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LETTER TO THE EDITOR

# Intermittent hypoxic training: risks versus benefits. A biomedical engineering point of view

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A recent Letter to the Editor "Intermittent hypoxic training: risks versus benefits" (Hinghofer-Szalkay 2010) recommended inquiring into the long-term risks of intermittent hypoxic training (IHT), pointing to the potential risk of reactive oxygen species (ROS) formation. In this context, it is important to separate the hazards associated with the use of a device/system and the physiological risks and benefits of the therapy itself.

Devices and systems for hypoxia intervention are called "hypoxicators". Hypoxicators fall under the common definition of a medical device because of their intended use, the "modification of physiological process" (Council Directive 93/42/EEC 1993). Any device for human or animal treatment must naturally meet essential requirements for medical devices, e.g. electrical medical safety (IEC 60601-1 2007); and the Australian Therapeutic Goods Administration recently recommended regulating all hypoxicators (Therapeutic Goods Administration 2008).

The working mechanism underpinning IHT is intimately linked to oxygen sensing mechanisms (Renshaw and Nikinmaa 2007). If there is a significant drop in cellular $pO_2$, the signalling protein responsible for oxygen level monitoring hypoxia-inducible factor 1 alpha (HIF-1$\alpha$) triggers the transcription of a large number of genes involved in diverse processes such as angiogenesis, erythropoiesis, vascular tone, metal transport, glycolysis, mitochondrial function, cell growth and survival (e.g. Webb et al. 2009).

The main advantage of IHT is that it creates a hypoxic challenge that is sufficiently strong to produce the desired adaptive responses in a drug-free fashion (Hellemans 1999; Hamlin et al. 2007, 2009), while avoiding any damaging effects.

Indeed, more-prolonged stays at extreme altitudes can cause oxidative stress (Huang et al. 2008). However, this adverse effect should not be automatically extrapolated onto other hypoxic protocols, such as IHT, since it is important to recognise that severe chronic hypoxia and shorter-term hypoxia often have directly opposite physiological effects (Bailey et al. 2000; Serebrovskaya et al. 2008).

In a recent review of various hypoxia training regimes (Millet et al. 2010), "medically supervised treatments" using "altitude houses" and "altitude domes" were given a preference over home-use "altitude tents". Such risk analysis is of some concern, since, in either system, there is typically no continuous physiological monitoring of subjects undergoing hypoxic training. Altitude houses and domes, driven by nitrogen inflow, create the hazard of a potentially life-threatening low-oxygen environment.

In our view, the greatest single hazard of IHT is the potential for prolonged levels of low arterial $O_2$ saturation ($SpO_2$) to or below the safe threshold of 70% (Westerman 2004). However, nowadays, noninvasive pulse-oximetry readily allows measurement of $SpO_2$. Properly designed hypoxicators thus address the residual risks by providing safety cutoffs, automatically preventing potentially dangerous reduction of inspired $pO_2$ and $SpO_2$ and limiting exposure time (Bassovitch and Serebrovskaya 2009).

To the best of our knowledge, there have been no reported adverse physiological effects when users have followed the recommendations of "a few minutes of targeted $SpO_2$ 75–88% at rest, alternated with reoxygenation"

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provided by some manufacturers (Bassovitch 2007). In her review, Serebrovskaya describes a 25-year IHT experience in which an estimated 2 million patients were treated with no reported adverse effects (Serebrovskaya 2002). Our own systematic post-market monitoring (Biomedtech 2006–2010) similarly suggests an absence of short- or long-term adverse effects. Since the risks of IHT have been reduced to the lowest practically achievable level whilst the health and fitness benefits are demonstrable, the therapeutic benefits clearly outweigh the risks.

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