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Brain tissue oxygen reactivity: clinical implications and pathophysiology

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INTRODUCTION

It is generally accepted that PbO_2 reflects the balance between O_2 delivery and consumption (Diringer et al., 2007; Diringer, 2008). However, implementation in the perioperative period of various ventilatory modes using high FiO_2 leads to a dramatic and non-physiologic increase in PbO_2 with approximating levels of 147 ± 36 mmHg (McLeod et al., 2003). This phenomenon doesn't correlate with the extent of slight increase in arterial O_2 content. At the same time, the jugular venous PO_2 increases only slightly (37–40 mmHg) (Forkner et al., 2007). Moreover, hyperoxia does not affect significantly the regional CBF, and there is no improvement in cerebral metabolism with oxygen therapy (Magnoni et al., 2003; Diringer et al., 2007; Diringer, 2008; Xu et al., 2012).

The PbO_2 increase is more pronounced in edematous (but not necrotized) brain tissues compared to normal areas (Meixensberger et al., 1993). Although, this can be considered a positive phenomenon, it masks the real state of rCBF and local oxidative metabolism. Recording of high PbO_2 absolute values may create a false impression of safety and negatively impact the clinical decision making. Apparently, better indicators of the status of energy exchange in the brain tissue are needed for practical use in the perioperative and critical care settings.

BRAIN TISSUE OXYGEN REACTIVITY: CLINICAL IMPLICATIONS

Dynamic assessment of relative changes in brain oxygenation to monitor the brain functionality is a better approach compared to relying on a single parameter. With such monitoring, both the current status of brain tissue oxygenation and the functional reserve capabilities can be accomplished.

Brain tissue oxygen reactivity (BTOR) is the measure (in percents) of PbO_2 changes relative to changes in PaO_2 ($\Delta PbO_2/\Delta PaO_2$) with oxygen inhalation (Johnston et al., 2003). The latter parameter can be easily adjusted to reach BTOR optimal values. The technique of measurement includes increasing the FiO_2 up to 1.0 with simultaneous recording of the PaO_2 and PbO_2 values.

Literature reports indicate that high BTOR values within the first 24 h after TBI are considered an indicator of unfavorable outcome and negatively correlate with the Glasgow Outcome Score (van Santbrink et al., 1996; Menzel et al., 1999).

It is not mandatory to apply the maximal FiO_2 of 1.0 to calculate the BTOR. Any other high inspired O_2 levels can be applied that will produce significant PbO_2 changes within 20 min. Such a time period is considered the minimal required interval adequate for equilibration and meaningful assessment. During this short period, the respiration, regional metabolism and the rCBF are assumed to remain stable, and the calculated values of $\Delta PbO_2/\Delta PaO_2$ will indirectly characterize the rCBF.

Low BTOR is considered a positive phenomenon even when the absolute PbO_2 values decrease, unless regional hypoperfusion (<20 ml/100 g/min) exists (Hlatky et al., 2008). Simultaneous elevations of PbO_2 and $\Delta PbO_2/\Delta PaO_2$ values reflect the imbalance between the oxygen delivery and consumption.

Under normal cardio-respiratory conditions, when the right to left pulmonary shunting is negligible, the FiO_2 is proportional to PaO_2. On the other hand, PbO_2 itself correlates with PaO_2. Therefore, one can presume that FiO_2 is proportional to PbO_2. Taking this into account, the formula used to calculate the BTOR can be modified to evaluate the correlation between the changes in PbO_2 and FiO_2. This new parameter ($\Delta PbO_2/\Delta FiO_2$) is considered an equivalent of BTOR and can be easily calculated. This is a simple and practical approach to BTOR assessment that can be readily used at bedside. Such an approach will allow for dynamic assessment of tissue oxygen reactivity.

BTOR: PATHOPHYSIOLOGY

In order to illustrate the importance of BTOR as an ultimate indicator of balance between the rCBF, oxygen delivery and consumption and justify the need for its monitoring, the hypothesis of hyperreactive, non-physiologic, luxurious PbO_2 elevation is proposed.

We hypothesize that the significant increase of PbO_2 with hyperoxia in the injured brain is explained by an excessive right shift of the oxyhemoglobin dissociation curve with resultant significant reduction in hemoglobin's affinity to oxygen molecules at the microcirculatory level. This is a result of a mismatch between the rCBF and existing cerebral metabolic rate of oxygen ($CMRO_2$), which leads to accumulation of CO_2, converted by erythrocyte carboanhydrase into HCO_3^- and H^+ ions (at a 1000 times faster rate compared to plasma and extracellular space). It is known that CO_2 and H^+, which are produced during the tissue metabolism, are heterotropic effectors of hemoglobin

that enhance oxygen release (Berg et al., 2002). The latter ions bind to hemoglobin with release of oxygen. With decrease in rCBF and/or relative increase of $CMRO_2$, hemoglobin gets saturated with protons and practically loses its affinity to oxygen in the microcirculatory bed.

The role of CO_2-induced local increase of PO_2 is particularly important in the brain tissue where, under normal conditions (glucose-dependant metabolism without chronic fasting), the respiratory quotient equals 1 and the CO_2 production almost 1.25 times exceeds that of the other tissues.

According to the above mentioned considerations, the rCBF determines PbO_2 values via two principal mechanisms: (a) as an oxygen delivery mechanism within the arterial compartment and (b) via a "non-physiologic" right shift of the oxyhemoglobin dissociation curve as a result of decreased removal rate of the flow-dependent metabolites in the microcirculatory bed.

Many drugs and techniques used commonly during therapy of severe TBI, including manitol, sodium thiopenthal, ketorolac, nimodipine, intra-arterial papaverine, hypothermia, deep sedation, etc., can reduce the PbO_2 in the damaged tissue (Steiner et al., 2001; Gupta et al., 2002; Stiefel et al., 2004, 2006; Sakowitz et al., 2007). On the other hand, the effects of medically induced augmentation of cerebral perfusion pressure on cerebral oxygenation are difficult to predict (Sahuquillo et al., 2000; Imberti et al., 2002; Le Roux and Oddo, 2013). In addition, Zygun et al. (2009) showed that even though transfusion of packed red blood cells in TBI patients may improve the brain tissue oxygenation, it won't have an appreciable effect on cerebral metabolism (Zygun et al., 2009). Thus, there is a complex interaction of multiple factors influencing the functional and metabolic activity of the injured brain including injury-related pathological mechanisms, drugs and methods used to manage these patients. Their overall effects are not straightforward and cannot be anticipated easily in an individual case. Apparently, Monitoring of PbO_2 in these patients will not provide reliable feedback and may be misleading in some cases. It is not justified to treat the severe TBI patients relying only on the PbO_2 as an indicator of adequacy of cerebral metabolism. Instead, dynamic oxygen reactivity should be routinely monitored as an indicator of overall brain tissue oxygenation and metabolism.

CALCULATIONS

Assuming CBF and $CMRO_2$ stability during oxygen therapy and equivalence of PbO_2 with capillary PO_2, (Kett-White et al., 2002) we can modify the standard formula for calculation of arteriovenous difference in oxygen (Kett-White et al., 2002) to determine the changes in hemoglobin saturation in the capillary blood:

$$Sv._aO_2 - Sv._bO_2 = [Ct_aO_2\,(a) - Ct_bO_2\,(a) - 0.003 * (Pb_aO_2 - Pb_bO_2)]\,/1.34xHb$$

where $Sv._aO_2$ and $Sv._bO_2$ are oxygen saturation at distal microcirculatory level after and before inhalation of oxygen; Ct_aO_2 (a) and Ct_bO_2 (a) are arterial oxygen content values after and before initiating oxygen therapy; Pb_aO_2 and Pb_bO_2 are PbO_2 values after and before starting inhalation of oxygen; and Hb is hemoglobin concentration in g/dL.

For example, if we increase PbO_2 from $P_{50} = 35$ mmHg (if hemoglobin saturation is 0.5 or 50%) to 100 mmHg and assume a change in CtO_2 (a) equal to 1 vol. %, the hemoglobin saturation at distal microcirculatory level will change in the following way (assuming a hemoglobin concentration 12 g/dL):

$$Sv_aO_2 - Sv_bO_2 = [1 - 0.003 * (100 - 35)]\,/1.34x12 = 0.05 \text{ or } 5\,\%$$

This means that the distal microcirculatory oxygen saturation under these arterial conditions ($PbO_2 = 100$ mmHg) will only increase 50% + 5% = 55%.

Calculations show the weak affinity of hemoglobin to oxygen under these conditions which results in allocation of additional oxygen amounts out of hemoglobin with creation of abnormally high PbO_2 in injured brain tissue areas.

CONCLUSIONS

Monitoring of BTOR or its equivalent $\Delta PbO_2/\Delta FiO_2$ is indicated during the intensive therapy of TBI patients. Both indices reflect the actual status of cerebral oxidative metabolism and help to reduce the risk of management errors which are otherwise masked by high FiO_2-induced "adequate" PbO_2 absolute values.

Blood transfusions, controlled hyperventilation and restoration of the regional acid-base balance should be performed under the guidance of above mentioned indices.

Further studies will help to establish the role of BTOR and $\Delta PbO_2/\Delta FiO_2$ monitoring in assessment of metabolic changes and adaptations taking place in the injured brain during the acute phase of TBI.

DISCLOSURE

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