INHERENT UNSATURATION. THE RISK OF CENTRAL NERVOUS SYSTEM OXYGEN TOXICITY PART 1

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ABSTRACT

The pressures of inert gases in the tissues of a human organism are in a state of dynamic balance with air components being subject to the atmospheric pressure. However, there are differences between dynamic oxygen pressures in arterial vessels, venous vessels and the tissues. This phenomenon is commonly referred to as inherent unsaturation of an oxygen window.
The article is an introduction to a theory underlying estimations concerned with central nervous system oxygen toxicity, which will be described in a subsequent part.
Key words: inherent unsaturation, central nervous system oxygen toxicity.

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OXYGEN WINDOW

A significant part of oxygen is transitioned from the lungs into the circulatory system; however, only its small part is subject to metabolic reactions. The part that enters into metabolic reactions[1] thus reducing the pressure of oxygen[2] diluted in the blood is known as an *oxygen window*[3]. The comparison of the pressures of gases present, in venous and arterial circulation, shows that the total pressure gap in regular conditions reaches the level of $8–13\%$ [1]. The factors mainly responsible for a reduction in the pressure of gases in an organism are the oxygen reactions leading to the production of water, which is present in such conditions not only as vapour but also in a condensed form[4]. The oxygen moves from arterial blood to tissues where it is used, leaving behind the already mentioned pressure gap. When breathing with air at atmospheric pressure, the oxygen partial pressure in arterial blood amounts to approx. $\pi_{O_2} \cong 100\ mmHg$. During the blood's circulation, the level of oxygen pressure is reduced, reaching in venous capillaries ca. $\pi'_{O_2} \cong 40\ mmHg$[5] – tab.1.

When using oxygen as a breathing mix, the pressure gap $\Delta\pi$ may be increased in the final decompression phase, thus causing shortening of the decompression time, as oxygen will wash inert gases out of the tissues, i.e. from the place where it is relatively quickly metabolised.

Tab. 1

Partial pressures of respiratory gases [2].

	Partial pressure of a gas [$mmHg$]					
Gas type	Inhaled air	Alveolar air	Arterial blood	Tissues	Venous blood	Exhaled air
Oxygen	158.0	100.0	95.0	40.0	40.0	116.0
Carbon dioxide	0.3	40.0	40.0	46.0	46.0	32.0
Nitrogen	596.0	573.0	573.0	573.0	573.0	565.0
Water vapour	5.7	47.0	47.0	47.0	47.0	47.0

MYOGLOBIN AND HAEMOGLOBIN

The recognition of the spatial structure of two proteins: myoglobin and haemoglobin constituted an important discovery in the field of biochemistry. The main function of myoglobin consists in storing oxygen in striated muscles[6], whereas haemoglobin is responsible for both oxygen storage as well as its transportation in the blood. Oxygen storage by myoglobin Mb is well depicted with a mathematical model regarding the kinetics of enzymatic reactions proposed by *Leonor Michaelis* and *Maud*

[1] biochemical transformations with accompanying energy transformations occurring in the cells of living organisms and providing the basis for all biological phenomena,
[2] thus creating a pressure gap,
[3] commonly the value of CO_2 pressure is subtracted from the oxygen window value, whereas the pressure of water vapour is omitted as it is concerned as a constant value,
[4] liquid or bounded,
[5] the oxygen window will reach ca. $\Delta\pi \cong 60\ mmHg$ and will be available for the transportation of inert gases,
[6] myoglobin creates a peculiar oxygen storage used in muscle contractions; in particular in the presence of the so-called oxygen debt, diving animals reveal increased levels of myoglobin,

Menten. Its algebraic formula is known as the *Michaelis–Menten equation*. The process of oxygen storage occurs with an indirect phase of production of a complex of myoglobin and oxygen MbO_2, which is followed by a release of oxygen into tissues, O_2^* , with the reconstruction of myoglobin molecule Mb:

$$Mb + O_2 \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} MbO_2 \xrightarrow{k_2} Mb + O_2^* \quad (1)$$

The existence of a transition state[7] is indicated by the fact of Mb saturation in the presence of high O_2 pressure[8] resulting from its filling of all the active places within the structure,

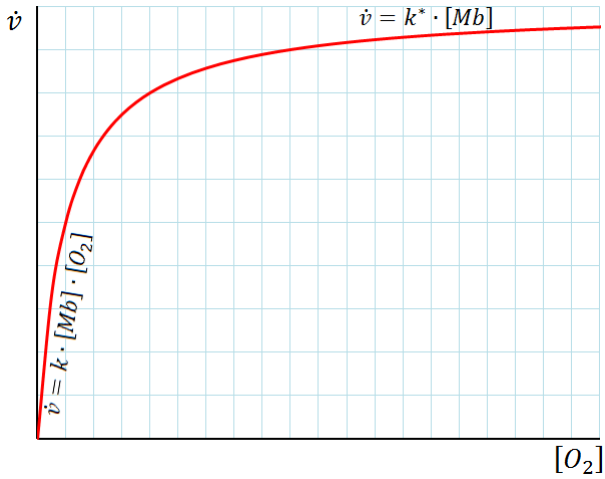

Fig. 1. Interrelation between the speed of dissociation $\dot{v}$ in the myoglobin–oxygen complex and oxygen concentration. $[O_2]$.

of Mb[9] – fig.1. In such a case, more MbO_2 complexes may be produced only after the disintegration of the existing ones. The existence of the MbO_2 complex has also been proven with other methods [3].

Further considerations allowed us to indicate the concentrations of particular chemical compounds in brackets: $[Mb]$ – myoglobin concentration, $[O_2]$ – oxygen conentration, $[MbO_2]$ –myoglobin-oxygen complex concentration.

In the *Michaelis–Menten* model presented in fig. 1 we may see that in the initial phase, with low oxygen concentrations $[O_2]$ –, the reaction rate $\dot{v}$ is proportional to the concentration of both myoglobin $[Mb]$ and oxygen $[O_2]$ –: $\dot{v} = k \cdot [Mb] \cdot [O_2]$, where: k is a reaction constant $[dm^6 \cdot mol^{-1} \cdot s^{-1}]$. With higher oxygen concentrations $[O_2]$, due to its excess, the reaction rate $\dot{v}$ begins to be entirely dependent on myoglobin concentration $[Mb]$: $\dot{v} = k^* \cdot [Mb]$,, where k^* is a constant for the maximum reaction rate $[dm^3 \cdot s^{-1}]$.

In accordance with the assumptions behind the model (1), after the reaction resulting in the formation of MbO_2 complex, it is disintegrated and oxygen is passed on to tissues O_2^* and the myoglobin molecule Mb is reconstructed. The rates of particular

[7] in the form of MbO_2 complex,

[8] this means that during the initial increase in O_2 pressure, binding of O_2 by Mb into the complex MbO_2 is accelerated; however, after exceeding a certain pressure limit, further increase of O_2 pressure does not cause a proceeding acceleration in forming MbO_2 complex,

[9] at this point the reaction rate $\dot{v}$ in the formation of MbO_2complex depends only on myoglobin concentration Mb: $\dot{v} = k \cdot [Mb]$,

reactions $\dot{v}$ for the chemical reaction (1) may be expressed as: $\dot{v}_1 = k_1 \cdot [Mb] \cdot [O_2]$, $\dot{v}_1' = k_1' \cdot [MbO_2]$ and $\dot{v}_2 = k_2 \cdot [MbO_2] Ks$ indicate reaction rate constants in accordance with previously adopted markings for the summary chemical reaction (1). Summary rate of myoglobin binding may be represented as: $-\frac{\partial [Mb]}{\partial t} = \dot{v}_1 - \dot{v}_1' = k_1 \cdot [Mb] \cdot [O_2] - k_1' \cdot [MbO_2]$

where t stands for time. According to (1) the speed of oxygen's passage to tissue cells is equal to: $\dot{v}_2 = k_2 \cdot [MbO_2]$, hence the rates in the concentration changes of the complex $[MbO_2]$ may be expressed as:

$-\frac{\partial [MbO_2]}{\partial t} = \dot{v}_1 - \dot{v}_1' - \dot{v}_2 = k_1 \cdot [Mb] \cdot [O_2] - k_1' \cdot [MbO_2] - k_2 \cdot [MbO_2]$.

In a steady state, the rate of changes in the concentration of the complex $[MbO_2]$ will be equal to zero $-\frac{\partial [MbO_2]}{\partial t} = 0$, whereas the summary content of myoglobin $[Mb]_0$ in a steady system will be the sum of concentrations of the bound form of $[MbO_2]$ and the free form $[Mb]$: $[Mb]_0 = [MbO_2] + [Mb]$. Using these calculations it is possible to express the concentration of the complex $[MbO_2]$ as follows:

(2)

$$[MbO_2] = \frac{k_1 \cdot [O_2]}{k_2 + k_1' + k_1 \cdot [O_2]} \cdot [Mb]_0$$

where: $[MbO_2]$ – concentration of oxygenated myoglobin $[mol \cdot dm^{-3}]$, $[Mb]_0$ – total concentration of myoglobin in the bound and free form, jointly $[mol \cdot dm^{-3}]$, $[O_2]$ – oxygen concentration $[mol \cdot dm^{-3}]$, k_1 – reaction rate connected with the formation of the bound form of myoglobin MbO_2 $[dm^6 \cdot mol^{-1} \cdot s^{-1}]$, k_1' – disintegration rate of bound myoglobin MbO_2 $[dm^3 \cdot s^{-1}]$, k_2 – rate of oxygen's passage to tissue cells by bound myoglobin MbO_2 $[dm^3]$.

When we insert equation (2) into the relation defining the rate of oxygen's passage into tissues: $\dot{v}_2 = k_2 \cdot [MbO_2]$, it will be possible to obtain an algebraic model of the rate of reaction of oxygen release by myoglobin:

$$\dot{v}_2 = \dot{v} = \frac{k_1 \cdot k_2 \cdot [O_2]}{k_2 + k_1' + k_1 \cdot [O_2]} \cdot [Mb]_0.$$

After the division of the numerator and the denominator by $k_1 \cdot [O_2]$ and substitution of $K_M = \frac{k_2 + k_1'}{k_1}$, we may write it down as: $\dot{v}_2 = \dot{v} = \{k_2 \cdot [Mb]_0\} : \{\frac{K_M}{[O_2]} + 1\}$. K_M is called the *Michaelis constant*[10]. When the K_M value is significantly lower than oxygen concentration $[O_2] \gg K_M$, then the fraction $\frac{K_M}{[O_2]}$ will aim towards zero and the reaction rate $\dot{v}_2$ will reach the maximum value of: $\dot{v}_{max} = k_2 \cdot [Mb]_0$, since the entire myoglobin will be bounded into a complex with oxygen MbO_2. Hence, the *Michaelis–Menten equation* applied in modelling the process of oxygen release by Mb will be expressed as:

$$\exists_{[O_2] \gg K_M} \quad \dot{v} = \frac{\dot{v}_{max}}{\frac{K_M}{[O_2]} + 1} \quad \Rightarrow \quad \frac{\dot{v}}{\dot{v}_{max}} = \frac{[O_2]}{K_M + [O_2]} \tag{3}$$

[10] as it will be shown later, *the Michaelis constant* stands for such an oxygen concentration with which the reaction rate of oxygen binding $\dot{v}$ is equal to half the maximum rate $\dot{v} = 0.5 \cdot \dot{v}_{max}$ – with the affinity for oxygen P_{50},

where: $\dot{v}$ — oxygen passage rate $[mol \cdot s^{-2}]$, $\dot{v}_{max}$ – maximum oxygen passage rate $[mol \cdot s^{-2}]$, $[O_2]$ – oxygen concentration $[mol \cdot dm^{-3}]$, K_M – *Michaelis constant* $[mol \cdot dm^{-3}]$.

AFFINITY FOR OXYGEN AND SATURATION LEVEL

The level of myoglobin saturation with oxygen x_{O_2} may be defined as a ratio of the concentration of the complex $[MbO_2]$ to the total myoglobin concentration $[Mb]_0 = [MbO_2] + [Mb]$: $x_{O_2} = \frac{[MbO_2]}{[MbO_2]+[Mb]}$.

In concord with the presented analysis of a problem situation, the saturation level x_{O_2} will be proportionate to the ratio of the rate $\dot{v}$ of oxygen binding by Mb to its maximum value $\dot{v}_{max}$: $x_{O_2} = \frac{\dot{v}}{\dot{v}_{max}}$. For the purpose of simplification of further analysis, it will be convenient to define the so-called Mb affinity for oxygen[11] P_{50} as oxygen partial pressure π_{O_2}, with which myoglobin saturation x_{O_2} will reach half of the maximum value[12] of $x_{O_2} = 0.5\, mol \cdot mol^{-1}$: $P_{50} \equiv \pi_{O_2}(x_{O_2} = 0.5)$.

After the multiplication of the numerator and the denominator of the right side of the equation (3) by the total pressure of gases present in the blood π we may write down the following: $\frac{\dot{v}}{\dot{v}_{max}} = \frac{\pi[O_2]}{\pi K_M + \pi[O_2]} = \frac{\pi_{O_2}}{\pi K_M + \pi_{O_2}}$. Assuming that $\dot{v}_{max} = 2 \cdot \dot{v}$, the saturation level of x_{O_2} for Mb will reach: $x_{O_2} = \frac{\dot{v}}{\dot{v}_{max}} = \frac{\dot{v}}{2 \cdot \dot{v}} = 0.5$. Using the definition of P_{50} affinity we may express what follows: $\frac{P_{50}}{\pi K_M + P_{50}} = 0.5 \Rightarrow \pi \cdot K_M = P_{50}$. Thus, the *Michaelis constant* K_M included in the equation (3), determining myoglobin's affinity for oxygen[13] may be replaced with the value of affinity for oxygen of $P_{50}(Mb) \leftarrow K_M$ when oxygen concentration $[O_2]$ will be replaced with the partial pressure of $\pi_{O_2} \leftarrow [O_2]$:

(4)

$$\exists_{\pi_{O_2} \gg P_{50}} \; x_{O_2} = \frac{\pi_{O_2}}{\pi_{O_2} + P_{50}}$$

where: P_{50} – Mb affinity for oxygen $[Pa]$, x_{O_2} – saturation of haemoglobin with oxygen $[mol \cdot mol^{-1}]$, π_{O_2} – oxygen pressure $[Pa]$.

The diagram of the algebraic model representing myoglobin Mb saturation with oxygen[14] (4) takes the form of a hyperbola –fig. 2 and fig. 3b. The model has been validated through experimentation with the definition of oxygen affinity for myoglobin of $P_{50}(Mb) = 1\ mmHg$, and with a complete convergence of the theoretical model and the experimental curve [3].

[11] the capability of myoglobin to form a complex with oxygen,

[12] the *Michaelis constant* from equation (3) with $\dot{v}_{max} = 2 \cdot \dot{v}$ will be equal to $K_M = \frac{2\dot{v}}{\dot{v}} \cdot [O_2] - [O_2] = [O_2]$,

[13] the smaller it is the greater the affinity, whereas a large value of the constant signals low affinity for oxygen,

[14] a dissociation model for the complex $myoglobin - oxygen$,

HILL'S SIGMOIDAL MODEL

Archibald Hill postulated that the process of oxygen binding with haemoglobin Hb could be expressed in the form of the following reaction:

Tab. 2

Derivation of Hill's equation according to reaction (5).

Specification	Equation
oxygen binding rate by Hb	$\dot{v}_1 = k_1 \cdot [Hb] \cdot [O_2]^n$
$Hb(O_2)_n$ complex disintegration	$\dot{v}_1' = k_1' \cdot [Hb(O_2)_n]$
oxygen transfer into cells by $Hb(O_2)_n$ complex	$\dot{v}_2 = k_2 \cdot [Hb(O_2)_n]$
summary Hb binding rate	$-\frac{\partial [Hb]}{\partial t} = \dot{v}_1 - \dot{v}_1' =$ $= k_1 \cdot [Hb] \cdot [O_2]^n - k_1' \cdot [Hb(O_2)_n]$
summary rate of concentration changes of the complex $Hb(O_2)_n$	$-\frac{\partial [Hb(O_2)_n]}{\partial t} = \dot{v}_1 - \dot{v}_1' - \dot{v}_2 =$ $= k_1 \cdot [Hb] \cdot [O_2]^n - k_1' \cdot [Hb(O_2)_n] - k_2 \cdot [Hb(O_2)_n]$
for steady state	$-\frac{\partial [Hb(O_2)_n]}{\partial t} \equiv 0 \ \wedge \ [Hb]_0 \stackrel{def}{\equiv} [Hb(O_2)_n] + [Hb]$
	$[Hb(O_2)_n] = \frac{k_1 \cdot [O_2]^n}{k_1' + k_2 + k_1 \cdot [O_2]^n} \cdot [Hb]_0$
oxygen transfer rate into cells through the complex $Hb(O_2)_n$	$\dot{v}_2 = k_2 \cdot [Hb(O_2)_n] = k_2 \cdot \frac{k_1 \cdot [O_2]^n}{k_1' + k_2 + k_1 \cdot [O_2]^n} \cdot [Hb]_0 \quad / k_1 \cdot [O_2]^n$
	$\dot{v}_2 = \frac{k_2}{\frac{k_1' + k_2}{k_1 \cdot [O_2]^n} + k_1 \cdot [O_2]^n} \cdot [Hb]_0 \quad / K \stackrel{def}{\equiv} \frac{k_1' + k_2}{k_1}$
	$\dot{v}_2 = \frac{k_2}{\frac{K}{[O_2]^n} + 1} \cdot [Hb]_0$
the condition for maximisation of oxygen transfer rate	$lim_{K/[O_2]^n \to 0} \quad \dot{v}_2 = \dot{v}_{max} = k_2 \cdot [Hb]_0$
the rate of oxygen transfer into cells through the complex $Hb(O_2)_n$	$\dot{v} \stackrel{def}{\equiv} \dot{v}_2 = \frac{\dot{v}_{max} \cdot [O_2]^n}{K + [O_2]^n}$

(5)

$$Hb + n \cdot O_2 \underset{k_1'}{\overset{k_1}{\rightleftharpoons}} Hb(O_2)_n \overset{k_2}{\rightarrow} Hb + n \cdot O_2^*$$

which leads us to a different form of mathematical algebraic model than equation (3), also referred to as the *Hill equation*: $\exists_{[O_2] \gg K} \quad \frac{v}{v_{max}} = \frac{[O_2]^n}{K+[O_2]^n}$ – tab.1.

As before, the *Hill equation* may be concerned with haemoglobin saturation with oxygen $x_{O_2} \leftarrow \frac{v}{v_{max}}$ expressed as a function of the partial pressure of oxygen $\pi_{O_2} \leftarrow [O_2]$ and the affinity of Hb for oxygen $P_{50}^n(Hb) \leftarrow K$, taking the following form[15]: $\exists_{\pi_{O_2} \gg P_{50}} \; x_{O_2} = \frac{\pi_{O_2}^n}{\pi_{O_2}^n + P_{50}^n}$, or an equivalent form:

(6)

$$\exists_{\pi_{O_2} \gg P_{50}} \quad \frac{x_{O_2}}{1-x_{O_2}} = \left(\frac{\pi_{O_2}}{P_{50}}\right)^n \Leftrightarrow x_{O_2} = \frac{\pi_{O_2}^n}{\pi_{O_2}^n + P_{50}^n}$$

The chart plotted for an algebraic model of Hb saturation with oxygen[16] (6) has a sigmoidal shape and was experimentally validated together with determination of the value for Hb's affinity for oxygen $P_{50}(Hb) = 26\ mmHg$, and the *Hill coefficient*[17] $n_{Hb} = 2{,}8$ [3,4]. The *Hill coefficient* calculated for myoglobin Mb amounts to $n_{Mb} = 1$ [3]. The charts for the algebraic dissociation models of the complexes *myoglobin – oxygen* and *haemoglobin – oxygen* are shown in fig.1.

A greater value of the *Hill coefficient* for Hb is called a cooperative binding of O_2 by Hb, i.e. binding of O_2 with one haem facilitates tlenu binding of O_2 within the same tetrameter of a haem [5]. If we assumed that Mb would participate in oxygen transportation through blood, as it is the case with Hb, the comparison of Hb saturation byO_2 would, depending on oxygen partial pressure, change to a greater degree than it does for Mb, althoughMb would become saturated to a greater extent than Hb[18] – fig. 3.

[15] providing the following substitution in the equation $\frac{v}{v_{max}} = \frac{[O_2]^n}{K+[O_2]^n}$ with the value $v_{max} = 2 \cdot v$ we may calculate the constant K, which will be equal to $K = \left(\frac{2 \cdot v}{v} - 1\right) \cdot [O_2]^n = [O_2]^n$; hence, in accordance with the affinity definition for oxygen P_{50}, the constant K may be replaced with the oxygen affinity value for haemoglobin $P_{50}^n \leftarrow K$ when oxygen pressure $[O_2]$is replaced with the value of its partial pressure $\pi_{O_2} \leftarrow [O_2]$

[16] a dissociation model for the complex $haemoglobin - oxygen$

[17] the *Hill model's* accuracy is sufficient with regard to the presented analyses; however, there have also been works on more precise haemoglobin dissociation models [17;18]

[18] assuming that the oxygen partial pressure in pulmonary alveoli will be within the level of $p_{O_2} = 100\ mmHg$ and the oxygen pressure in capillary vessels will amount to $\pi_{O_2} = 46\ mmHg$ – fig. 3,

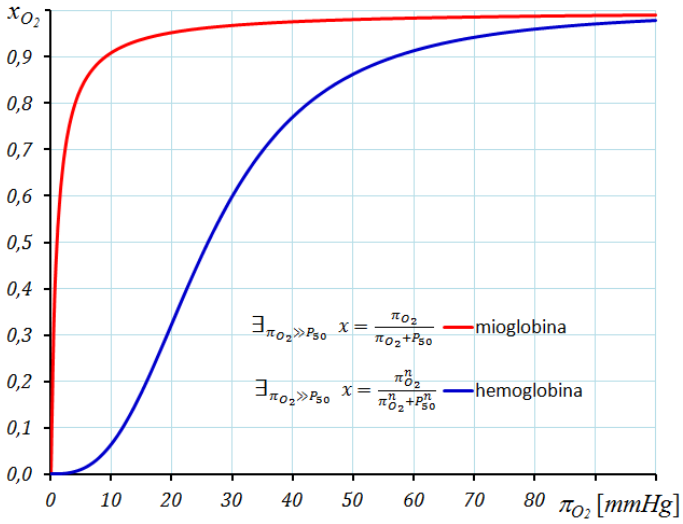

Fig. 2. *Red – myoglobin, blue – haemoglobin.
Dissociation charts for the complexes myoglobin – oxygen and haemoglobin – oxygen as relation of oxygen saturation $x_{O_2} = \frac{[AO_2]}{[AO_2]+[A]} \mid A = \{Hb; Mb\}$ in the function of oxygen pressure in the blood π_{O_2}.

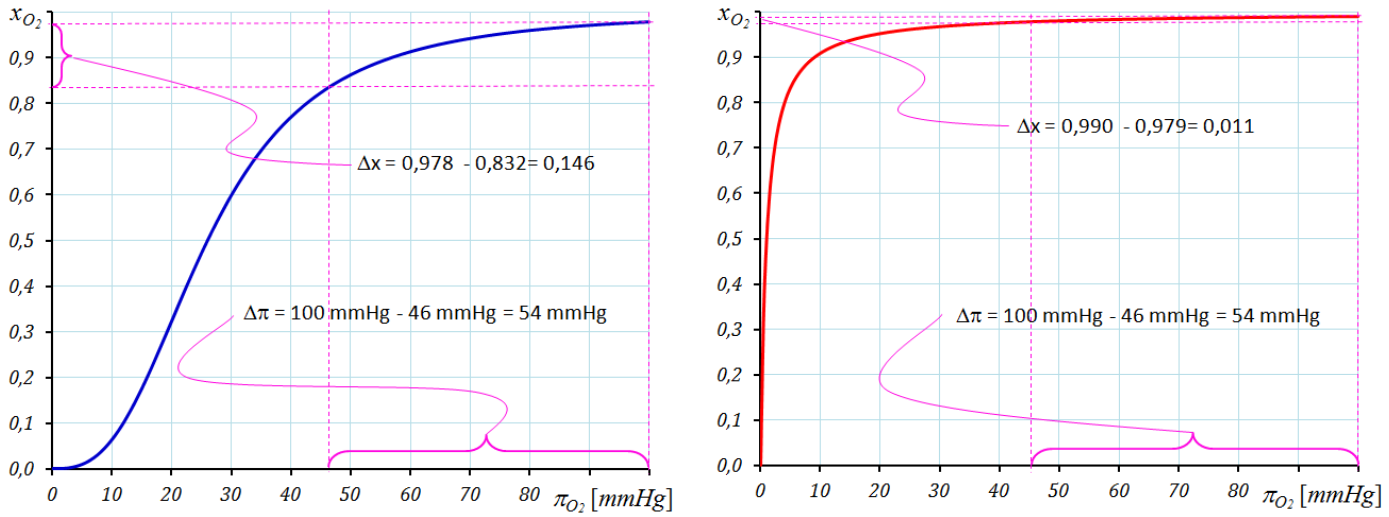

Fig. 3. Dissociation charts of the complexes a) haemoglobin – oxygen, b) myoglobin – oxygen as a relation of oxygen saturation $x_{O_2} = \frac{[AO_2]}{[AO_2]+[A]} \mid A = \{Hb; Mb\}$ in the function of oxygen pressure π_{O_2} in blood with the assumption of an oxygen partial pressure value in pulmonary alveoli at the level of $p_{O_2} = 100\ mmHg$ and the oxygen pressure in capillary vessels reaching $\pi_{O_2} = 46\ mmHg$.

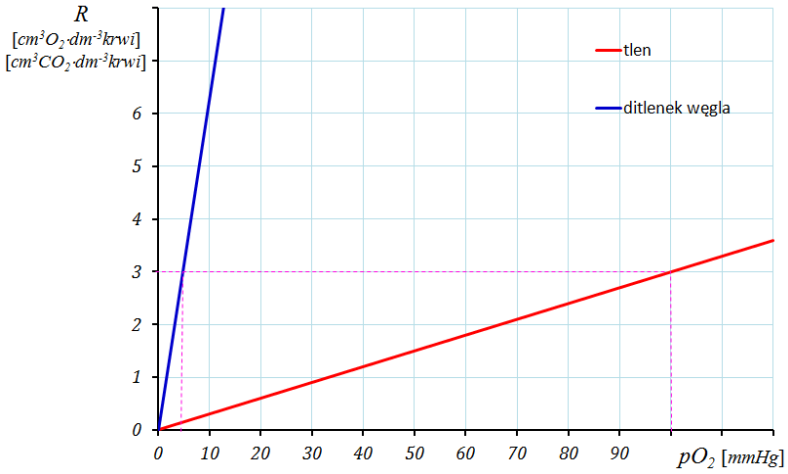

Fig. 4. *Red: oxygen, blue: carbon dioxide.
Comparison of physical solubility R of oxygen and carbon dioxide in blood in the function of oxygen partial pressure p_{O_2} in the inhaled breathing mix.

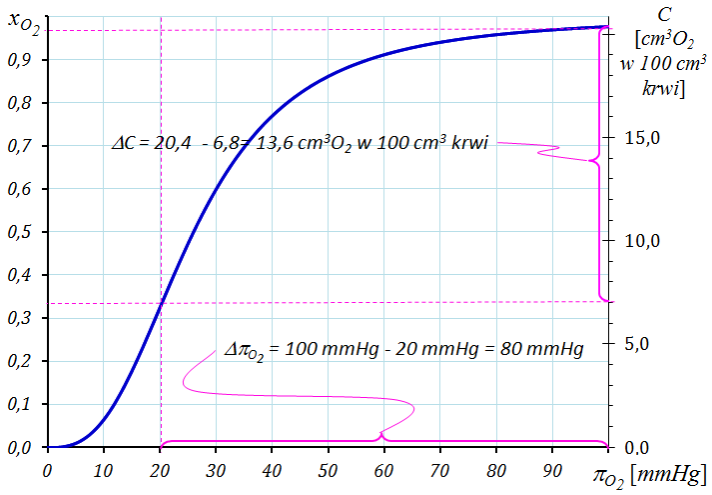

Fig. 5. *krwi – blood, w 100 cm3 krwi – in 100cm3 of blood.
Differences in oxygen content ΔC in small pulmonary arteries and capillary vessels correspondent to a reduction in oxygen pressure $\Delta\pi_{O_2}$ in the blood as associated with light exertion[19] according to tab.3.

[19] in a healthy man the stream of blood is contained within the range of $\dot{V} \in [5;6] dm^3$ with the adopted difference in oxygen pressure $\Delta\pi_{O_2}$; in accordance with fig. 5, oxygen consumption reaches $13.6\ cm^3\ O_2 \cdot 100\ cm^{-3}\ blood$, hence the global stream of the consumed oxygen reaches ca. $\dot{v}_{O_2} = 136\ cm^3\ O_2 \cdot dm^{-3}\ blood \cdot 5\ dm^3 blood = 680\ cm^3\ O_2 \cong 0.7\ dm^3\ O_2 \cdot min^{-1}$, which according to tab. 2 corresponds to a light effort,

Tab. 3

Streams of consumed oxygen and lung ventilation depending on physical effort [2].

Physical effort		Stream of oxygen consumed	Number of breaths per minute	Lung ventilation	Minimum stream of oxygen consumed
Intensity	Example	$[dm^3 \cdot min^{-1}]$	$[min^{-1}]$	$[dm^3 \cdot min^{-1}]$	$[dm^3 \cdot min^{-1}]$
very light	lying in bed	0.25	up to 20	8–10	up to 0.5
	relaxed sitting position	0.30			
	standing still	0.40			
light	walking at $3.5\ km \cdot h^{-1}$	0.7	20–25	10–20	0.5–1.0
moderate	marching at $6.5\ km \cdot h^{-1}$	1.2	25–30	20–30	1.0–1.5
hard	swimming at $3.0\ km \cdot h^{-1}$	1.8	30–35	30–50	1.5–2.0
very hard	running at $13\ km \cdot h^{-1}$	2.0	35–40	50–65	2.0–2.5
extremely hard	running uphill	4.0	>40	>65	>2.5

PHYSICAL SOLUBILITY OF OXYGEN IN THE BLOOD

In normal conditions nearly the entire oxygen quantity that is transported with blood occurs in a complex with haemoglobin Hb[20] [3]. Only its small part is physically dissolved[21] in blood, nonetheless this is the factor which plays a crucial role in the diffusional mechanism in oxygen's passage to the cells. Physical solubility of oxygen in the blood in the function of pressure $R(p)$ reaches approximately $R(p) \cong 3 \cdot 10^{-2}\ cm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot dm^{-3}\ blood$. According to (6) oxygen saturation would be equal to $x_{O_2} = 0.97 \Rightarrow \pi_{O_2} = 89.5\ mmHg$. Physical concentration of dissolved oxygen will reach ca.: $R \cong R(p) \cdot \pi_{O_2} \cong 2.7\ cm^3\ O_2 \cdot dm^{-3} blood$[1]– fig. 4.

OXYGEN TRANSPORTATION

Similarly to myoglobin's Mb role as an oxygen store for the muscle tissue, haemoglobin Hb serves the same purpose in relation to the blood. A decrease in the pressure of oxygen that saturates blood in a physical manner causes its release from the haemoglobin Hb.

In normal conditions, maximum haemoglobin saturation Hb reaches ca. $\gamma_{Hb} \cong 1{,}39\ cm^3 O_2 \cdot g^{-1}\ Hb$. In a healthy human, the average haemoglobin content C_{Hb} in $1\ dm^3$ of blood is equal to ca. $C_{Hb} \cong 150\ g\ Hb \cdot dm^{-3} blood$. The values C_{Hb} and γ_{Hb} served

[20] creating a coordination bond, i.e. haemoblogin with oxygen creates a weaker bond as compared with typical chemical compounds,

[21] subject to *Henry's law* – tranfer without the formation of a chemical bond ,

[1]

to calculate an additional concentration scale of oxygen C bounded by haemoglobin in the blood Hb[23], as represented in fig. 5.

When remaining at rest, in a sitting position, the blood flow $\dot{V}$ is at the level of $\dot{V} \in [4; 6]\ dm^3 \cdot min^{-1}$ with oxygen consumption by tissues of $\dot{v} \in [13; 100]\ cm^3 \cdot min^{-1}$ – tab. 4. The average oxygen consumption $\dot{v}_{O_2}$ in a human organism is at the level of $\dot{v}_{O_2} \in [0.2; 0.3]\ dm^3 \cdot min^{-1}$ [7]. The said level grows together with work load – tab. 3. Under normal pressure, oxygen pressure in small pulmonary arteries reaches ca. $\pi_{O_2} \cong 100\ mmHg$, whereas at the level of capillary vessels of a working muscle it is equal to approx. $\pi_{O_2} \cong 20\ mmHg$ [8]. Such a decrease in oxygen pressure is correspondent to the consumption of ca. $\dot{v}_{O_2} \cong 0.7\ dm^3 \cdot min^{-1}$ when applying a light effort – fig. 5.

OXYGEN CONSUMPTION

Tab. 3 depicts typical global consumption of oxygen $\dot{v}_{O_2}$, which tends to be highly diversified when considering particular organs – tab. 4.
Based on an analysis of fig. 2–3 and fig. 5 we may conclude that the greater the oxygen consumption is, the wider the oxygen window should be.

Tab. 4

Oxygen streams carried to tissues from the blood [6].

Organ	Oxygen uptake from the blood on the level of tissues $[cm^3 \cdot dm^{-3}\text{blood}]$
Heart	100
Brain	60
digestive system	60
muscles at rest	50
Kidneys	13
Other	50

[23] e.g. for
$x_{O_2} = 0.97 \Rightarrow C = 1.39\ cm^3\ O_2 \cdot g^{-1}\ O_2 \cdot 150\ g\ Hb \cdot dm^{-3}\ blood \cdot 0.97 \cong 202\ cm^3\ O_2 \cdot dm^{-3}\ blood$

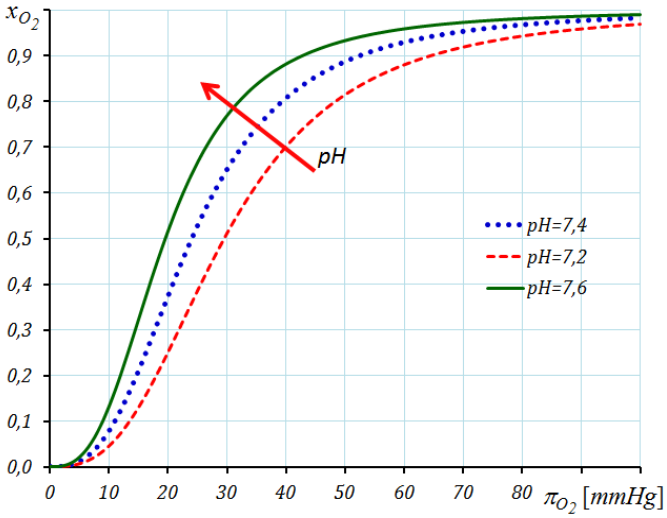

Fig. 6. Relation of the degree of saturation of haemoglobin x_{O_2} with low affinity for oxygen HbA in the function of oxygen pressure π_{O_2} and blood level pH (9).

This does not translate directly into the risk of central nervous system oxygen toxicity $CNSyn$ affecting particular organs, since their immunity to the produced harmful metabolites is also highly diversified. Thus, despite the fact that in comparison with other organs the nervous system consumes significant amounts of oxygen, its sensitivity is also higher and it not possible to simply apply an oxygen window value in order to assess the hazard of $CNSyn$.

ENVIRONMENTAL IMPACT

The qualitative interrelation of the x_{O_2}saturation level for haemoglobin HbA[24] in the function of oxygen pressure π_{O_2} and pH[25], is shown in fig. 6 [9]. The chart shows that with the growth in the value of hydronium activity[26] $a_{H_3O^+}$ the affinity for oxygen HbA is reduced, thus causing an easier release of oxygen[27]. An increased pH value on the other hand elevates the affinity for oxygen HbA, and leads to an impeded release of O_2 in tissues. The direction of changes for each Hb type is the same as for HbA. This phenomenon is known as the $Bohr\ effect$. In an organism this effect is commonly induced by carbonic acid IV produced from the CO_2 that is dissolved in the blood, which under the impact of *carbonic anhydrase* is decomposed into a hydronium cation H_3O^+ and a hydrogen carbonate anion HCO_3^-:

$$H_2CO_3 \xrightarrow{carbonic\ anhydrase} H_3O^+ + HCO_3^-$$

Apart from the said impact of CO_2 content, another recognised factor that induces changes in the affinity of haemoglobin for oxygen is temperature– fig. 7.

[24] a type of haemoglobin with relatively low affinity for oxygen [16],
[25] $pH = -\log a_{H_3O^+}$, where: $a_{H_3O^+}$ –hydronium activity,
[26] reduction in pH value,
[27] easier decomposition of the complex $Hb(O_2)_n$,

HALDANE EFFECT

The *Haldane effect* consists of an increased capability of binding CO_2 by reduced haemoglobin, as compared with the reaction of exchange with oxyhaemoglobin, and is related with the already discussed *Bohr effect* involving a decrease in the affinity of haemoglobin Hb for oxygen with decreasing pH of the blood– fig. 7.

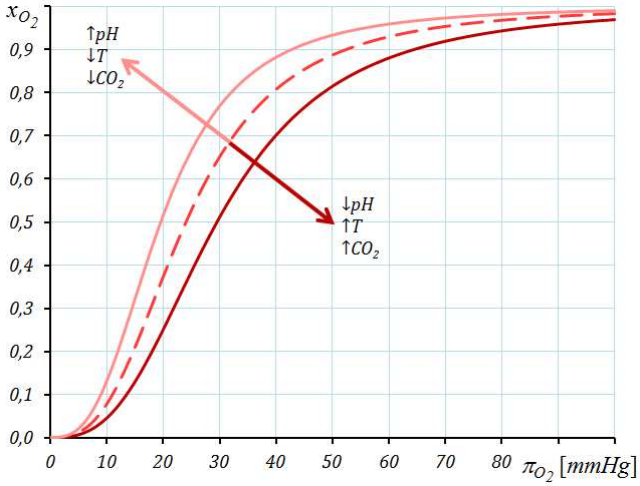

Fig. 7. Direction of changes in the saturation level x_{O_2} of haemoglobin Hb in the function of oxygen pressure π_{O_2} in the blood, pH, temperature T and CO_2 content.

Carbon dioxide is carried with blood from tissues into the lungs in several ways. Approximately $60\%\ of\ CO_2$ is transported in the form of hydrocarbonate ions[28] produced from water and CO_2 in the presence of an enzyme – $carbonic\ anhydrase$.

About $(5-30)\%\ \text{of}\ CO_2$ is transported in the form of a carbamino-heamoglobin complex $O_2 - Hb$[29]. Transportation with the help of a bond with haemoglobin vanishes when breathing pure oxygen under the pressure of ca. $300\ kPa$, since Hb is then nearly completely blocked by oxygen and the metabolic reactions are based only on oxygen that was physically dissolved in the blood [10]. On this basis it was presumed that the blockage of CO_2 carriage via this manner is accompanied by its retention evoking the symptoms of oxygen toxicity – however, it seems that the actual mechanism is different[30] [8].

Approximately $10\%\ \text{of}\ CO_2$ is transported with blood plasma in the form of caramino compounds with plasma protein. Carbamates are products of the direct binding of CO_2 with amino groups without the necessity of CO_2 hydration, and the actual CO_2 pressure has a minor impact on the quantity of CO_2 carried in the form of carbamates.

[28] the dissociation from carbonate ion has no significant meaning in the mechanism of carbon dioxide carriage with blood as it occurs with relatively high pH values: $pH > 9$,
[29] the occurrence of $CO_2 - Hb$ complex is accompanied with the emission of hydronium H_3O^+ causing pH reduction in the tissues and blood in relation to the lungs,
[30] as discussed later in the chapter,

THE RISK OF CNSYN

Measurements show that an increase in the level of oxygen partial pressure in a breathing mix up to ca. $p_{O_2} \cong 345\ mmHg$ may cause its pressure in arterial blood to reach ca. $\pi_{O_2} \cong 300\ mmHg$, whereas its level in venous capillaries would remain the same, i.e. ca. $\pi'_{O_2} \cong 40\ mmHg$ or slightly exceed it. With the pressure of CO_2 of ca. $\pi_{CO_2} \cong 7\ mmHg$ we could assume that the total pressure of O_2 and CO_2 in venous vessels would reach ca. $\pi_{CO_2+O_2} \cong\cong 50\ mmHg$. By subtracting this value from oxygen pressure in arterial blood π_{O_2} we may estimate the value of the oxygen window as $\Delta\pi \cong 300 - 50 = = 250\ mmHg$. Such a pressure defect may become available to other gases that should leave an organism in the process of decompression [11].

In the experiment SEA–LAB II conducted at the depth of $200\ fsw$[2], during a 14-day stay of divers breathing with a breathing mix with 4.5% of O_2[3], the average oxygen pressure in arterial blood was determined at the level of $\pi_{O_2} \cong 192\ mmHg$, when its level in venous vessels reached $\pi'_{O_2} \cong 40\ mmHg$ [11]. Based on these data and equation (**6**) it is possible to estimate the saturation x_{O_2} of arterial blood with oxygen pressure $\pi_{O_2} = 192\ mmHg\ O_2$ at the level of: $x_{O_2}(192\ mmHg\ O_2) \cong 0.996$. And in the case of venous blood, for which oxygen pressure was at the level of $\pi'_{O_2} = 40\ mmHg\ O_2$ it will reach only $x'_{O_2}(40\ mmHg\ O_2) \cong 0.770$. This corresponds to the volumetric content of oxygen x_v bounded by the haemoglobin Hb in the arterial blood at the level of $x_v = 0.2085\ dm^3O_2 \cdot dm^{-3}blood \cdot 0.996 \cong 0.208\ dm^3O_2 \cdot dm^{-3}blood$[4]. Similarly, with regard to oxygen transportation with the haemoglobin Hb in the venous blood, we may determine the content of the transported oxygen at the level of ca. $x'_v \cong 0.161\ dm^3O_2 \cdot dm^{-3}blood$. The content of oxygen physically dissolved in arterial blood is equal to $x_v = 3 \cdot \cdot 10^{-5}\ dm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot dm^{-3} \cdot 192\ mmHg \cong 0.006\ dm^3O_2 \cdot dm^{-3}\ blood$, whereas in venous blood to:
$x'_v \cong 3 \cdot 10^{-5}\ dm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot dm^{-3} \cdot 40\ mmHg \cong 0.001\ dm^3O_2 \cdot dm^{-3}blood$.
Altogether, arterial blood carries $x_v \cong 0.214\ dm^3O_2 \cdot dm^{-3}blood$, whereas venous blood transports $x'_v \cong 0.162\ dm^3O_2 \cdot dm^{-3}blood$. The difference in the oxygen content in one litre of arterial and venous blood amounts to $\Delta V_{O_2} \cong 0.052\ dm^3O_2$ in normal conditions.
In normal conditions and with oxygen consumption within $\dot{v}_{O_2} \in (0.5\ ;\ 3.0)\ dm^3O_2 \cdot min^{-1}$, the blood flow $\dot{V}$ constitutes an approximate linear function of oxygen consumption $\dot{v}_{O_2}$: $\dot{V} = f(\dot{v}_{O_2})$, that may be expressed as: $\dot{V}(\dot{v}_{O_2}) \cong 6\ dm^3blood \cdot dm^{-3}O_2 \cdot \dot{v}_{O_2} + 2\ dm^3blood \cdot min^{-1}$ [7]. Below the minimum value of oxygen consumption of ca. $\dot{v}_{O_2} < 0.5\ dm^3O_2 \cdot min^{-1}$ the blood flow is stabilised at the level of approximately $\dot{V} \cong 5\ dm^3blood \cdot min^{-1}$.
An obstacle to estimating oxygen consumption $\dot{v}_{O_2}$as a function of heart rate is the phenomenon of bradycardia[5]. The average oxygen consumption $\dot{v}_{O_2}$during the SEA–LAB II

[2]which was equivalent to ca. $0.7\ MPa$,
[3]oxygen partial pressure amounted to ca. $237\ mmHg$,
[4] $x_v = \gamma_{Hb} \cdot C_{Hb} \cdot x_{O_2} \cong 1.39 \cdot 10^{-3}\ dm^3\ O_2 \cdot g^{-1}Hb \cdot 150\ g\ Hb \cdot dm^{-3}blood \cdot 0.996 \cong 0.208\ dm^3\ O_2 \cdot dm^{-3}blood$, where: γ_{Hb} – maximum Hb saturation with oxygen, C_{Hb} – average content of haemoglobin in the blood,
[5]bradycardia – here: a state when the heart rate decreases in a situation when an organism is under hyperbaric exposure as compared with the heart rate in normobaria,

experiment may be estimated at the level of $\dot{\mathbb{m}}_{O_2} \cong 0.25\ dm^3O_2 \cdot min^{-1}$ with approximate blood flow $\dot{V}$ at $\dot{V} \cong 5\, dm^3 blood \cdot min^{-1}$, which according to **tab.3** is consistent with a very light effort.

Tab. 5 and fig. 8 illustrate the directions of changes in the oxygen content C_{O_2} in the function of its pressure π_{O_2} with regard to a very light effort[6] [8]. In normal conditions, maximum saturation of $1\ g\ Hb$ amounts to ca. $1.39\ cm^3O_2$. On average, in a healthy man $1\ dm^3$ of blood contains ca. $150\ g\ Hb$, hence in concord with (**6**) the content of O_2 bounded into a complex with Hb will reach $x_v = 1.39\ cm^3O_2 \cdot g^{-1} \cdot 150\ g \cdot dm^{-3}\ blood \cdot x_{O_2}$. Physical solubility of oxygen in the blood $R(p)$ is equal to ca. $R(p) \cong 3 \cdot 10^{-2}\ cm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot dm^{-3}\ blood$, thus the content of oxygen physically dissolved in the blood may be expressed with the following formula:

Tab. 5

Oxygen pressures and contents [8].

Breathing mix	Pressure		Oxygen partial pressure / Oxygen content		
	Total	partial (oxygen)	Aorta	Superior vein	Difference
	$[mmHg]$	$[mmHg]$	$\frac{[mmHg]}{[\%_{vol.}]}$	$\frac{[mmHg]}{[\%_{vol.}]}$	$\frac{[mmHg]}{[\%_{vol.}]}$
Oxygen	760	760	$\frac{130^*}{21.0}$	$\frac{40}{13.4}$	$\frac{90}{7.6}$
	2660	2660	$\frac{2100}{26.0}$	$\frac{75}{17.8}$	$\frac{2025}{8.2}$
Air	760	160	$\frac{91}{18.7}$	$\frac{55.7}{12.6}$	$\frac{35.3}{6.1}$
heliox	5320	239	$\frac{192}{20.8^*}$	$\frac{40}{16.1^*}$	$\frac{152}{4.7^*}$

*–calculated values

[6]in the course of the experiments divers breathed from inhalers while sitting inside a hyperbaric chamber with ensured thermal comfort,

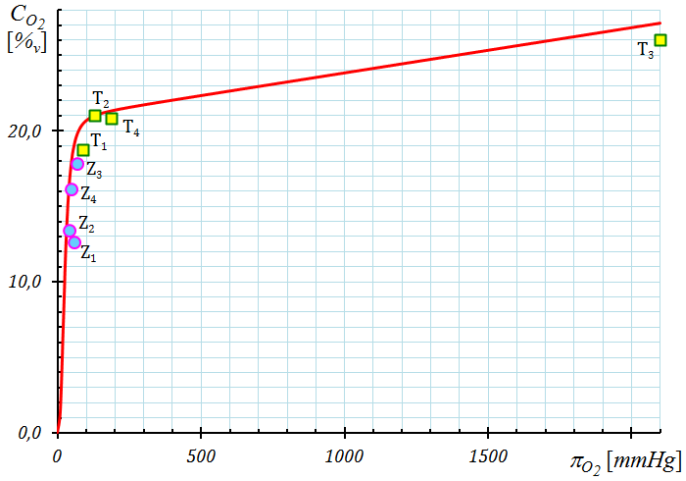

Fig. 8. Oxygen content C_{O_2} in the function of its pressure π_{O_2} in the blood where the continuous line represents values resulting from the said adopted model, and the marked points indicate practical values – tab. 5 [8].

The continuous line $C_{O_2} = x_v \cdot 100\%$ shown in fig. 8 represents a sum[36] of the content of oxygen bounded with haemoglobin C_{Hb} and physically dissolved oxygen C: $C_{O_2} = C_{Hb} + C$. The indicated points, on the other hand, provide averaged values where: T refers to arterial blood, Z - venous blood, index 1 - breathing with air in normal conditions, 2 - breathing with oxygen in normal conditions, 3- breathing with pure oxygen under the pressure of $2660\ mmHg$[37] and 4 - the results of the experiment SEA–LAB II– tab. 5.

During the passage of arterial blood through the tissues, ca. $6\%_{vol.}\ of\ O_2$ enters in biochemical reactions in cells. These reactions, first of all, lead to the production of H_2O and CO_2. Oxygen consumption[38] is dependent only on the demand for the energy stored in the bonds of the molecules[39] GTP and ATP, being practically independent of oxygen partial pressure p_{O_2} in the inhaled breathing mix[40].

During breathing with air in normal conditions accompanied with light effort, the observed difference in the oxygen pressures $\Delta\pi_{O_2}$ in arterial and venous blood reaches $\Delta\pi_{O_2} \cong 49\ mmHg$[41]. T_1 represents oxygen pressure π_{O_2} when breathing with air in normal conditions. In such conditions Hb is nearly completely saturated with oxygen – with the theoretical saturation level of $x_{O_2} \cong 0.971$. The said consumption of ca. $6\%_{vol.} O_2$ in metabolic reaction leaves the theoretical Hb saturation at the level of ca. $x_{O_2} \cong 0.894$.

[36] from the point of view of the conducted analysis the *Hill model's* accuracy seems to be sufficient; however, there are also more precise models used in the description of summary oxygen solubility in the blood [17]; an overview of several other models was prepared by Lobdell[18],

[37] what should be observed is a decrease in the blood flow related to divers' being subject to an increased pressure related to bradycardic state,

[38] in oxygen cascade and other biochemical cycles

[39] Adenosine triphosphate – ATP, guanosine triphosphate – GTP,

[40] i.e. the decreased oxygen content should be maintained at the same level with the same burden on a diver,

[41] in fig. 8 and tab. 5 the difference between T_1 and Z_1 is slightly smaller, as it concerns an extremely low oxygen consumption [8],

Breathing with O_2 under an increased pressure, causes its greater part to be carried by the blood plasma whereas Hb remains bounded the entire time[42] with O_2. Above the oxygen partial pressure value of ca.. $\pi_{O_2} \cong 150\ mmHg$ we may observe an elevated content of C_{O_2} connected only with its physical dissolution in the blood induced by an increasing value of oxygen partial pressure p_{O_2} in the inhaled breathing mix. With the pressure value over $\pi_{O_2} \cong 150\ mmHg$ the width of the oxygen window begins to diminish and the C_{O_2}content that is physically dissolved in the blood increases above the typical value of $C_{O_2} > 3 \cdot 10^{-3}\ cm^3\ O_2 \cdot 100\ cm^{-3}\ blood$ – fig. 8. This way tissues are exposed to growing values of oxygen partial pressure π_{O_2} due to the perfusing[43] arterial blood. The said pressures may be treated as directly proportional to the risk involving the possibility of occurrence of harmful, highly oxygenised metabolites and radicals, which may induce $CNSyn$ symptoms – a biochemical theory of oxygen toxicity.

In simpler words, we may postulate that exceeding of the value of oxygen partial pressure p_{O_2} in the inhaled breathing mix causes complete saturation of Hb in the arterial blood and leads to deactivation of the protective effect of the oxygen window related to the maintenance of the oxygen partial pressure π_{O_2} that maintains the physical saturation of the blood within a safe level. From this point on, the time of safe breathing with an atmosphere enriched with O_2 is limited.

Breathing with O_2 is accompanied with an effect of an increased resistance in the cerebral blood flow, which initially limits the exposure of the nervous tissue to the activity of a stream of O_2 physically dissolved in blood [8]. When breathing with oxygen under the pressure of $p_{O_2} = 350\ kPa$ the resistance of cerebral vessels increases by 50% resulting in the limitation of the blood flowing through the brain by ca. 25%. Such an effect is approximately twice as strong as compared with the cerebral blood flow limitation observed while breathing with O_2 under normal pressure [8].

The pressure of oxygen C_{O_2} physically dissolved in the arterial blood in breathing with O_2 under the pressure of $p_{O_2} = 350\ kPa$, in accordance with **tab.5**, reaches: $C \cong 100\% \cdot 2100\ mmHg \cdot 0.003\ cm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot 100\ cm^{-3}\ blood \cong 6.3\%_{vol.}$ and is by over an order of magnitude higher as compared with its content during breathing with air under normal pressure: $C \cong 100\% \cdot 91\ mmHg \cdot$ $\cdot 0.003\ cm^3\ O_2 \cdot mmHg^{-1}\ O_2 \cdot 100\ cm^{-3}\ blood \cong 0.3\%_{vol.}$. A reduced cerebral blood flow causes a 25% compensation in the increase of the content of O_2 physically dissolved in blood, thus having an impact on how long the CO_2 produced in the course of metabolic transformations lingers. The retention is not usually high enough to cause clear symptoms of hypercapnia[7], although in some cases it may lead to an oxygen black-out. With time, the increased presence of CO_2 results in a decreased pH and the buffering mechanism[8] of the blood cannot counteract this effect, thus causing further O_2 release from oxyhaemoglobin into the blood– **fig.6**. Such an effect causes the brain to be exposed to higher oxygen partial

[42] haemoglobin saturation with oxygen remains at all times at the level of 100% both in venous and arterial blood,

[43] here perfusion means the blood flow through a tissue or an organ; usually it is defined as a percentage share in the cardiac output,

[7]hypercapnia is a condition of an increased partial pressure of CO_2 in blood above $p_{CO_2} > 45\ mmHg$, here the symptoms of CO_2 poisoning,

[8]a solution whose pH value after adding small quantities of strong acids or alkalis, as well as after its dilution with water reveals nearly no changes,

pressures π_{O_2}, which may produce harmful metabolites[9]. The result may consist in a delayed, spontaneous occurrence of $CNSyn$ symptoms.

A partial confirmation of the above mechanism could be sought in a relatively low haemoglobin saturation reaching 89% in the subclavian vein observed in breathing with O_2 with oxygen partial pressure of $p_{O_2} = 350\ kPa$ [8].

The discontinued CO_2 discharge from cerebral vessels into peripheral venous vessels leads to a decrease in its pressure, thus resulting in the observed reduction in respiratory activity[10] in the phase preceeding $CNSyn$.

No direct impact of CO_2 retention in peripheral venous vessels was observed with regard to $CNSyn$ induction through hypercapnia. Such a retention is rather proven to cause another increase in ventilation[11] immediately before $CNSyn$.

CONCLUSIONS

The theory of an oxygen window was traditionally used in planning and assessing the safety of decompression, and constituted a theory concerned with the phenomena occurring in the process of decompression following both short and saturation dives [11,12]. It was also applied in planning hyperbaric treatment [13].

Using oxygen for breathing in the last decompression stations[49] causes the oxygen window to become wide enough to eliminate nitrogen six times faster as compared with breathing with air[50] [1]. Despite the application of oxygen in the last phase of the decompression process, it is still necessary to reduce the divers'
ascent speed due to the kinetics behind the removal of excess inert gas[51], which should be disposed of from an organism without the formation of a free gas phase. The oxygen window ensures a weakened tendency to form the free gas phase. However, the toxic effect of oxygen imposes a certain limitation in the application of this practice. Another inconvenience consists in the fact of the non-linearity of the width of an oxygen window in the function of oxygen partial pressure in the inhaled breathing mix resulting from the same properties of haemoglobin [6] – fig. 1.

The concept of a widened oxygen window[52] was used by Prof. T. Doboszyński in the preparation of trimix and nitrox tables for continuous decompression following saturation, resulting in an unquestionable success of the Polish bathynautic line of

[9] an organic or inorganic product of metabolism,

[10] stimulated by the respirator centre,

[11] and the related exposure of tissues to an increased effect of the stream of oxygen physically dissolved in the blood,

[49] beyond the toxicity zone,

[50] e.g. if it is assumed that in the process of breathing with air ca. $0.45\ kg$ of nitrogen is removed within approx.. $30\ min$, then during isobaric breathing with oxygen the time needed to dispose of the same quantity of nitrogen from the human organism will reach ca. $5\ min$,

[51] For example, when Bühlmann used the concept of an oxygen window in his works, he limited the speed of a diver's ascent to the surface to $10\ mH_2O\ min^{-1}$. He also introduced an obligatory one-minute decompression stop at the depth of $3\ mH_2O$ in situations when diving did not require such stops. *The American Academy of Underwater Sciences* provided evidence in favour of Bühlmann's perspective. It was shown that a decrease in the ascending speed and the implementation of
a decompression safety stop in dives with zero decompression caused a reduction in the silent gas phase by at least six times, whereas nitrogen pressure in quick theoretical tissues reached between 12% and 21% with only miminal increase in slower theoretical tissues [14],

[52] maximum oxygen window for saturated dives was estimated by Prof. T. Doboszyński at $150\ mmHg$, which he referred to as a widened oxygen window [15],

thought[53]. The idea of such an application of the theory of oxygen window was compliant with observations made by other scientists, yet they decided to abandon it[54].

Using the oxygen window concept in the explanation of phenomena related to oxygen toxicity has not been so far described, hence the theories stipulated in this article lack their reflection in other reports and require a careful approach[55]. They constituted an attempt at a theoretical interpretation of the observed phenomena.

The article provides a suggestion that it is the transgression of oxygen partial pressure in the inhaled breathing mix that causes a limitation in the protective effect of oxygen window leading to an increased risk of $CNSyn$, i.e. the time of a safe stay above a particular oxygen partial pressure value is limited.

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[53] bathynautics [gr. bathýs 'deep' and *nautikós* 'nautical'] is here defined as the entirety of knowledge on carrying out underwater activities,

[54] in the quoted SEA–LAB II experiment the oxygen window was at the level of ca. $150\ mmHg$ [11], i.e. it was equal to the maximum oxygen window value adopted by prof. T. Doboszyński as the so-called widened oxygen window [15],

[55] especially since they have they not been confirmed with our own studies.

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