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Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

journal homepage: www.elsevier.com/locate/colsurfb

Osmotic phenomena in application for hyperbaric oxygen treatment

A. Babchin^a, E. Levich^a, Y. Melamed M.D.^b, G. Sivashinsky^{a,*}^a Tel Aviv University, Tel Aviv 69978, Israel^b Hyperbaric Medical Center, Elisha and Rambam Hospitals, Haifa 34636, Israel

ARTICLE INFO

Article history:

Received 1 October 2010

Received in revised form 5 November 2010

Accepted 8 November 2010

Available online 18 November 2010

Key words:

Hyperbaric oxygen treatment

Non-electrolyte osmosis

Capillary osmosis

Normal osmosis

Anomalous osmosis

Osmosis and biophysics

Osmosis in human body

ABSTRACT

Hyperbaric oxygen (HBO) treatment defines the medical procedure when the patient inhales pure oxygen at elevated pressure conditions. Many diseases and all injuries are associated with a lack of oxygen in tissues, known as hypoxia. HBO provides an effective method for fast oxygen delivery in medical practice. The exact mechanism of the oxygen transport under HBO conditions is not fully identified. The objective of this article is to extend the colloid and surface science basis for the oxygen transport in HBO conditions beyond the molecular diffusion transport mechanism. At a pressure in the hyperbaric chamber of two atmospheres, the partial pressure of oxygen in the blood plasma increases 10 times. The sharp increase of oxygen concentration in the blood plasma creates a considerable concentration gradient between the oxygen dissolved in the plasma and in the tissue. The concentration gradient of oxygen as a non-electrolyte solute causes an osmotic flow of blood plasma with dissolved oxygen. In other words, the molecular diffusion transport of oxygen is supplemented by the convective diffusion raised due to the osmotic flow, accelerating the oxygen delivery from blood to tissue. A non steady state equation for non-electrolyte osmosis is solved asymptotically. The solution clearly demonstrates two modes of osmotic flow: normal osmosis, directed from lower to higher solute concentrations, and anomalous osmosis, directed from higher to lower solute concentrations. The fast delivery of oxygen from blood to tissue is explained on the basis of the strong molecular interaction between the oxygen and the tissue, causing an influx of oxygen into the tissue by convective diffusion in the anomalous osmosis process. The transport of the second gas, nitrogen, dissolved in the blood plasma, is also taken into the consideration. As the patient does not inhale nitrogen during HBO treatment, but exhales it along with oxygen and carbon dioxide, the concentration of nitrogen in blood plasma drops and the nitrogen concentration gradient becomes directed from blood to tissue. On the assumption of weak interaction between the inert nitrogen and the human tissue, normal osmosis for the nitrogen transport takes place. Thus, the directions of anomalous osmotic flow caused by the oxygen concentration gradient coincide with the directions of normal osmotic flow, caused by the nitrogen concentration gradient. This leads to the conclusion that the presence of nitrogen in the human body promotes the oxygen delivery under HBO conditions, rendering the overall success of the hyperbaric oxygen treatment procedure.

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1. Introduction

Osmotic phenomena's relevance for the oxygen transport in Hyperbaric Oxygen treatment was clearly emphasized by Hills [1]. The intent of this article is to quantify this effect for a non-steady state problem and express results using a conventional colloids and surfaces science approach. As this paper is interdisciplinary the necessary information for understanding of hyperbaric oxygen treatment is provided in the Introduction, which will be followed by the solution for the osmotic problem and discussion of its biophysical application.

The administration of oxygen is not generally viewed as a treatment although it is obvious that many diseases and all injuries are associated with a lack of oxygen in tissues known as hypoxia. There is also good evidence that a restriction of oxygen availability in the tissues may inhibit or even prevent recovery and this applies to tissues as diverse as bone and brain. The role of oxygen in metabolism is beyond question [2], but research has now shown that oxygen is also critical to the regulation of at least 30 genes [3].

The body normally responds to hypoxia, for example that induced by exercise, by increasing the volume of blood flow through the tissue but this may not be possible when, for example, an artery is blocked or when an increase in tissue water compresses the capillaries of the microcirculation. In the latter condition it is necessary to increase the gradient for oxygen transport to tissue

* Corresponding author.

E-mail address: grishas@post.tau.ac.il (G. Sivashinsky).

by raising the inspired partial pressure of the gas. This is a function of the percentage of oxygen respired and the ambient atmospheric pressure.

The range of atmospheric pressures inhabited by Man varies from 800 mm Hg at the Dead Sea in Israel, to 475 mm Hg in La Paz in Bolivia. It has been shown that patients with lung disease benefit from visiting the Dead Sea [4] and it is common knowledge that patients heal more slowly at high altitudes [5]. Sea level pressure is normally 760 mm, but weather systems change sea level pressure by more than 10% and, as this determines the inspired partial pressure of oxygen, it too will have a modest influence on recovery from disease and injury.

The maximum oxygen tension possible when breathing air at 760 mm Hg is less than 160 mm Hg (21%) because of the presence of water vapor and mixing with the exhaled carbon dioxide. However, there is a second reason for a reduced tension; areas of the lung which are ventilated may not receive the optimum blood flow. This is known as the ventilation-perfusion mismatch. The normal dissolved oxygen tension at sea level of about 100 mm Hg is, nevertheless, capable of ensuring that the four sites for oxygen binding on the hemoglobin molecule are occupied resulting in about 19 ml of oxygen per 100 ml of blood being transported. Because this parameter can be easily measured so-called hemoglobin 'saturation' has become a clinical endpoint. However the oxygen must be dissociated from hemoglobin to be available for transport from blood to the tissues and it is the level of oxygen available to tissue that is critical [6].

Although the bulk of oxygen is transported by hemoglobin, the sole determinant of the transport of oxygen to the tissues is the concentration of oxygen dissolved in plasma. Because of the poor solubility of oxygen in plasma, which is close to the value for sea water, only 0.35 ml of oxygen is transported in a solution per 100 ml of blood. This value, however, can be increased linearly by increasing both the inspired oxygen percentage and the ambient pressure. Breathing 100% at three times atmospheric pressure (three atmospheres absolute, 3 ATA) sufficient oxygen is transported in the solution to meet the resting needs of the body and hemoglobin oxygen transported is not required [7]. To allow the pressure surrounding a patient to be increased an enclosure, known as a hyperbaric chamber, is needed, hence the term 'hyperbaric' oxygen treatment [8]. There is wealth of clinical evidence demonstrating that hyperbaric oxygen treatment can improve recovery in a wide variety of conditions but the physical effects of an abrupt change of ambient pressure have not been fully explored.

The first effect of an increase in the dissolved oxygen content of blood is an increase in the concentration gradient for the transport of oxygen into tissues. Oxygen will dissolve in the cells of the capillary wall and then transfer via the interstitial fluid dissolving through the cell membrane to finally reach the internal mitochondria. This is by far the most important mechanism for oxygen transport. However the volume of interstitial fluid is often increased in pathological conditions and it is important to rate limit the loss of fluid from blood into tissues. This is dependent on capillary permeability and an increased oxygen tension reduces cardiac output and blood flow. So, paradoxically, breathing oxygen under increased partial pressure of oxygen can simultaneously reduce blood flow whilst increasing the concentration gradient for the transport of oxygen to tissues. This mechanism is of unique importance in those conditions where hypoxia is due to microcirculatory closure due to an increase in the tissue water content. Another mechanism which requires experimental validation relates to osmotic forces created by the abrupt change of gas concentrations in plasma. Osmotic pressure causes convective diffusion transport in addition to the molecular transport of oxygen.

2. Normal and anomalous osmosis through a leaking membrane

Kylstra et al. [9] provided an experimental example of the osmotic pressure and flow through leaking membrane induced by concentration gradient of a gas (nitrous oxide) dissolved in water. For accuracy we cite the original authors: 'The pressure in an osmometer filled with nitrous oxide-saturated water separated from water by a polyurethane polyether membrane 2.5 μm in thickness, rose slowly by 8–20 mm (of water) in 10 min before gradually returning to close to zero within 2 h.' 'It is concluded that dissolved gases exert osmotic pressure. Partial pressure gradients of dissolved gases in the tissues of animals and man should cause flows of water along osmotic gradients, which may partially account for some of the symptoms and signs of dysbarism.'

The provided description of experimental results indicates two time scales of osmotic flow and solute transport through porous membrane:

- (1) Short time osmotic flow of the solvent with correspondent convective solute transfer, and,
- (2) Long time molecular diffusion of solute leading to the equilibrium state.

Interpreting the observed data in the language of physicochemical hydrodynamics [10], a standard equation of convective diffusion quantifies the solute flux within porous membrane:

$$J = vC - D \left(\frac{dC}{dx} \right) \quad (1)$$

where J is the molar flux of the solute (mol/s cm^2), C is the solute concentration, D is the solute diffusion coefficient inside porous membrane, x is the coordinate in the direction normal to the membrane surface.

The averaged velocity v of the liquid within the porous membrane is expressed by Darcy law:

$$v = \left(\frac{K}{\mu} \right) \left(\frac{\Delta P_{\text{osm}} - \rho g H}{L} \right) \quad (2)$$

K denotes the membrane's absolute permeability to the hydrodynamic flow, μ is the viscosity of liquid, ΔP_{osm} is the difference in osmotic pressures between two sides of membrane, L is membrane width, ρ is the fluid density, g is the gravity acceleration constant and H is the height of hydrostatic column caused by osmotic pressure and observed as the difference in the position of the liquid-gas surfaces in compartments separated by the membrane. Evidently, the osmotic pressure and the gravity head, induced by hydrostatic column, act in opposite directions.

It should be noted, that the origin of osmotic pressure exerted by leaking (capillary) membranes in the case of non-electrolyte solute is due to the long range molecular forces and was first explained by Derjaguin et al. [11]. This subject was further developed by Derjaguin, Dukhin, Churaev with co-workers in numerous publications [12–16]. Osmotic pressure for a non-electrolyte solution (oxygen dissolved in water is an example) can be determined locally in the

vicinity of solid surface as follows [12,13]:

$$P_{\text{osm}}(z) = RT[C(z) - C_0] \quad (3)$$

where $C(z)$ is the solute concentration within the diffuse adsorption layer and C_0 (mol/cm³) is the bulk solute concentration beyond the adsorption layer, R is gaseous constant and T is absolute temperature. In the case of dilute solutions, the concentration of solute molecules in the field of long range molecular forces is expressed by the Boltzmann distribution:

$$C(z) = C_0 \exp\left[\frac{-U(z)}{kT}\right] \quad (4)$$

Here k is the Boltzmann constant, and $U(z)$ is the energy of a solute molecule at the distance z from the solid surface. The value of $U(z)$ is negative if a solute molecule experiences attraction to the surface. In this case the concentration of solute molecules near solid–liquid interface exceeds their concentration in the bulk of the solution. However, if the solid surface repels solute molecules the value of $U(z)$ is positive, rendering the concentration deficit of the solute near the solid surface or within porous body. In the case of high specific surface of porous media, which corresponds to small pore sizes, the diffuse adsorption (desorption) layers overlap. With strongly overlapping diffuse molecular layers the difference between the energies of solute molecules within this layer can be assumed much smaller than the characteristic value U^* of solute molecules near the interface. This approximation was initially applied for the description of osmotic flow in electrolyte solutions by Babchin and Frenkel [17]. Incorporation of the characteristic value of molecular interactions U^* , allows rewriting Eq. (4) as:

$$C^* = C_0 \exp\left(\frac{-U^*}{kT}\right) \quad (5)$$

Combining Eqs. (3) and (5) results in the following relation for the osmotic pressure:

$$P_{\text{osm}}^* = RT C_0 \left[\exp\left(\frac{-U^*}{kT}\right) - 1 \right] \quad (6)$$

In the case of small molecular energies $U^*/kT \ll 1$, Eq. (6) becomes:

$$P_{\text{osm}}^* = RT C_0 \left(\frac{-U^*}{kT}\right) \quad (7)$$

Having two values of bulk concentration, one in each compartment, separated by a membrane, the osmotic pressure difference driving the fluid through membrane may be written as:

$$\Delta P_{\text{osm}}^* = RT(C_0' - C_0'') \left(\frac{-U^*}{kT}\right) \quad (8)$$

C_0' and C_0'' denote the solute bulk concentrations on each side of the membrane. With Eqs. (2) and (8) taken into account, the Darcy velocity ν within porous membrane reads:

$$\nu = \left(\frac{K}{\mu L}\right) \left[RT(C_0'' - C_0') \left(\frac{U^*}{kT}\right) - \rho g H \right] \quad (9)$$

Guided by the experimental data, provided by Kylstra et al. [9], it is assumed that commencement of the osmotic transport process is dominated by the convective term. The solvent flows from the low concentration to the higher solute concentration compartment. The volume conservation requirement for incompressible fluid allows expression of the rate of change in the observed hydrostatic column in terms of the Darcy velocity as:

$$\frac{dH}{dt} = B_1 \nu \quad (10)$$

where B_1 is the dimensionless constant, determined by the osmotic cell geometry. With ν determined by Eq. (9), the following dif-

ferential equation describes $H(t)$ behavior at the beginning of the process:

$$\frac{dH}{dt} = \frac{B_1 K}{\mu L} \left[RT(C_0'' - C_0') \left(\frac{U^*}{kT}\right) - \rho g H \right] \quad (11)$$

Considering the concentration difference as a constant at the beginning of the process, the solution of Eq. (11) can be represented as:

$$H(t) = \frac{K_2}{K_1} \left[1 - \exp\left(\frac{K_1 t}{L}\right) \right] \quad (12)$$

where $K_1 = \rho g B_1 K / \mu > 0$, $K_2 = (B_1 K / \mu)(U^*/kT)(C_0'' - C_0')$.

The hydrostatic column $H(t)$ marks the difference between liquid levels in the compartment with higher concentration of the solute C'' and in the compartment with the lower solute concentration C' . The case of normal osmosis assumes the fluid flow through porous membrane to be directed from lower to higher solute concentration. Under these conditions the values of $H(t)$ should be positive. The coefficient K_1 in Eq. (12) is always a positive constant. Thus, the direction of flow depends on the sign of K_2 . With $(C'' - C') > 0$, the effect of normal osmosis will take place and will be observed at $U^* > 0$. Positive energies of the solute molecules near the membrane surfaces signify that these molecules experience repulsion in the vicinity of the membrane material. On the contrary, when membrane material surfaces attract solute molecules, their energy $U^* < 0$, the coefficient K_2 becomes negative, rendering a negative sign for the hydrostatic column $H(t)$. Experimental observation will exhibit the depression of the liquid level in the compartment with higher concentration C'' of the solute and elevation of the liquid level in the compartment with lower solute concentration C' . Observation of this kind leads to the irrefutable conclusion that osmotic flow is directed from the higher to lower solute concentration values and is directed opposite to the solute concentration gradient. Since the direction of flow in this case is opposite to one in normal osmosis this phenomenon is historically called anomalous osmosis. There is nothing anomalous in the attraction of the solute molecules to interfaces and the terminology is rather archaic, having its root in times when only semi permeable membranes were tested for osmotic phenomena. Experimentally the anomalous osmosis in leaking membranes was observed long before theoretical explanations [18].

The fast process of solution transport by convection, caused by osmotic pressure gradient, recedes in time when the hydrostatic column reaches its maximum. At this time moment osmotic flow is opposed by a counter flow caused by gravity head, so that the actual total flow of liquid through the membrane is zero. The solute transport experiences reversal (in the case of normal osmosis) since it is governed by slow molecular diffusion and directed from higher to lower solute concentration. The time dependent molecular flux of the solute at this stage can be expressed as:

$$J(t) = \frac{-D[C''(t) - C'(t)]}{L} \quad (13)$$

where D is the diffusion coefficient of the solute within porous membrane. At the first approximation D may be expressed (accounting for the porosity (ϕ) and tortuosity (τ) of porous membrane), as $D = (\phi/\tau)D_{\text{bulk}}$.

As transport of the solvent through the membrane is much faster than one of the solute, the relaxation of $H(t)$ to zero will be controlled by the molecular diffusion of the solute. As the concentration difference between compartments decreases, the column $H(t)$ decreases as well. The osmotic pressure, which characterizes $H(t)$, will experience the consequence of steady states controlled by a concentration difference at a given moment of time. Thus, only the molecular flux, described by Eq. (13) along with initial concentrations and cell geometry affect the characteristic time of

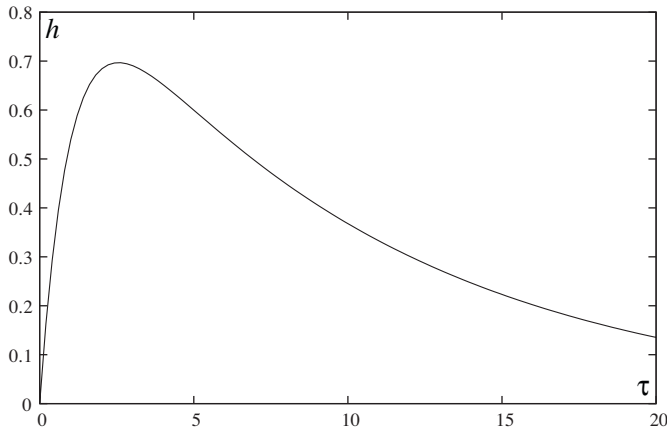


Fig. 1. Temporal evolution of the hydrostatic column height (scaled).

relaxation process. Considering osmotic cell as having two equal compartments, each of volume V , the equation for the solute mass conservation becomes:

$$\frac{Vd(C'' - C')}{dt} = AJ(t) = \frac{-AD(C'' - C')}{L} \quad (14)$$

and

$$\frac{d(C'' - C')}{(C'' - C')} = -\frac{AD}{VL} dt \quad (15)$$

where A is the membrane area separating two compartments. The initial condition for Eq. (15) is: $C'' - C' = C''_0 - C'_0$, which yields the solution:

$$C''(t) - C'(t) = (C''_0 - C'_0) \exp\left(\frac{-ADt}{LV}\right) \quad (16)$$

In the discussed consequence of steady states Eq. (8) can be extended to the time dependent expression for the osmotic pressure difference:

$$\Delta P_{osm}^*(t) = RT \left(\frac{U^*}{kT}\right) [C''(t) - C'(t)], \quad (17)$$

which determines the momentary value of the gravity head $\rho gH(t)$. Thus,

$$H(t) = \frac{RTU^*}{\rho gkT} (C''_0 - C'_0) \exp\left(\frac{-ADt}{LV}\right) \quad (18)$$

The time dependent solution for the experimentally observed hydrostatic column during the overall process time may be represented by asymptotic matching of Eqs. (12) and (18).

The matching can be performed through the conventional procedure [19], provided that the typical time-scale L/K_1 of Eq. (12) is much smaller than the time-scale LV/AD of Eq. (18). In this case the long-time limit of $H(t)$ governed by Eq. (12) should coincide with the short-time limit of $H(t)$ governed by Eq. (18). Hence,

$$\frac{K_2}{K_1} = \frac{RTU^*}{\rho gkT} (C''_0 - C'_0) = Q = \frac{N_{av}U^*}{\rho g} (C''_0 - C'_0), \quad (19)$$

where N_{av} is the Avogadro number.

The expression for $H(t)$, uniformly valid over the entire time interval, then reads:

$$\begin{aligned} H(t) &= \text{short-time } H(t) + \text{long-time } H(t) - Q \\ &= Q \left[\exp\left(\frac{-ADt}{LV}\right) - \exp\left(\frac{-K_1 t}{L}\right) \right] \end{aligned} \quad (20)$$

Fig. 1 plots the scaled height $h = H/Q$ versus scaled time $\tau = K_1 t/L$ at $AD/VK_1 = 0.1$. Combining Eqs. (19) and (20), the final result for

$H(t)$ as a measurement of time dependent osmotic pressure reads:

$$H(t) = \frac{N_{av}U^*}{\rho g} (C''_0 - C'_0) \left[\exp\left(\frac{-ADt}{LV}\right) - \exp\left(\frac{-K_1 t}{L}\right) \right] \quad (21)$$

As a conclusion to this physicochemical part of the paper, it should be noted that similarity with normal and anomalous osmosis can be found in the diffusiophoreses, the phenomenon reciprocal to the capillary osmosis. This similarity is well explained by Anderson et al. [20]: 'When a particle is placed in a fluid in which there is a non-uniform concentration of solute, it will move toward higher or lower concentration depending on whether the solute is attracted to or repelled from the particle surface.'

Numerical example: at the oxygen concentration difference in blood plasma and tissue of $60 \text{ mg/L} = 2.10(-6) \text{ mol/cm}^3$, and assuming rather strong molecular interaction between the oxygen and tissue with $U^* = -0.5(kT)$, the resulting osmotic pressure, calculated from Eq. (21) at maximum $H(t)$ comes to 24 cm of water column. This value drops to about 5 cm at $U^* = -0.1 kT$.

3. Discussion

The transport of oxygen from capillary blood to surrounding tissue has been the subject of considerable analysis, dating from the Krogh tissue cylinder model [21]. We too begin with the Krogh model, where each blood capillary nourishes a surrounding co-axial cylinder of tissue. The radius of the tissue cylinder is obviously larger than the radius of the blood capillary. Within the Krogh model the oxygen transport is considered as a molecular diffusion from the blood into the tissue. As the walls of blood capillaries constitute membrane, permeable for H_2O , O_2 and N_2 , but blocking red cells and plasma proteins from entering the tissue, only the oxygen dissolved in plasma is capable to penetrate from blood to tissue.

Hemoglobin acts as the oxygen storage, supplying plasma with oxygen and supporting oxygen concentration in plasma accordingly to the Henry law. At ambient conditions the concentration of O_2 in plasma should be expected to be about the same as concentrations of O_2 in sea water at equilibrium with air at 35°C . This value is tabulated and equal to 6 mg/L . At hyperbaric treatment conditions with pressure 2 ATA and with pure oxygen inhalation, the Henry law provides the value of oxygen concentration in blood plasma equal to 60 mg/L . This number is very close to the tabulated value of sea water in equilibrium with oxygen at 2 ATA. Thus, after pressurisation in a hyperbaric chamber the blood plasma in the capillary and in the tissue cylinder are in non-equilibrium state in respect to O_2 concentration. Not only will the molecular flux from blood to tissue through the wall membrane, but the osmotic flow also cause the transport of oxygen. The process kinetics was demonstrated by the model experiments provided by Kylstra et al. [9] and supported by original calculations for time dependent and essentially non-steady state osmotic flow and transport, presented for the first time in this paper. At this point the direction of the osmotic flow should be indicated. As human tissue tends to adsorb and even to react chemically with oxygen, the molecular energy of oxygen is at a lower level within the tissue in respect to the energy level in blood plasma. As a consequence, all theoretical conditions are satisfied for anomalous osmosis, causing flow from higher oxygen concentration to the lower one, or from blood capillary into the tissue. Certain amounts of oxygen enriched plasma will temporarily enter the tissue and assist in the healing process. As tissue is elastic in nature, the influx of oxygen enriched plasma will be compensated by counter flow raised by pressure in plasma due to elasticity. From this point on, the molecular diffusion controls the oxygen transport and the osmotic pressure. Essentially it is similar to model experiments, with elastic forces acting instead of gravity head, as gravity is not a factor in this biophysical problem.

The longer the treatment session in a hyperbaric chamber, the smaller is becomes the difference in the oxygen concentration between blood and tissue. However, the transport effect is initially stronger, so the final time should be determined by other causes, medical in nature. It should be noted at this point, that the strong interaction between oxygen and tissue renders the direction of osmotic flow from higher to lower oxygen concentration, namely from blood to tissue. Were it otherwise, the flow direction from tissue to blood would oppose and prevent the oxygen transport from blood to tissue. The temporarily small additional swelling of tissue by plasma will begin to relax after osmotic pressure reaches its maximum, which is on the time scale of 10 min in the model experiments. When the chamber is depressurised and pure oxygen inhaling is terminated, the oxygen concentration in the blood drops to the ambient level in a matter of minutes. Then again the system finds itself in a state far from equilibrium. This time the oxygen concentration in tissue exceeds the equilibrium level. As the process is reversed, the osmotic flow will be directed from the tissue into the blood capillary. The drainage process will be assisted by forces of elasticity and no traces of additional swelling will be found. Here we can only hypothesize: the hyperbaric treatment session will contribute to restoration of elasticity of the initially damaged tissue. If this statement is correct, the amount of the liquid drained from the damaged tissue will exceed the volume of plasma which initially entered the tissue. The net effect observed is contraction of the swelling. On the assumption that the damaged tissue elasticity is being restored whilst breathing oxygen, the swelling reduces coherently. The scenario presented here will not be complete, unless another component of air, namely nitrogen N_2 , initially present in blood plasma and tissue as the second solute is examined for its impact on the oxygen O_2 transport. At the start of hyperbaric treatment the patient inhales pure oxygen and exhales N_2 along with O_2 and CO_2 . No new intake of nitrogen follows during the treatment in the hyperbaric chamber until the end of the session. This leads to the fast loss of N_2 , initially dissolved in the blood. This process proceeds simultaneously and with a similar rate as the blood plasma saturation with additional oxygen. In comparison with O_2 , nitrogen is an inert gas, not chemically interacting with the tissue. This means that conditions for normal osmosis caused by N_2 as a solute in blood plasma are satisfied. As nitrogen concentration in the blood plasma becomes lower than its concentration in the tissue, the normal osmosis will cause an additional inflow of plasma into the tissue (from lower to higher concentration of N_2). Thus, the direction of osmotic flow caused by anomalous osmosis due to oxygen coincides with the direction of normal osmosis due to nitrogen concentration gradient. Both components of osmotic flow are directed from blood to tissue. Therefore the presence of N_2 enhances the rate of O_2 transport. At the end of the hyperbaric treatment session, depressurization and air inhalation will reverse boundary conditions for osmosis and flow will be directed from tissue into the blood stream, draining plasma from the tissue.

The presented mechanism for oxygen transport during hyperbaric treatment is based on solid physical-chemical grounds.

Osmotic phenomena in leaking (sometime called capillary) membranes constitute a very fine chapter in Colloid and Surface Chemistry.

4. Conclusion

Motivated by the problem of oxygen physiology under elevated pressure conditions, a time-dependent model for capillary osmosis is formulated and analyzed. Using an increase in ambient pressure with an increase in the inspired oxygen fraction to improve oxygen transport to diseased or injured tissue is fully supported by the physico-chemical and biophysical explanations presented here. However, it is recognized that these are not complete and the role of osmotic mechanisms should be the subject of further research.

Acknowledgements

The authors wish most profoundly to thank Philip James, M.D., for sharing his knowledge and his thoughts on the problem.

These studies were supported in part by the Israel Science Foundation (Grant 32/09).

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