Characteristics and Clinical Significance of Microcirculation in Populations Residing at Different Altitudes

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Abstract

Background: This study aimed to evaluate changes in microcirculation, physiological characteristics, and the pathomechanism of and potential treatment alternatives for severe septic shock among healthy individuals residing at different altitudes.

Methods: Seventy individuals, 35 from Xining and 35 from Nanjing, were recruited, and their body temperature, pulse, respiration, mean arterial pressure, peripheral blood oxygen saturation, and blood cell parameters were determined. Microcirculation indices of sublingual microcirculation were monitored using the sidestream dark field method.

Results: Erythrocyte counts and hemoglobin levels were significantly higher among individuals from Xining than among those from Nanjing ($P < 0.05$); however, platelet counts were significantly lower among those from Xining ($P < 0.05$). Microcirculation indices of total vessel density, perfused vessel density, and the proportion of perfused vessels were significantly higher among individuals from Xining than among those from Nanjing; however, the microvascular flow index was lower among those from Xining. Microvascular density was significantly higher among individuals from Xining than among those from Nanjing.

Conclusion: Microvascular density may be a physiological adaptation among populations at moderate-to-high altitudes.

Introduction

Oxygen transport occurs in systemic circulation and through diffusion along the oxygen partial pressure gradient in tissues. Microcirculation is important, as it provides oxygen to local tissues and adjusts its distribution to meet oxygen demand [1]. Sublingual microcirculation can be monitored to detect low perfusion associated with severe infection, organ dysfunction due to septic shock, and mortality [2, 3]. Sidestream dark field (SDF) imaging, a next-generation microcirculation imaging method providing clear images, is noninvasive and portable and facilitates visual and semi-quantitative analysis as well as real-time monitoring of superficial tissue and microcirculation perfusion characteristics [4]. Changes in microcirculation among individuals after rash entry into high plateau areas has been previously reported [5, 6]; however, changes among individuals permanently residing in hypoxic areas remain unclear.

Currently, the primary methods for monitoring microcirculation are orthogonal polarization spectral (OPS) and SDF imaging. The primary underlying principle of SDF is that the LEDs emit light at 530 nm, and as red blood cells (RBC) are the major constituents of blood, imaging of RBC flow can be considered a capillary dynamic image for blood vessels. When the light is absorbed by hemoglobin in RBCs, it clearly reflects their flow within capillaries. These images also potentially reflect microcirculation parameters, including microvessel diameter, blood velocity, and functional capillary density, all of which combinatorially reflect capillary perfusion in microvessels [7].

Xining is located in the Qinghai-Tibetan plateau at an average elevation of 2260 m, and atmospheric oxygen content is only 78.6% of that at sea level. Upon stimulation of bone marrow erythrocytes resulting from hypoxia on the plateau, RBC count and blood viscosity increase, and a healthy person can adapt to changes in microcirculation under these conditions [8]. Assessment of microcirculation under chronic hypoxia may elucidate the underlying characteristic physiological changes and the mechanism underlying plateau adaptation. However, these pathophysiological changes may significantly differ between plain and high-altitude areas. Assessment of the characteristics of microcirculation and changes in individuals residing in a plateau may provide clear scientific evidence and treatment strategies and improve the survival rate of individuals with plateau shock syndrome [9, 10].

This study aimed to evaluate changes in microcirculation, physiological characteristics, and the pathomechanism as well as potential treatment alternatives for severe septic shock among healthy individuals residing at different altitudes.

Materials And Methods

Participant selection

This study was approved by the Ethics Committees of Nanjing Southeast University and Qinghai Provincial People's Hospital. Healthy volunteers were recruited, and written, informed consent was obtained from all participants. Healthy volunteers from Xining were considered direct descendants (for ≥ 2 generations) of the native high-altitude population in Xining (altitude, 2260 m), Qinghai, China. Lowlanders were recruited from Nanjing (altitude, 20 m), Jiangsu, China; they were not considered descendants of a native high-altitude population.

The healthy Xining volunteers comprised 20 men and 15 women; the healthy Nanjing volunteers, 19 men and 16 women. The inclusion criteria were as follows: healthy subjects with no known diseases, aged 19–33 years, and residing in Xining or Nanjing. The exclusion criteria were as follows: subjects aged < 18 years; presence of chronic heart, lung, or kidney disease; hemoglobin levels > 180 g/L; and pregnancy.

Observation of vital signs

Vital signs, including body temperature, pulse, respiration, noninvasive arterial blood pressure, and pulse oxygen saturation, were monitored using an IntelliVue MP50 patient monitor (Philips, Eindhoven, Netherlands).

Sample collection

All volunteers were fasted overnight for 8 h, and blood was sampled from their anterior elbows to determine the white blood cell, RBC, and platelet counts as well as hemoglobin levels and hematocrit using an XE-2100 automatic blood cell analyzer (Sysmex, Kobe, Japan).

Observation of sublingual microcirculation

Sublingual microcirculation was visualized using an SDF flow instrument (Micro Scan, Micro Vision Medical, Netherlands) at three sites: left, right, and middle. The examiner ensured that the acquired videos were stable and without pressure artifacts or bubbles for at least 20 s. The videos were analyzed using AVA3.0 (Micro Scan) on a Dell Studio 1558 computer (Dell, Round Rock, TX, USA). The following parameters were determined using either AVA3.0 or visual assessment: total vessel density (TVD) of small vessels, perfused vessel density (PVD) of small vessels, proportion of perfused vessels (PPV) in small vessels, and the MFI.

Statistical analysis

Data were analyzed using GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA, USA) and are expressed as means $\pm$ standard deviation values. The two groups were compared using an independent Student's *t*-test. Values of *P* < 0.05 were considered statistically significant.

Results

General information and vital signs of individuals from Xining and Nanjing

The sex ratio and average age were similar between the two groups; the average age of volunteers from Xining was 28.3 ± 3.2 years; Nanjing, 25.6 ± 2.5 years. Moreover, no significant differences (*P* > 0.05) were observed between body temperature, pulse, respiration, mean arterial pressure, or pulse oxygen saturation (SpO₂) values in the two groups (Table 1).

Table 1
Comparison of vital signs between healthy individuals from Nanjing and Xining

Group	Case	Temperature (°C)	Pulse (/min)	Respiration (/min)	Arterial mean pressure (mmHg)	Pulse oxygen saturation (%)
Nanjing	35	36.59 ± 0.28	75.20 ± 5.19	18.91 ± 1.33	92.34 ± 4.45	97.14 ± 1.51
Xining	35	36.54 ± 0.27	73.62 ± 5.58	18.54 ± 1.48	94.17 ± 5.09	96.60 ± 1.31
t		0.730	1.219	1.101	-1.599	1.602
P		0.468	0.227	0.275	0.115	0.114
Values are presented as means $\pm$ standard deviation.						

Comparison of blood parameters between individuals from Xining and Nanjing

The RBC count and hemoglobin levels were significantly higher among individuals from Xining than among those from Nanjing; however, the platelet count was lower among those from Xining (Table 2).

Table 2
Comparison of routine blood parameters between the Xining and Nanjing healthy groups

Group	Case	WBC (× 10 ⁹ /L)	RBC (× 10 ¹² /L)	HGB (g/L)	HCT (%)	PLT (× 10 ⁹ /L)
Nanjing	35	5.70 ± 1.43	4.07 ± 0.16	134.31 ± 10.05	43.24 ± 3.26	262.02 ± 45.41
Xining	35	6.25 ± 1.22	4.89 ± 0.41	148.82 ± 16.49	44.02 ± 3.80	208.77 ± 48.81
t		-1.723	-7.741	-4.445	-0.916	4.725
P		0.089	0.001	0.001	0.363	0.001
Values are presented as means ± standard deviation.						

Comparison of sublingual microcirculation between healthy individuals from Xining and Nanjing

As shown in Fig. 1, TVD, PVD, and PPV values in small vessels were significantly higher among individuals from Xining than among those from Nanjing, while MFI was significantly lower among those from Xining ($P < 0.05$).

The microvascular blood flow index was significantly lower ($P < 0.05$) in individuals from Xining than among those from Nanjing potentially because of increased RBC counts within microvessels and increased blood viscosity, which are adaptations to hypoxic environments.

Contrast analysis of sublingual microcirculation images

A complete data set of microcirculation images was obtained from all 70 subjects at altitudes of 20 m and 2260 m. The SDF camera efficiently recorded images at the maximum altitude. Typical images captured on the plain (20 m) and at high altitude (2260 m) are shown in Fig. 2. With the increase in altitude, blood flow velocity markedly decreased, while microvascular density and microvascular flow significantly increased in a uniform manner.

Discussion

In this study, we validated the use of OPS and SDF imaging using a novel lightweight computer-controlled imaging sensor-based microscope. This results show that SDF imaging yielded higher-quality images, especially of blood samples of individuals residing at a high altitude. This study shows the differences in microcirculatory responses to different altitudes.

Microcirculation refers to arterioles and venules with diameters $< 100 \mu\text{m}$. Exchange of tissue fluid, blood, lymph, and substances in the tissue fluid occur at the microcirculatory level. Microcirculation is responsible for the transport of all blood-borne hormones and nutrients to tissues and mediates immune function and homeostasis [11]. Based on different classifications of microvascular function, capillaries can be divided into resistant capillaries, exchange capillaries, microvascular capillaries, and capacity capillaries. Capillaries are the primary mediators of exchange between the blood and tissue owing to their thin walls, high permeability, and large contact area, which decelerates blood flow ($0.5\text{--}1.0 \text{ mm/s}$) [12].

Low arterial blood oxygen partial pressure (PaO_2); low arterial blood oxygen saturation (SaO_2); and hemorheological characteristics, including blood viscoelasticity, thixotropy, degeneration and aggregation of RBC, and platelet adhesion and aggregation, significantly contribute to circulation, especially microcirculation, in hypoxic environment such as that on the Qinghai-Tibetan plateau [13].

The physiological response to high-altitude chronic hypoxia involves an increase in the RBC count in microcirculation to compensate for the lack of oxygen in the atmosphere [14]. Our results show that RBC counts, hemoglobin levels, and hematocrit were significantly higher in individuals from Xining than from Nanjing. However, hypoxia exerts adverse effects on the body, resulting in changes in capillary and microvessel blood flow, including capillary contraction, a reduction in the diameter of fine arteries, and deceleration of capillary blood flow [15], concurrent with our results. Long-term chronic hypoxia potentially promotes capillary proliferation, especially of those in the brain, heart, and skeletal muscles. An increase in the density of capillaries can shorten the distance of blood oxygen dispersion to cells and increase cellular oxygenation. Deceleration of microcirculatory blood flow could be an adaptive response and might increase the tissue transit time of RBCs and improve oxygen diffusion. A prolonged course through the capillary network may enhance oxygen off-loading in the presence of a reduced partial pressure gradient between the capillary and mitochondria. Changes to the capillary wall might lead to the adherence and aggregation of WBCs. Increased permeability in capillaries and small veins is accompanied by an increase in blood density and viscosity. When WBCs adhere to capillary walls, capillary resistance is increased, and when coupled with RBC aggregation, blood flow is further decelerated. Under normal circumstances, the RBC surface is negatively charged; hence, RBCs repel each other and do not aggregate. However, capillary endothelial cell damage may occur in individuals residing at high altitudes; accordingly, the negative charge on the RBC surface can be reduced, the membrane composition and plasma proteins can be changed, and these alterations in blood flow can lead to increased RBC and platelet adhesion and aggregation, which may increase intravascular pressure, vascular permeability, plasma spillover, and spontaneous bleeding, leading to ecchymosis [16]. These changes in blood flow characteristics not only lead to microthrombosis and significantly reduce blood flow velocity but also reduce the frequency of gas exchange, slowing metabolite elimination. This potentially results in the accumulation of acidic products and a lower pH, which directly affects tissues, organs, and cell metabolism and causes serious cell degeneration, necrosis, and alterations in tissue organization. These changes directly affect the exchange of substances, switching time, and exchange rate. A modest increase in RBC and hemoglobin can increase the oxygen carrying capacity of blood and blood oxygenation, which is a compensatory mechanism. However, excessive RBC hyperplasia can

increase blood viscosity and lead to blood flow resistance, thus reducing blood flow and increasing the load on the heart. Excessive RBC proliferation serves as an adaptation to hypoxic conditions on the plateau to enhance blood flow rate, cellular metabolism, and nutrient exchange as well as to increase the number of capillaries.

Herein, TVD, PVD, and PPV were significantly higher in individuals from Xining than among those from Nanjing. An increase in capillary density in the skeletal muscles has been observed not only in humans but also in animals residing on the plateau. Animal studies have shown that dogs and other animals on the plateau in chronic hypoxic conditions have increased capillary densities in both the myocardium and gray matter. Blood capillary hyperplasia decreases the distance of oxygen circulation between capillaries and tissues and improves tissue oxygen levels and cellular adaptive responses to hypoxia. Increased vascular density is the body's response to hypoxic environments and may involve recruitment or peripheral vascular angiogenesis [17]. Both chronic and acute hypoxia alter capillary density. Martin recorded the MFI and vascular density of 24 healthy volunteers who climbed from sea level to a plateau at an altitude of 5300 m, 14 of whom further climbed to a higher altitude (6400 m), and reported that the MFI in small blood vessels ($< 25 \mu\text{m}$, $P < 0.0001$) and secondary vessels ($26\text{--}50 \mu\text{m}$, $P = 0.006$) was significantly lower at either altitude than that at sea level and significantly higher at 6400 m than at 5300 m ($P = 0.017$ and 0.002 , respectively). Additionally, the number of small blood vessels ($< 25 \mu\text{m}$) and secondary vessels ($26\text{--}50 \mu\text{m}$) decreased from 2.8 to 2.5 and 2.9 to 2.4, respectively. Herein, although the density of small blood vessels ($< 25 \mu\text{m}$) did not significantly increase, the number of secondary vessels ($26\text{--}50 \mu\text{m}$) significantly increased (1.68 ± 0.43 vs $2.27 \pm 0.57 \text{ mm/mm}^2$, $P = 0.005$), and vascular density at other altitudes also significantly increased ($P < 0.001$) [5].

Deceleration of blood flow results in a longer microcirculation perfusion time in tissues. Furthermore, improvement of the local pressure gradient can reduce oxygen diffusion between capillaries and mitochondria. Daniel et al. reported that individuals on a plateau presented a significant reduction in MFI during acute hypoxia and a significant increase in vascular density. The major mechanism underlying capillary hyperplasia is the upregulation of vascular endothelial growth factor (VEGF) [18], a specific glycoprotein that influences vascular endothelial cells; regulates almost all phenomena related to blood capillary hyperplasia, including gene expression in endothelial cells, degradation of the basement membrane, and endothelial cell migration and proliferation; and increases the permeability of microvascular endothelial cells. Furthermore, VEGF is significantly upregulated during septic shock [19]. This mechanism in endothelial cells in microvessels is the same in septic shock and hypoxia.

Sepsis is characterized by severe microvascular dysfunction and can cause septic shock [20]. Microvascular dysfunction during septic shock is associated with increased capillary permeability, which manifests as the destruction of the microvascular endothelial barrier (involving factors potentially associated with capillary leakage syndrome, e.g., endogenous pro-inflammatory cytokines, angiogenin 2, and VEGF) [21].

Conclusions

This study shows that increased vascular density is physiologically favorable during either acute hypoxia or chronic hypoxia and constitutes a major physiological adaptation among individuals residing on the Qinghai-Tibetan plateau. However, this alteration in vascular density owing to compensatory hyperplasia suggests the need for significantly more fluid in fluid resuscitation of patients with severe septic shock at high altitude. With a marked increase in vascular permeability in individuals from Xining, intravascular fluid leakage into the interstitial space may have led to tissue edema. Increased vascular permeability is an important characteristic of sepsis, which can cause systemic edema. Therefore, during the treatment of septic shock among individuals residing on the plateau, increased attention should be paid to microcirculation and fluid supplementation to prevent body water loss. Increased awareness of this phenomenon may improve identification of cases and provide better insights into the treatment of capillary leak syndrome.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committees of Nanjing Southeast University and Qinghai Provincial People's Hospital. All participants provided written, informed consent to their data appearing in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

All authors read and approved the final manuscript.

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Figures

Figure 1

(A) Differences in total vessel density between individuals from Xining and Nanjing. (B) Differences in perfused vessel density between individuals from Xining and Nanjing ($P \geq 0.05$). (C) Differences in the proportion of perfused vessels between individuals from Xining and Nanjing. (D) Differences in the mean fluorescence intensity between individuals from Xining and Nanjing. $*P < 0.05$.

Figure 2

Typical still image captured from video footage of sublingual microcirculatory blood flow on the plain (20 m) and at high altitude (2260 m).