CD34 +/CD45-dim stem cell mobilization by hyperbaric oxygen — Changes with oxygen dosage ?

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Highlights

- CD34+-CD45-dim stem cells double by 2 hours after hyperbaric oxygen exposures.
- 2.5 versus 2.0 ATA exposures cause 1.9 to 3.0-fold higher stem cells by 20 treatments.
- Newly mobilized stem cells exhibit higher concentrations of regulatory proteins.

Abstract

Because hyperbaric oxygen treatment mobilizes bone marrow derived-stem/progenitor cells by a free radical mediated mechanism, ***we hypothesized that there may be differences in mobilization efficiency based on exposure to different oxygen partial pressures.*** Blood from twenty consecutive patients was obtained before and after the 1st, 10th and 20th treatment at two clinical centers using protocols involving exposures to oxygen at either 2.0 or 2.5 atmospheres absolute (ATA). Post-treatment values of CD34 +, CD45-dim leukocytes were always 2-fold greater than the pre-treatment values for both protocols. Values for those treated at 2.5 ATA were significantly greater than those treated at 2.0 ATA by factors of 1.9 to 3-fold after the 10th and before and after the 20th treatments. Intracellular content of hypoxia inducible factors - 1, - 2, and - 3, thioredoxin-1 and poly-ADP-ribose polymerase assessed in permeabilized CD34 + cells with fluorophore-conjugated antibodies were twice as high in all post- versus pre-treatment samples with no significant differences between 2.0 and 2.5 ATA protocols. We conclude that putative progenitor cell mobilization is higher with 2.5 versus 2.0 ATA treatments, and all newly mobilized cells exhibit higher concentrations of an array of regulatory proteins.

Introduction

Stem/progenitor cells (SPCs) capable of multipotent differentiation can be mobilized from bone marrow and adipose tissue, enter the blood stream and migrate to peripheral sites where they may facilitate recovery from injuries (To et al., 1997, Gil-Ortega et al., 2013 and Asahara et al., 1997). SPCs mobilization occurs after wounding, physical exertion and in response to a variety of chemical agents (Fiorina et al., 2010, Fukaya et al., 2014, Albanese et al., 2009, Asahara et al., 1999, Rehman et al., 2004, Reyes et al., 2002 and Takahashi et al., 1999). Exposure to hyperbaric oxygen (HBO2) appears to be a reliable way to mobilize SPCs in humans and also has been shown in rodents and horses (Thom et al., 2006, Thom et al., 2011, Ma et al., 2011, Milovanova et al., 2009 and Dhar et al., 2012). Animal studies indicate that one mechanism is based on activation of nitric oxide synthase type 3 (NOS-3) in bone marrow stromal cells with subsequent liberation of stem cell factor (Thom et al., 2006 and Goldstein et al., 2006). Separate from mobilization, HBO_2 improves engraftment and differentiation of several progenitor cell types in organs such as the spleen, bone marrow, brain, peripheral nerve, pancreas, cartilage and heart (Aljitawi et al., 2013, Lee et al., 2013, Cherng et al., 2012, Khan et al., 2012, Zhang et al., 2010, Zhang et al., 2011 and Pan et al., 2009). One area of interest with circulating SPCs is the identification of the sub-set having propensity to form vascular endothelium, so-called endothelial progenitor cells (EPCs) (Hirschi et al., 2008). Quantification of mobilized EPCs is based on flow cytometric detection of cell surface proteins and phenotypic manifestations of laboratory-grown clones (Hirschi et al., 2008 and Mund et al., 2012). Cells mobilized by HBO_2 exhibit many of these surface markers and when cultured, some clones show lectin binding consistent with an endothelial phenotype (Thom et al., 2006 and Thom et al., 2011). Animal studies have documented that HBO_2-mobilized SPCs form blood vessels in vivo and hasten wound healing (Milovanova et al., 2009, Goldstein et al., 2006 and Gallagher et al., 2007).

HBO_2-mobilized SPCs have greater content of hypoxia inducible factors (HIFs) and thioredoxin-1 (Trx), which in the murine model confers improved neovascularization (Thom et al., 2011, Milovanova et al., 2008 and Milovanova et al., 2009). Subsequent to HBO_2 treatments of refractory wounds and diabetic patients, the number of wound margin SPCs is increased and local HIFs and Trx appear to be within these localized SPCs (Thom et al., 2011 and Ma et al., 2011). This suggests that SPCs play a role in supplying factors required for wound healing. Hence, evaluating intracellular proteins may have greater importance to assess SPCs function versus ex vivo manipulations. Assessment of intracellular regulatory proteins of cells selected based on surface markers precludes studying ex vivo cell growth because of need to permeabilize the cell membranes.

HBO_2 treatment involves breathing 100% O_2 at 2 to 3 atmospheres absolute (ATA) pressure for 1.5 to 2 h once or twice daily. HBO_2 has been shown to improve refractory diabetic wounds and delayed radiation injuries in randomized trials and use is supported by independent evidence-based reviews (Bennett et al., 2008, Clarke et al., 2008, Kranke et al., 2012, Goldman, 2009, Fife et al., 2007, Duzgun et al., 2008 and Londahl et al., 2010). ***Several studies have failed to identify clinical efficacy (Annane et al., 2004 and Margolis et al., 2013). Notably, these studies involved exposures to 2.0 ATA or use of face masks with questionable seals thus reducing the fraction of inspired O_2;*** whereas several prospective randomized trials documenting therapeutic benefit utilized pressures of 2.4 or 2.5 ATA in pure O_2-filled chambers or using head-covering hoods (Londahl et al., 2010 and Marx et al., 1985). Whether clinical results may differ because of treatment protocols is unclear. The goal of this investigation was to evaluate whether mobilization of cells with surface markers considered consistent with SPCs (CD34 + and CD45-dim) and content of intracellular regulatory proteins differed between two commonly used HBO_2 protocols (Pober, 2012).

Methods

Patient Management Protocols

All procedures were approved by the Institutional Review Boards and patients signed informed consent. A consecutive series of patients was approached who had been referred for HBO_2 treatment because of complications from radiotherapy for cancer. On the basis of current standard of care, they were to receive at least 20 HBO_2 therapy sessions. Patient characteristics are shown in Table 1 (excerpted from this shortened abstract). Venous blood was collected prior to and after the 1st, 10th and 20th HBO2 treatments into Cyto-Chex BCT test tubes (Streck, Inc., Omaha, NE) that contain a proprietary preservative. Samples from the same day of treatment (pre- and post-HBO_2) were analyzed concurrently within 3 days of collection.

The standard Penn-based practice for delivering O2 involved placement of a balloon-cushioned face mask that is normally used for continuous positive airway pressure respiratory therapy. Treatments were conducted at 2.0 ATA for 2 h daily, 6 days/week. Intermittently the fractional inspired O2 content in the mask was verified to be 100%. Syracuse-based treatments were conducted in an acrylic chamber pressurized with pure O2 so that no special mask was required to assure 100% O2 delivery. Treatments were at 2.5 ATA for 90 min daily, 6 days/week.

Flow cytometry

CD34 + and CD45-dim cells and relative concentrations of intracellular proteins were evaluated with a 10-color FACSCanto (Becton Dickinson, San Jose, CA) using standard acquisition software following published techniques (Thom et al., 2011, Milovanova et al., 2008 and Milovanova et al., 2009). Briefly, nucleated cells were segregated from debris by DRAQ5 DNA staining and gates were based on true-negative controls according to fluorescence-minus-one analysis. Anti-actin fluorescence confirmed uniform cell permeabilization for intracellular protein analysis. Fluorescence/cell was determined and used to compare pre- versus post-HBO2 cell populations.

Materials

Chemicals were purchased from Sigma-Aldrich (St. Louis, MO). Antibodies were purchased from the following sources: From BD Pharmingen, San Jose, CA. R-phycoerythrin (PE)-conjugated mouse anti-human CD34 (Clone 581, a class III CD34 epitope; catalog number 555822), fluorescein isothiocyanate (FITC)-conjugated mouse anti-human CD45, catalog number 5558710 and allophycocyanin (APC)-conjugated mouse anti-human poly-ADP ribose polymerase (PARP) catalog number 558710; from R & D Systems, Minneapolis, MN, APC-conjugated anti-human hypoxia inducible factor (HIF)-1, catalog number IC1935P; from Novus Biologicals, Littleton, CO , PE-conjugated anti-human HIF-2 (catalog number NB100-122), FITC-conjugated anti-human HIF-3 (catalog number NB100-2529) and anti-human Trx catalog number EPR 6111 with secondary from Invitrogen, Grand Island, NY catalog number T-2769.

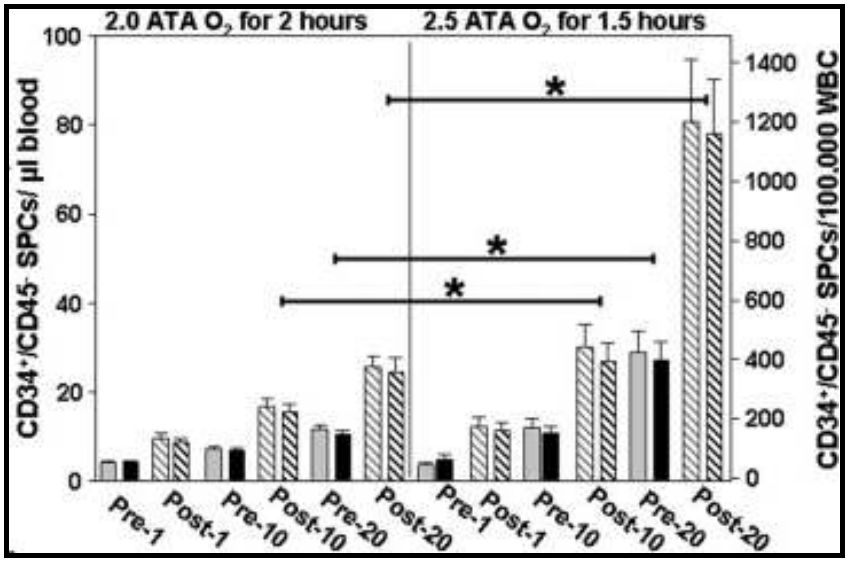
Statistical Analysis

Statistical analysis of stem cell numbers and quantitative changes in wound protein markers were carried out by repeated measures analysis of variance followed by the Tukey test for multiple comparisons (SigmaStat, Jandel Scientific, San Rafael, CA). Statistical significance was taken as $p < 0.05$. Data sets were found to be normally distributed so results are displayed as mean ± SE, n = 20 for all groups. Pre- and post-treatment comparisons were made within each type (2.0 ATA and 2.5 ATA) and between the 2.0 and 2.5 ATA treatments for each number (1st, 10th and 20th) by two-tailed t-test.

Results

Circulating Cells

Circulating CD34 + and CD45-dim leukocytes increased in blood from 20 consecutive patients undergoing HBO_2 therapy following a protocol of either 2.0 ATA or 2.5 ATA (Fig. 1). There were no significant differences in age, gender or radiation dose between groups (Table 1). Following the 10th as well as before and after the 20th treatment cell counts were significantly higher with the 2.5 ATA versus the 2.0 ATA protocol. Findings were essentially the same whether normalized to volume of blood (left axis of Fig. 1) or to total circulating leukocyte count (right axis) because total leukocyte counts for patients did not differ significantly over the course of the HBO_2 treatments (data not shown).



Leukocyte mobilization by HBO_2

Ref. To above figure:

The number of circulating CD34 +, CD45-dim cells in blood before and after the 1st, 10th and 20th treatment of 20 patients exposed to at either 2.0 or 2.5 ATA. Data were normalized to blood volume (gray boxes quantified on the left ordinate axis) or to total circulating leukocyte count (black boxes quantified on the right ordinate axis) and are mean ± SE, * indicates significant difference between 2.0 and 2.5 ATA groups (ANOVA). **All post-HBO2 values are significantly different from pre-HBO2 values at each treatment time in both groups (t-test).**

Our approach for assessing intracellular markers after membrane permeabilization precludes ex vivo growth analysis, which is why we probed for HIF-3. In animals we have found HBO2-mobilized SPCs that form new blood vessels and hence not CECs are well endowed with HIF-3, whereas HIF-3 normally is highly tissue restricted (to thymus, lung and a lesser extent in brain, heart and kidney) (Milovanova et al., 2009 and Gu et al., 1998). **Therefore, we conclude that the cells mobilized by hyperoxia are SPCs and that treatment pressure influences mobilization efficiency.** Functional consequences of this response require further study.

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Acknowledgment: This work was supported by funds provided by NIH grant R01-DK094260 and the Office of Naval Research Grant N00014-13-10614 to SRT.