Mechanisms of action of HBO_2

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Introduction:

Several mechanisms of action have been attributed to hyperbaric oxygen treatment (HBO_2T) that range from enhanced diffusion of O_2 and vascular effects to the modulation actions of the inflammatory response and/or apoptosis (for review see Buras 2007, Matchett 2009, Thom 2009). Moreover, modulation of oxidative and/or nitrosative stress has been reported to assume crucial importance, in particular in the context of HBO_2T-induced anti-microbial properties. Clearly, the vast majority of data originates from experimental studies. Finally, it should be noted that some mechanistic aspects of normobaric hyperoxia (for review see Asfar 2015, Hafner 2015) are most likely also valid for HBO_2T.

HBO_2T enhances the resolution of bubbles

Inert gas washout creates a concentration gradient with subsequent diffusion of O_2 into the bubble and, simultaneously, that of inert gas out of the bubble. Thereby, O_2 molecules are now capable of passing into the bubble and inert gas bubbles getting out, concomitant reduction of inert gas concentration. Due to chemical binding and metabolic utilisation of O_2, bubbles subsequently shrink, finally, leading to bubble collapse and inert gas dissolution [Van Liew 1993, Hyldegaard 2001, Blatteau 2006]. This is the initial mechanism of action of HBO_2T during gas embolism and decompression injury [Melamed 1992, Muth 2000].

HBO_2T increases tissue PO_2 during ischemia

HBO_2T improves O_2 delivery to the ischemic tissue as a result of the increased diffusion gradient from the capillary into surrounding “tissue cylinder”, and may thereby restore/improve local tissue metabolism. This may be particularly true in penumbral and or watershed-like regions after an ischemic insult [Veenith 2014]. Again, this rational is supported by data from patients after traumatic brain injury (TBI) by the sustained increase in brain tissue PO_2 even after termination of HBO_2T, and the concomitant fall of both lactate concentrations and the lactate/pyruvate ratios in the cerebrospinal fluid and brain tissue (the latter by microdialysis) [Rockswold 2010, 2013]. Other clinical situations supporting this rational are necrotizing soft tissue infections [Clark 1999, Korhonen 2000], radionecrosis [Thorn 1997], and crush injury [Bouachour 1996].

HBO_2T has vasoconstrictor properties without impairing tissue O_2 delivery

It is well-established that both pure O_2 breathing produces vasoconstriction, which is particularly pronounced in coronary and cerebral circulation. Mechanisms of hyperoxia-induced vasoconstriction are i) decreased ATP release from red blood cells [Ellsworth 1995], ii) reduced local NO release from cysteine-binding in the hemoglobin molecule [Stamler 1997 Allen 2009], and iii) increased NO quenching due to hyperoxia-related increased formation of reactive oxygen species (ROS) [Mak 2002, McNulty 2007]. The vasoconstrictor effect of HBO_2T was already demonstrated in 1965 [Whalen 1965], but does not seem to impair tissue O_2 delivery: e.g. in severe pancreatitis [Christophi 2007] and after traumatic brain injury (TBI) HBO_2T decreased intracranial pressure (ICP) and increased cerebral perfusion pressure without impairment of cerebral O_2 delivery [Hayakawa 1971, Rockswold 2001, 2010, 2013].

Data on HBO_2T effects on the microcirculation are scarce: in experimental animals microcirculatory flow and perfusion indeces were restored to normal [Sirsjö 1996 Cuthbertson 2008]; the only data in humans (14 patients with septic shock) showed improved capillary recruitment, the mechanism being unclear [Ferré 2011].

Finally, during crush injury, HBO_2T (in addition to the above-mentioned increase in the O_2 diffusiongradient) also indirectly improved tissue perfusion *via* its vasoconstrictor properties as a result of reduced tissue edema [Bouachour 1996].

HBO_2T restores mitochondrial respiration

HBO_2T competitively antagonizes with the binding of other gaseous molecules (e.g. CO, NO, H_2S, CN^- etc…) to heme moieties, in particular complex IV (cytochrome c oxidase) of the mitochondrial respiratory chain, and thereby restores normal electron transfer. Consequently, mitochondrial membrane potential is preserved [Palzur 2008]. This effect also explains the decreased ROS formation induced by HBO_2T during CO intoxication: the normalization of the electron transfer also decreases uncoupling of the mitochondrial respiration and thereby reduces ROS release and subsequent formation of peroxynitrite [Ischiropoulos 1996 Stamler 1996]. Ultimately, the protective effect on mitochondrial function and morphological integrity results in attenuation of the “intrinsic pathway” of apoptosis [Palzur 2004].

HBO_2T has antimicrobial properties and thereby INDIRECT anti-inflammatory properties

Some data do not refer improved survival in experimental polymicrobial sepsis to antibacterial activity [Thom 1986], but to an IL-10-dependent mechanism [Buras 2006]. Nevertheless, it is well-established that HBO_2T does exert *direct* antimicrobial properties due to ROS formation and enhanced leukocyte bacteria killing [Gottlieb 1971 Park 1992] and *indirectly via* additive/synergistic effects with antibiotics [Park 1991]. It is noteworthy in the context of necrotizing soft tissue infections that O_2 partial pressures of approx. 100-150 mmHg suffice to reduce the number of colonies of *Clostridium perfringens* [Kaye 1967], whereas approx. 250 mmHg are needed to block alpha toxin production [Gottlieb 1971].

HBO_2T has DIRECT anti-inflammatory properties

Anti-inflammatory effects of HBO_2T are due to various mechanisms, e.g.

i) HBO_2T causes actin-S-nitrosylation and thereby inhibits polymorphonuclear leukocyte β_2 integrin, which results in attenuation of neutrophil rolling and adhesion [Chen 1996, Thom 1997, Buras 2007]

ii) HBO_2T may cause activation of all NO synthase isoforms in endothelial cells, thereby attenuating neutrophil rolling and adhesion via inhibition of P-selectin, E-selectin, VCAM-1, and ICAM-1 [Thom 2009, Fosen 2014, Buras 2007]

iii) HBO_2T may cause inactivation of HIF-1α and thereby attenuate hyper-inflammation [Matchett 2009, Calvert 2006, Sun 2008, Zhang 2008]

iv) Conversely, *delayed* HBO_2T may activate oHIF-1α [Sunkari 2015 Fosen 2014]

v) HBO_2T may inhibit MMP-9 and thereby reduce apoptosis [Matchett 2009,Cummins 2009]

HBO_2T triggers anti-oxidative capacity

HBO_2T induces HO-1 [Speit 2002, Gröger 2005, 2008] as well as the anti-oxidative enzymes SOD, catalase and GPx [Li 2008], and thereby strengthens anti-oxidative capacity.

HBO_2T promotes angiogenesis

In tissues with O_2 deficit, HBO_2T induces VEGF [Yuan 2009, Patel 2005]. Moreover, it can promote vasculogenesis [Grassmann 2015] *via* redox stress-related stimulation

of circulating progenitor cells [Goldstein 2006, Milovanova 2009, Thom 2011, Gallagher 2012, Lee 2013, Fosen 2014, Heyboer 2014].

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