Microvascular Research 93 (2014) 30–33

Contents lists available at ScienceDirect

Microvascular Research

journal homepage: www.elsevier.com/locate/ymvre

Nail fold capillary diameter changes in acute systemic hypoxia

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ARTICLE INFO

Article history:
Accepted 26 February 2014
Available online 6 March 2014

Keywords:
Capillary
Capillary recruitment
Capillary diameter
Acute systemic hypoxia
Hypoxemia
Nail fold
Capillaroscopy
Microcirculation
Venous occlusion
Post-occlusive reactive hyperemia

ABSTRACT

The present study was undertaken to determine the effect of arterial blood hypoxemia induced by acute systemic hypoxia ($pO_2 = 12\%$) on capillary recruitment and diameter, and red blood cell (RBC) velocity in human nail fold capillaries during rest, arterial post-occlusive reactive hyperemia (PRH), and venous occlusion (VO) using intravital video-capillaroscopy. Capillary recruitment was unchanged in acute systemic hypoxia (H) versus normoxia (N). There was no difference in RBC velocity measurements between normoxia and hypoxia ($P < 0.63$). However, a statistically significant increase in nail fold capillary total width (N, 39.9 ± 9.1 vs. H, 42.7 ± 10.3 μm; $P < 0.05$), apical diameter (N, 15.5 ± 4.3 vs. H, 16.8 ± 4.3 μm; $P < 0.05$), arterial diameter (N, 11.9 ± 3.5 vs. H, 13.9 ± 4.1 μm; $P < 0.05$), and venous diameter (N, 15.5 ± 4.3 vs. H, 17.2 ± 4.8 μm; $P < 0.05$) was observed and continued to be significant most often during post-occlusive reactive hyperemia (PRH) and venous congestion (VO). These data suggest that acute systemic hypoxia does not increase capillary recruitment, but instead increases capillary diameter, resulting in increased capillary blood flow.

Introduction

Blood flow in the microcirculation plays an important role in maintaining healthy tissues and organs by delivering oxygen and nutrients (Jeong et al., 2006). The influence of hypoxia on skin blood flow is poorly understood. It has been suggested that this stimulus causes vasodilation in human skin (Simmons et al., 2007), but the mechanisms of this phenomenon are at the microcirculatory level, such that moderate decreases in oxygen delivery cause dilation of the terminal arterioles, thereby allowing a more homogeneous distribution of oxygen through the capillary network and the diffusion of oxygen to the target tissue (Marshall and Davies, 1999). In contrast, it is known that acute exposure to hypoxia evokes changes in local vasodilator and neural vasoconstrictor factors that significantly influences vascular tone. In healthy human studies (Dinenno et al., 2003), mild-to-moderate systemic hypoxia doesn't blunt the sympathetic vasoconstriction via α-adrenergic receptors. However, recent evidence suggests that the responsiveness of the sympathetic adrenergic system can be modulated by factors associated with the cutaneous active vasodilator system (Shibasaki et al., 2008). During systemic hypoxia, when sympathoadrenal influence on vascular tone is eliminated, blood flow in the forearm is controlled by local vasodilator mechanisms (Markwald et al., 2011). The same effect is observed in cutaneous vasculature (Simmons et al., 2007). Moreover, when oxygen delivery falls below a critical value, oxygen utilization becomes delivery dependent and decreases in a linear fashion (Curtis et al., 1995). During normoxia, oxygen is supplied to the tissue mostly by arterioles, whereas in hypoxia, oxygen is supplied to tissues by capillaries through a NO concentration-dependent mechanism that controls capillary perfusion and tissue pO_2 (Bertuglia and Giusti, 2005). Therefore, this study was performed in order to determine the effect of arterial blood hypoxemia induced by acute systemic hypoxia ($pO_2 = 12\%$) on capillary recruitment, capillary diameter, and red blood cell (RBC) velocity in human nail fold capillaries during rest, arterial post-occlusive reactive hyperemia (PRH), and venous occlusion (VO).

Material and methods

Subjects

The study included nineteen healthy young adult (8 women and 11 men) volunteers (Table 1) who did not have a history of peripheral vascular pathology such as Raynaud's syndrome, dermatologic diseases, or systemic diseases such as diabetes or hypertension. All respondents were non-smokers. The subjects were familiarized with the experimental procedures and provided written informed consent according to the Declaration of Helsinki. The study protocol was approved by the Scientific Investigation Ethics Commission of the University of Latvia Institute of Experimental and Clinical Medicine.

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http://dx.doi.org/10.1016/j.mvr.2014.02.013
0026-2862/

Table 1
Characteristics of study subjects.

Characteristics		
Subjects		
Total, n		19
Male, n		11
Female, n		8
Age, y		21 ± 2.0
Body mass index, kg/m^2		25 ± 3.6
Characteristics	Normoxic conations (pO_2 = 21%)	Hypoxic conditions (pO_2 = 12%)
SBP, mmHg	123 ± 11.7	127 ± 12.3*
DBP, mmHg	70 ± 10.0	71 ± 11.4
MAP, mmHg	88 ± 9.6	89 ± 10.1
HR, bpm	65 ± 15.3	73 ± 16.5†
SpO_2, %	97 ± 1.3	78 ± 4.6†
$TcpO_2$, mmHg	60 ± 15.6	14 ± 9.6†
$TcpCO_2$, mmHg	69 ± 8.2	71 ± 14.8

Values are mean ± SD. SBP indicates systolic blood pressure; DBP, diastolic blood pressure, MAP, mean arterial pressure; HR, heart rate; SpO_2, Oxygen saturation; $TcpO_2$, Transcutaneous oxygen tension; and $TcpCO_2$, Transcutaneous carbon dioxide tension. *P < 0.05, †P < 0.001 from normoxic vs. hypoxic conditions used Wilcoxon ranked-sum test.

Experimental condition and protocol

To simulate systemic hypoxia (normobaric hypoxia), a hypoxicator (GO2Altidude, Biomedtech, Melbourne, Australia) which has an air separation system employing semi-permeable membrane technology (Spurling et al., 2011) was used, continuously pumping air at a flow rate of 20 l/min^{-1} into an air bag which was connected to a facial mask to deliver lower atmospheric O_2 concentration to the subjects (GO2Altitude, Biomedtech, Melbourne, Australia). Gas concentrations in the bag (oxygen mixture at 12%) were monitored by an oxygen sensor (Cambridge Sensotec, Cambs, UK). Arterial blood oxygenation (SpO_2) and heart rate (HR) were recorded online with a pulse oximeter (GO2Altitude, Biomedtech, Melbourne, Australia). In addition, blood pressure (HEM-711 AC, OMRON Healthcare, Kyoto, Japan) was recorded at every capillary measurement occasion. Gas partial pressure in the skin was continuously recorded by transcutaneous monitors (TCM4, Radiometer, Copenhagen, Denmark). The transcutaneous probe was applied on the same hand 2–3 cm proximal from the thumb.

Intravital video capillaroscopy

Intravital-capillaroscopy was used to visualize surface microvessels in the nail fold area of the right middle finger. Three types of physiological conditions were observed in normoxic and acute systemic hypoxic conditions. First, basal functional capillary density was observed in normoxia and hypoxia after 20 min of acclimatization in a supine position. At this time, collection of resting data was begun. After recording the resting data, arterial occlusion was applied for 3 min, and upon release of the forearm cuff (Hokanson Inc., Bellevue, WA, USA), the response of post-occlusion reactive hyperemia (PRH) was recorded for 30 s (CAM1 L300, CapiScope, KK-Technology, Bridleways Holyford, Devon, England). The reactivity of capillaries was observed after arterial occlusion, and the structural density of capillaries was observed during 2 min of venous congestion (Serne et al., 2001; Penna et al., 2008). Capillary density was defined as the number of erythrocyte-perfused capillaries per square millimeter of nail fold skin (Serne et al., 2001). In all phases the images were stored on video. The number of capillaries was counted offline by two experienced investigators (A.P. and K.N.M) from a freeze-framed reproduction of the video and analyzed using CapiScope Image Acquisition and Analysis software (CapiScope V.3.6.4.0, KK-Technology, Bridleways Holyford, Devon, England). Capillary diameters were measured according to previously described methods by Allen et al. (2003). The percentage change in capillary recruitment was calculated by dividing the absolute change in capillary density during post-reactive hyperemia (PRH) and venous occlusion (VO) by basal capillary density (×100) (Tibirica et al., 2007).

Statistical analysis

The Kolmogorov–Smirnov test was used to establish normality of the data. The differences between normoxia and hypoxia were analyzed using a paired Student's *t* test for normally distributed data or the Wilcoxon ranked-sum test for nonparametric distribution. Significance was accepted at P < 0.05 and all values are expressed as mean ± SEM (standard error of the mean).

Results

Table 1 shows the characteristics of the study subjects. Table 2 shows, respectively, the capillaroscopy data of the subjects' middle finger nail fold obtained at baseline, during PRH and during VO in normoxic (N) conditions (n = 19), in comparison with hypoxic (H) conditions (n = 19). Mean capillary density of the finger at baseline was not different between N and H (22.6 ± 9.3 and 21.6 ± 8.2 capillaries/mm^2; P = 0.13). The same was observed during PRH (N = 24.2 ± 9.5 and H = 22.5 ± 8.3 capillaries/mm^2; P = 0.08) and VO (N = 23.8 ± 9.1 and H = 22.6 ± 8.8 capillaries/mm^2; P = 0.12). There was a slight, but significant capillary recruitment during PRH in N, and no recruitment after the same maneuver in H. A quantitative estimate regarding the increase in capillary blood flow can be provided considering constant velocity (Table 2) and increased diameter (Table 3). In N a significant difference was observed between the mean capillary density at baseline and during PRH (22.6 ± 9.3 and 24.2 ± 9.5, respectively; P < 0.05). In contrast, no difference was observed between the mean capillary density at baseline and during VO (P > 0.05). RBC velocity was not change (N = 0.61 ± 0.26 [n = 88] and H = 0.63 ± 0.24 [n = 87]; P = 0.63) in acute systemic hypoxia. These data are displayed in Table 2.

Table 3 shows nail fold capillary loop diameters in study subjects. There was a statistically significant increase of nail fold capillary loop total width at baseline between N and H (39.9 ± 9.1 vs. 42.7 ± 10.3 μm; P < 0.001), with the same increases observed in the apex (N = 15.5 ± 4.3 vs. H, 16.8 ± 4.3 μm; P = 0.002), arterial limb (N = 11.9 ± 3.5 vs. H = 13.9 ± 4.1 μm; P < 0.001) and venous limb (N = 15.5 ± 4.3 vs. H = 17.2 ± 4.8 μm; P < 0.001). In PRH, the significant increase in overall nail fold capillary loop size (P < 0.001) is observed with one exception: there is no significant increase in apex loop diameters (P < 0.095). The observation in VO is the same as seen during H, namely, a significant increase in nail fold capillary diameters (P < 0.05) in both conditions. These data are displayed in Table 3.

Discussion

The main findings of this study are: 1) acute systemic hypoxia does not change capillary recruitment in nail fold capillaries, 2) nail fold capillaries increase in diameter in healthy young subjects, and 3) red blood cell velocity is not changed by hypoxic signal.

During systemic hypoxia, which causes arterial blood hypoxemia, an increase in capillary diameter in the nail fold area is observed (Table 3) without a change in red blood cell velocity (Table 2) in the basal hypoxic state and in the functional tests (reactive hyperemia and venous congestion). Our data demonstrating lack of changes in capillary recruitment is consistent with previous reports by Antonios et al. (1999) and Tibirica et al. (2009) when comparing control subjects. However, there are large capillary circulation differences in various skin areas, which can therefore be responsible for different adaptation mechanisms. For example, only 55% of the perfused capillaries in foot skin are used under normal conditions (Lamah et al., 2001), meaning that