

Intermittent hypobaric hypoxia applicability in myocardial infarction prevention and recovery

Fabian Sanchis-Gomar^{a, b, *}, Jose Viña^{a, b}, Giuseppe Lippi^c

^a Faculty of Medicine, Department of Physiology, University of Valencia, Valencia, Spain

^b Fundación Investigación, Hospital Clínico Universitario/INCLIVA, Valencia, Spain

^c Clinical Chemistry and Haematology Laboratory, Department of Pathology and Laboratory Medicine, Academic Hospital of Parma, Parma, Italy

Received: September 14, 2011; Accepted: December 5, 2011

Abstract

Intermittent hypobaric hypoxia (IHH) has been the focus of important research in cardioprotection, and it has been associated with several mechanisms. Intermittent hypobaric hypoxia inhibits prolyl hydroxylases (PHD) activity, increasing the stabilization of hypoxia-inducible factor-1 (HIF-1) and activating crucial adaptative genes. It has been hence suggested that IHH might be a simple intervention, which may offer a thoughtful benefits to patients with acute myocardial infarction and no complications. Nevertheless, several doubts exist as to whether IHH is a really safe technique, with little to no complications in post-myocardial infarction patients. Intermittent hypobaric hypoxia might produce instead unfavourable changes such as impairment of vascular hemodynamics and hypertensive response, increased risk of hemoconcentration and thrombosis, cardiac rhythm perturbations, coronary artery disease and heart failure, insulin resistance, steatohepatitis and even high-altitude pulmonary oedema in susceptible or nonacclimatized patients. Although intermittent and chronic exposures seem effective in cardioprotection, IHH safety issues have been mostly overlooked, so that assorted concerns should be raised about the opportunity to use IHH in the post-myocardial infarction period. Several IHH protocols used in some studies were also aggressive, which would hamper their widespread introduction within the clinical practice. As such, further research is needed before IHH can be widely advocated in myocardial infarction prevention and recovery.

Keywords: hypobaric chamber • cardioprotection • hypoxia-inducible factor • erythropoietin • endothelium

Introduction

High-altitude exposure has been considered a major cardiorespiratory, endocrine, metabolic, nutritional, thermal and psychological strain for the human body [1]. The atmospheric low oxygen partial pressure affects oxygen (O₂) cascade inducing metabolic adaptations, such as changes in cell oxidative metabolism [1]. Acute, chronic or intermittent hypoxia (IH) exposure studies have been carried out with animals and humans in hypobaric chambers simulating high-altitude hypoxia conditions [2]. As a rule, IH refers to discontinuous use of hypoxia to reproduce features of altitude acclimatization using different methods, protocols and devices [3].

Specifically, IHH consists in temporary sessions expositions to acute hypobaric hypoxia conditions of a precise barometric pressure and thus to an equivalent altitude [2]. The IHH exposition is typically performed in hypobaric chambers. The ascent and descent of the chamber from ambient pressure to altitude occurred at a certain speed, and the oxyhemoglobin saturation of the patients is monitored at all times [4,5].

A hypobaric chamber, also known as altitude chamber, is hence used during aerospace or high terrestrial altitude research or training to simulate the effects of high altitude on the human body, especially hypoxia (low oxygen) and hypobaria (low ambient air pressure). Intermittent hypobaric hypoxia has been the focus of important research for recovery of post-myocardial infarction function over the past decades. Wang *et al.* observed that IHH improves post-ischaemic recovery of myocardial contractile function *via* redox signalling in rats [6]. In another recent investigation, Xu *et al.* demonstrated that IHH attenuates progressive myocardial remodelling and improves overall myocardial contractility [7]. In both studies, experimental animals were

*Correspondence to: Fabian SANCHIS-GOMAR, M.D.,
Department of Physiology, Faculty of Medicine, University of Valencia,
Av. Blasco Ibañez, 15, Valencia 46010, Spain.
Tel.: +(34) 96 386 46 50
Fax: +(34) 96 386 46 42
E-mail: fabian.sanchis@uv.es

intermittently exposed to an equivalent altitude of 5000 m in a hypobaric chamber for 4 weeks, concluding that IHH might reveal as a promising therapeutic approach for ischaemic heart diseases.

Cardiac protection by IHH has been associated with several mechanisms, including attenuated infarct size, myocardial fibrosis and apoptotic cardiomyocytes [7], elevated reactive oxygen species (ROS) production during early reperfusion [6], preserved Ca²⁺ homeostasis [8], calcium/calmodulin-dependent protein kinase II activity regulation [9], reduced myocardial apoptosis [10], induced opening of mitoKATP channels [11,12], increased vascularization [13], as well as antiarrhythmic and antioxidant effects [14,15]. It has been thus suggested that IHH is a simple intervention, which may offer a thoughtful benefits to patients with acute myocardial infarction and with little side effects or adverse reactions [6,8,12,14,16].

It has been recently observed that hypoxia-inducible factor-1 alpha (HIF-1 α), inducible nitric oxide synthase (iNOS) and PHD are also involved in IHH induced cardioprotection, which can hence be considered potential therapeutic targets [17]. The transcription factor HIF-1 is a key regulator responsible for the induction of genes that facilitate adaptation and survival of cells and the whole organism from normoxia (~21% O₂) to hypoxia (~1% O₂) [18–21]. Hypoxia-inducible factor-1 is composed of HIF-1 α and HIF-1 β . Of these two subunits, HIF-1 β is constitutively expressed, whereas HIF-1 α is tightly regulated by oxygen tension in terms of its protein stability and activity [22–25]. Under continuous oxygen supply, two distinct prolyl residues within the oxygen-dependent degradation domain of HIF α subunits are hydroxylated by prolyl-4-hydroxylase domain-containing enzymes (PHDs). Hydroxy-HIF α is recognized by the von Hippel–Lindau tumour suppressor protein and subsequently targeted for proteasomal degradation [22,26]. It has also been described that the presence of high ROS concentrations efficiently stabilizes HIF-1 α [27–30].

Overall, IHH inhibits PHD activity, increasing the stabilization of HIF-1 and activating crucial adaptive genes for erythropoiesis, iron homeostasis and angiogenesis such as erythropoietin (Epo), transferrin, transferrin receptor and vascular endothelial growth factor [31–33], as well as genes that regulate vasomotor control, glucose and energy metabolism, pH regulation, cell proliferation and viability [34]. Hypoxia-inducible factor-1 is also involved in the induction of cardioprotective molecules, such as iNOS and hemeoxygenase 1 [34].

Nevertheless, several doubts exist as to whether IHH is a really safe technique, with little to no adverse effects in post-myocardial infarction patients. Intermittent hypobaric hypoxia might produce unfavourable biochemical changes, including decreased anti-oxidative capacity and increased lipid peroxidation, which would lead to suppression of vascular endothelial function and impairment of vascular hemodynamics. Moreover, IH causes oxidative stress that may limit bioavailability of the endothelium-derived vasodilator nitric oxide, and contribute to generate a hypertensive response [35]. Cellular hypoxia is characterized by an increased levels of reduced equivalents as a result of insufficient availability of O₂ to be reduced in the mitochondrial electron transport chain [36]. In both the animal models and in humans exposed to different altitudes (*e.g.* 3000–8500 m), an oxidative stress has been clearly shown, as reflected by increased lipid, protein and DNA oxidation [37–40]. It has also been demonstrated

that the activity of enzymes such as cyclooxygenase, NAD(P)H oxidase and xanthine oxidase are crucial for the ROS generation under hypoxic conditions [36]. In this perspective, ROS participate in cardioprotection induced by ischaemic conditioning [6,41,42], and their generation might hence be beneficial after an acute myocardial infarction [8,43].

It is also noteworthy that erythropoiesis stimulation with an increase in Epo concentration [44–47], thereby enhancing red blood cells mass, hematocrit, blood viscosity and platelet count, have significant effect on blood rheology and blood pressure, exposing patients with high risk of cardiovascular events to hemoconcentration and thrombosis, especially during episodes of dehydration [48,49]. Elevated systemic hematocrit increases the risk of cardiovascular disorders, such as stroke and myocardial infarction. One possible pathophysiological mechanism involves an impairment of the ‘blood–endothelium interface’ [50]. Moreover, erythrocytosis predisposes to a prothrombotic state and hematocrit is a prognostic marker in patients with ST-segment elevation MI. Patients with elevated hematocrit are at increased risk of short-term mortality [51], as arterial thrombi usually forms under high blood flow conditions [52]. Although it has been suggested that the IH-induced, adverse myocardial consequences might be reversed by Epo administration [53], this appears rather unlikely, considering the previously mentioned mechanisms. In this perspective, it should be considered that systemic effects of hypoxia exposure are also dependent upon the so-called ‘hypoxic dose’, especially in terms of time of exposure, level of simulated altitude, type of hypoxic strategy. For instance, it has been shown that natural *versus* artificial hypoxia can produce very different haematological results [54–56]. Conversely, there is trustworthy evidence in the current scientific literature to show that the most effective method to stimulate accelerated erythropoiesis with the ‘Living High-Training Low’ strategy requires 2500 m altitude, 22 hr a day for at least 28 days [57]. The empirical evidence regarding the efficacy of IH is, however, still partially unclear. Several studies, have failed to demonstrate significant alterations in the erythropoietic response after different protocols [58–60]. Neya *et al.* also showed that normobaric IH (3000 m) was insufficient to enhance erythropoiesis [61], whereas exposure to more elevated simulated altitude (*i.e.* 4000 m) through intermittent normobaric hypoxia [46,47], or up to 5000–6300 m through IHH [62,63], induced a significant increase in several haematological parameters.

Obstructive sleep apnoea is associated with increased risk of atherosclerosis and, therefore, myocardial infarction and stroke [64], essential and resistant hypertension, cardiac rhythm perturbations (*e.g.* atrial fibrillation, bradyarrhythmias, supraventricular and ventricular arrhythmias) and heart failure [65]. As this condition is characterized by episodic cycles of hypoxia and normoxia during the sleep, Park and Suzuki observed that IH increases the susceptibility of the heart to oxidative stress, thereby worsening the risk of ischaemia-reperfusion-induced myocardial injury [66]. In obese or diabetic patients, IH exacerbates the insulin resistance and induces steatohepatitis, suggesting that it might account for the metabolic dysfunction in obesity [67].

Considering the original findings of Wang *et al.* [6], and Xu *et al.* [7], who reported that prolonged exposure of mice to an

equivalent altitude of 5000 can initiate the cardioprotective response, and even of other authors who tested the cardioprotection effects of IHH to an equivalent altitude of 7000 m [43,68], the acute exposure to similar or equivalent altitude might induce pulmonary oedema in susceptible or nonacclimatized patients [69–71].

Although intermittent and chronic exposures have been demonstrated to be effective in increasing coronary vasculature, decreasing infarction size and providing more efficient metabolism and better cardiac functional recovery post-ischaemia [72], IHH safety issues have been mostly overlooked, so that assorted concerns should be

raised about the opportunity to use IHH in the post-myocardial infarction period at this point in time. Several IHH protocols used in some studies were also aggressive, which would hamper their introduction within the clinical practice. As such, further research is needed before IHH can be widely advocated in myocardial infarction prevention and recovery.

Conflict of interest

None of the authors have any conflict of interest.

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