissue pressure rising, particularly in muscle encased in a tough fascial sheath of low compliance. The resulting vicious cycle of hypoxia, ischaemia and oedema is depicted in Figure 1.

It is generally assumed that the problem is resolved by HBO by oxygen simply diffusing into the tissue to break the vicious cycle at the point of hypoxia. However, if tissue oxygen tensions are increased as marginally as indicated

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FIGURE 1

Shows the vicious cycle between hypoxia, ischaemia and oedema characteristic of soft-tissue injury
by the other disorders discussed above, viz. air embolism and hyperbaric radiotherapy, why should HBO do so in hypoxic injury, so what other mechanism could be acting to promote its effect?

GAS-INDUCED OSMOSIS

In the early 1970s, there was considerable interest in a phenomenon termed ‘gas-induced osmosis’, which was discovered by observing unexplained fluid shifts that occurred in deep-sea divers as they compressed, decompressed and switched inert gases. This mechanism can also explain the haemoconcentration that occurs during decompression and haemodilution upon voluntary hyperventilation. The phenomenon was demonstrated for inert gases in vitro using both natural and synthetic membranes, by which gases in solution can exert an osmotic pressure like any other solute of comparable molecular size. This mechanism was tested in vivo using lungs separately ventilated at the same PIO by means of a Carlan’s tube so as to maintain steady-state gradients. The heavier gas steadily ‘pulled’ fluid away from the lighter inert gas.

OXYGEN

A similar steady-state situation arises with the metabolic gases with a permanent gradient of CO₂ ‘pulling’ fluid in the opposite direction to that of O₂. These forces are roughly balanced under normobaric air-breathing with a typical respiratory exchange ratio of 0.8 (see Fig. 2). At least, when applied to the lungs for air breathing under normobaric conditions, there is a slight osmotic gradient pulling water out of the air spaces in helping to resolve any oedema. Upon elevating the PIO, however, the O₂ concentration in the fluid lining to the alveolus increases, increasing the oxygen gradient across the pulmonary membrane without a corresponding change in CO₂, nor one in the PO₂ of venous blood perfusing the lung. Thus, as PIO₂ is elevated, a point is reached at which the net osmotic ‘pull’ induced by the gas gradient changes direction and starts to ‘pull’ fluid into the air spaces. It may be fortuitous, but this switch-over level just happens to coincide with the PIO₂ for the onset of pulmonary oxygen toxicity, which is characterized by increased perivascular filtration and lymph flow.

FIGURE 2. Illustrates the concentration differences of various gases present between arterial blood and tissue and how these can generate osmotic forces for shifting fluid in the directions indicated by the arrows. Note how the net force is negligible during air breathing but is very much greater with HBO and, moreover, acts in the direction needed to resolve oedema.
SOFT TISSUES

If oxygen tension gradients can shift fluid as indicated above, it raises the possibility that they can do the same in traumatized tissue. Arterial blood with a PaO2 of 2 Atmospheres (202 kPa) will now have an appreciable osmotic ‘pull’, especially in the arterioles before the oxygen diffuses into the tissue where its metabolic consumption provides the ‘sink’ for this gas. This large O2 gradient will now ‘pull’ water out of the traumatized tissue, resolving the oedema and restoring blood perfusion. It can be argued that any increase in blood flow is desirable, whether the blood contains a little more oxygen or not.

QUANTITATIVE ASPECTS

The following equation has been derived17 to describe the osmotic gradient (ΔII) in terms of the gradient in gas partial pressure (ΔP) as:

\[ \Delta II/\Delta P = \alpha \sigma (T/273)^3 \]

where \( \alpha \) is the Bunsen coefficient (solubility) of the gas, \( T \) is the absolute temperature and \( \sigma \) is the Staverman reflection coefficient describing the ‘leakiness’ of the membrane to the solute. For large molecules such as albumen, or high-molecular-weight dextran used as an infusion solution in the tissue where its metabolic consumption provides the ‘sink’ for this gas. This large O2 gradient will now ‘pull’ water out of the traumatized tissue, resolving the oedema and restoring blood perfusion. It can be argued that any increase in blood flow is desirable, whether the blood contains a little more oxygen or not.

Hypothesis

The foregoing arguments lead to the hypothesis that a steady-state gradient of oxygen arising between its source in arterial blood and its site of metabolic consumption in tissue can ‘pump’ fluid up the concentration gradient just like any other solute of comparable molecular size. Under normal conditions this osmotic ‘pull’ is approximately balanced by that of CO2 diffusing in the opposite direction. However the O2 gradient pumping water can be greatly increased if the tissue is hypoxic and PaO2 is elevated by the subject breathing oxygen at several atmospheres pressure. Thus, in HBO therapy, oxygen-induced osmosis could be a potent force in resolving the oedema which occurs in soft-tissue injury and break the vicious cycle between hypoxia, ischaemia and oedema at the point of oedema – see Figure 1.

Discussion

The ‘oxygen pump’ offers an intriguing mechanism by which the O2 tension gradients induced by HBO can shift fluid. Moreover, the shift is in the desired direction of resolving the oedema – see Figures 2 and 3 – thus posing the concept that, in soft-tissue injuries, the vicious cycle (Figure 1) is broken at the point of ‘oedema’ rather than ‘hypoxia’ as generally assumed. An increase of 10-fold in the P\textsubscript{O2} and, hence, in the ‘fluid shift’ in switching from air breathing to O2 at 2 ATA (Figure 2) would seem more likely to benefit the tissue than a few percent increase in delivered oxygen before allowing for decreased cardiac output and reflex vasoconstriction.19 Ironically perhaps, the low P\textsubscript{O2} resulting from the tissue hypoxia has a beneficial aspect by increasing the O2 gradient, thus promoting the fluid shift – at least until the circulation is restored and hypoxia resolved by reducing ischaemia.

It could be argued that a membrane rendered ‘leaky’ by injury would also be ‘leaky’ to the oxygen gradient and would therefore compromise the ‘oxygen pump’ proposed above. There are two responses to this criticism. Firstly, injury is unlikely to be homogeneous such that adequate membrane integrity could be maintained to allow the ‘oxygen pump’ to function in some areas whereas colloid has leaked in others. Secondly, it is a moot point whether any membrane is actually needed in the case of a steady-state gas gradient, the injury producing a viscous fluid milieu across which gas gradients will be established as depicted in Figure 3. Osmosis is almost invariably studied by physical chemists in equilibrium situations20 by balancing an osmotic pressure against a hydrostatic pressure. Osmosis is essentially a manifestation of the drive for solutions to become uniform in concentration. Just as diffusion represents the movement of solute molecules to reduce concentration gradients, so osmosis represents the movement of solvent molecules to achieve the same end thermodynamically. This movement would occur whether a membrane is present or not, and so it can be argued that a membrane is only needed when it is necessary to manifest...
an osmotic pressure as a hydrostatic pressure, as occurs in standard equilibrium studies of osmosis. The physical chemistry of osmosis under non-equilibrium conditions more relevant to physiological situations has been discussed in more detail by Hammel & Schölander. If this thermodynamic argument is correct, it would mean that the osmotic gradient induced by HBO could be appreciably larger than the ΔII value of 2.1 mmHg calculated above where the limitation was imposed by the value of σ = 0.05 for a membrane that is very leaky by virtue of the molecular size of the solute (O2). Any opposing effect of nitrogen will be transient, lasting only until that gas is washed out; while any resulting drop in efficacy will be reversed, and the benefit recouped as the N2 re-enters tissue upon return to air breathing.

The ‘oxygen pump’ mechanism expounded above does not exclude the conventional assumption that HBO simply delivers more O2 to resolve the hypoxia. Both will act together to resolve the problem. However the ‘oxygen pump’ also offers an explanation for the failure of HBO in non-hypoxic situations, such as hyperbaric radiotherapy and its effectiveness in resolving air embolism and decompression sickness where a rise of PO2 reciprocating the fall in PN2 at the bubble site would defeat the object of the exercise. Hence the osmotic induction of fluid shifts by HBO could offer a simple physiological mechanism by which to reconcile the efficacy of HBO in hypoxic situations with earlier experience of this modality and, hopefully, one that will persuade other ‘disbelievers’ like myself to return to the fold.

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Professor Brian A Hills, PhD, is Director of the Paediatric Respiratory Research Centre at the Mater Children’s Hospital, Brisbane.

Address for correspondence:
Paediatric Respiratory Research Centre, Mater Children’s Hospital, Brisbane, WA 4104, Australia
E-mail: <bhills@mmri.mater.org.au>

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