Microvascular Research 102 (2015) 1–5

Contents lists available at ScienceDirect

Microvascular Research

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

Effect of acute systemic hypoxia on human cutaneous microcirculation and endothelial, sympathetic and myogenic activity

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ARTICLE INFO

Article history:
Received 2 April 2015
Revised 21 July 2015
Accepted 21 July 2015
Available online 26 July 2015

Keywords:
Acute systemic hypoxia
Microcirculation
Spectral analysis
Skin blood flow
Local regulation

ABSTRACT

The regulation of cutaneous vascular tone impacts vascular vasomotion and blood volume distribution as a challenge to hypoxia, but the regulatory mechanisms yet remain poorly understood. A skin has a very compliant circulation, an increase in skin blood flow results in large peripheral displacement of blood volume, which could be controlled by local and systemic regulatory factors. The aim of this study was to determine the acute systemic hypoxia influence on blood flow in skin, local regulatory mechanism fluctuations and changes of systemic hemodynamic parameters. Healthy subjects (n = 11; 24.9 ± 3.7 years old) participated in this study and procedures were performed in siting position. After 20 min of acclimatization 15 min of basal resting period in normoxia (pO_2 = 21%) was recorded, followed by 20 min in acute systemic hypoxia (pO_2 = 12%), and after 15 min of recovery period in normoxia (pO_2 = 21%). HRV was used to evaluate autonomic nervous system activity to heart from systemic hemodynamic parameters which continuously evaluated cardiac output, total peripheral resistance and mean arterial blood pressure. Regional blood flow was evaluated by venous occlusion plethysmography and skin blood flow by laser-Doppler flowmetry. To evaluate local factor influences to cutaneous circulation wavelet analysis was used; fluctuations in the frequency intervals of 0.0095–0.021, 0.021–0.052, and 0.052–0.145 Hz correspondingly represent endothelial, sympathetic, and myogenic activities. Our results from HRV data suggest that acute systemic hypoxia causes statistically significant increase of sympathetic (LF/HF; N1 = 0.46 ± 0.25 vs. H = 0.67 ± 0.36; P = 0.027) and decrease of parasympathetic (RMSSD; 80.0 ± 43.1 vs. H = 69.9 ± 40.4, ms; P = 0.009) outflow to heart. Acute hypoxia causes statistically significant increase of heart rate (RR interval; N1 = 960.3 ± 174.5 vs. H = 864.7 ± 134.6, ms; P = 0.001) and cardiac output (CO; N1 = 5.4 (5.2; 7.9) vs. H = 6.7 ± 1.4, l/min; P = 0.020). Regional blood flow and vascular conductance were not changed during acute systemic hypoxia, but forearm skin blood flow (skin blood flow; N1 = 39.7 (34.0; 53.2) vs. H = 51.6 ± 13.9, PU; P = 0.002) increases however local regulatory factor activity was not changed by acute systemic hypoxia. Acute systemic hypoxia causes sympathetic stimulation to heart which results in increased heart rate and larger cardiac output which could be the reason of forearm skin blood flow increase in acute systemic hypoxia without impact of local regulatory factors.

Introduction

Hypoxic stimulus induces a homeostatic disruption to enhance physiological adaptation. Recently suggested hypothesis is that skin microvascular function can mirror the state of microcirculation in other microvascular beds (Jung et al., 2001; Shamim-Uizzaman et al., 2002), including cardiac muscle (Rossi et al., 2009). However, control of cutaneous microcirculation is primarily mediated by the autonomic nervous system (Johnson and Kellogg, 2010) and these rhythmic variations in cutaneous blood flow are under the influence of autonomic innervation of the skin microvasculature (Rossi et al., 2008). One of most popular methods to evaluate non-invasively autonomic nervous systems activity is heart rate variability (HRV), which is a widely accepted indicator of autonomic nervous system (ANS) functions (Koelwyn et al., 2013), but limitation on this method is, that it shows just autonomic influences to heart (Akselrod et al., 1981), even more - it represents parasympathetic activity (Goldberger et al., 2001), but not common activity of autonomic nervous system in other organs.

Hypoxic vascular responses are not uniform across vascular beds and the mechanisms of hypoxic vasodilation appear to be tissue specific (Halliwill, 2003). Newer less, the vascular response to hypoxia is mediated by autonomic nervous system (Johnson and Kellogg, 2010), but

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http://dx.doi.org/10.1016/j.mvr.2015.07.005
0026-2862/

also the endothelial cell lining of blood vessels, as well as the underlining smooth muscle cells independent from endothelium (Kourembanas et al., 1998) can alert vascular tone in complex ways (Halliwill, 2003). Vascular tone represents the balance between local vasodilator mechanisms which attempt to secure adequate blood flow for metabolic demand and neuronal vasoconstrictor reflexes attempting to maintain arterial pressure (Halliwill, 2003). The regulation of cutaneous vascular tone impacts vascular vasomotion and blood volume distribution as a challenge to hypoxia, but the regulatory mechanisms yet remain poorly understood.

A skin has a very compliant circulation, an increase in skin blood flow results in large peripheral displacement of blood volume (Minson, 2003), which could be controlled by local (Clifford, 2011) and systemic (Hodges and Johnson, 2009) regulatory factors. Regulation of human cutaneous circulation could be evaluated by laser-Doppler flowmetry (Kvandal et al., 2003) and spectral analysis (Hodges and Del Pozzi, 2014) of blood flow. The previous researches suggest that vasomotion (Rossi et al., 2008) fluctuations in the frequency intervals of 0.0095–0.021, 0.021–0.052, and 0.052–0.145 Hz correspondingly represent endothelial, sympathetic, and myogenic activities (Hodges and Del Pozzi, 2014) and vasomotion components in the frequency interval of 0.6–1.6 Hz and of 0.2–0.6 Hz, due to the transmission to the skin microcirculation of the hemodynamic modification synchronous with heart activity and respiration (Rossi et al., 2006).

Vasomotion can be independent of systemic factors, because it is observed even in isolated blood vessels (Gustafsson et al., 1994). Pharmacological and physiological testing allows us to accept the premise that fluctuations in different spectral bands represent local regulatory activity. The spectral analysis of skin vasomotion allowed the identification of different flow motion waves in the total spectrum of 0.009–1.6 Hz, with the different frequency bands representing different regulatory activities (Rossi et al., 2006). However, the most important consideration is whether power or amplitude of a spectral band represents the total activity of a regulatory factor. Based on previous pharmacological testing, the endothelial vasomotion amplitude was increased due to acetylcholine (endothelium-dependent vasodilation) administration in comparison to sodium nitroprusside (endothelium-independent vasodilation) in the frequency band 0.0095–0.021 Hz (Kvandal et al., 2003). Comparing the myogenic fluctuations, a greater "activity" deduced from a larger weight of the component in the frequency analysis implies a larger or stronger effect on vascular tone. Sheppard et al. (2011) demonstrated that, during vasoconstriction induced by local cooling, myogenic oscillations become more synchronized, i.e. are increased in spectral power; conversely, with comparatively less vasodilation induced by local heating, oscillations become smaller. The relative wavelet amplitude of the myogenic component can be considered to be a measure of the contribution of myogenic activity (Jan et al., 2012).

The aim of our study was to determine the acute systemic hypoxia influence on blood flow in skin, local regulatory mechanism fluctuations and changes of systemic hemodynamic parameters.

Methods

Subjects

Eleven subjects (4 males and 7 females) participated in this study (Table 1). Subjects were non-smokers, were not taking any medications, and did not have any cardiopulmonary, neurological, metabolic or peripheral vascular diseases. 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.

Table 1
Characteristics of study subjects.

Characteristics		
Subjects		
Total, n		11
Male, n		4
Female, n		7
Age, years		24.9 ± 3.7
Mass, kg		63.7 ± 6.7
Height, m		1.71 ± 0.08
Body mass index, kg/m^2		21.8 ± 2.4
Characteristics	Normoxic conditions (pO_2 = 21%)	Hypoxic conditions (pO_2 = 12%)
HR, bmp	64.6 ± 12.8	70.9 ± 10.6*
SBP, mm Hg	116.8 ± 13.4	117.6 ± 14.1
DBP, mm Hg	61.0 ± 8.2	62.3 ± 8.5
MAP, mm Hg	82.7 ± 10.5	83.4 ± 10.8
SpO_2, %	98.1 ± 0.7	88.4 ± 3.8†

Values are mean ± standard deviation. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SpO_2, oxygen saturation.
* $P < 0.05$.
† $P < 0.01$ from baseline normoxia vs. acute hypoxia used paired t-test.

Experimental condition and protocol

Procedures were performed while the subject was in sitting position. After 20 min of acclimatization in a quiet temperature-controlled room (25 °C) 15 min of basal resting period in normoxia (pO_2 = 21%) was recorded, followed by 20 min in acute systemic hypoxia (pO_2 = 12%), and after 15 min of recovery period in normoxia (pO_2 = 21%). Forearm (non-glabrous) cutaneous blood flows were continuously measured 10 cm distal from ankle joint via laser-Doppler flowmetry (moorLDI2, Moor Instruments, Devon, UK) at a frequency of 40 Hz. Measuring place was heated locally by local heating probe till 33 °C (thermo-neutral) and held for the whole experiment. Heart rate and RR intervals were registered beat-to-beat, through a heart rate monitor (Polar S810i) with a 1000 Hz sampling frequency, fastened by an elastic band across chest in heart level. Polar S810i is a valid method to record RR interval and to obtain a valid analysis of HRV (Parrodo et al., 2010). Analysis of HRV measurements was conducted with the aid of Kubios HRV Analysis Software 2.1 (MATLAB, the Biomedical Signal Analysis Group, University of Kuopio, Kuopio, Finland) and data interpretation was made on the basis of previous researches (Huang et al., 2009; Wang and Huang, 2012). 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) was recorded online with a pulse oximeter (GO2Altitude, Biomedtech, Melbourne, Australia). Continuous arterial blood pressure and cardiac output were measured with non-invasive Finameter monitoring system (FinameterMIDI, FMS, Amsterdam, Netherlands). Regional blood flow was measured using strain gauge venous occlusion plethysmography (EC6, Hokanson Inc., Bellevue, USA).

Spectral analysis

Based on previous researches (Kvernmo et al., 1998; Kvandal et al., 2003; Hodges and Del Pozzi, 2014) spectral analysis of skin blood flow oscillations can be used as a valid tool for evaluation of different local