The Use of Skeletal Muscle Near Infrared Spectroscopy and a Vascular Occlusion Test at High Altitude

Daniel S. Martin,^{1,2} Denny Z.H. Levett,¹ Rick Bezemer,³ Hugh E. Montgomery,⁴ Mike P.W. Grocott,^{1,5,6}
and the Caudwell Xtreme Everest Research Group

Abstract

Martin, Daniel, Denny Levett, Rick Bezemer, Hugh Montgomery, and Mike Grocott. The use of skeletal muscle near infrared spectroscopy and a vascular occlusion test at high altitude. *High Alt Med Biol* 14:256–262, 2013.—Microcirculatory function, central to tissue regulation of oxygen flux, may be altered by the chronic hypoxemia experienced at high altitude. We hypothesized that at high altitude, adaptations within skeletal muscle would result in reduced oxygen consumption and reduced microcirculatory responsiveness, detectable by near infrared spectroscopy (NIRS) during a vascular occlusion test (VOT). The VOT comprised 3 min of noninvasive arterial occlusion; thenar eminence tissue oxygenation (Sto₂) was measured by NIRS during the VOT at sea level, 4900 m and 5600 m (after 7 and 17 days at altitude, respectively) in 12 healthy volunteers. Data were derived from Sto₂ time-curves using specifically designed computer software. Mean ($\pm$ SD) resting Sto₂ was reduced at 4900 m and 5600 m (69.3 ($\pm$ 8.2)% ($p=0.001$) and 64.2 ($\pm$ 6.1)% ($p<0.001$) respectively) when compared to sea level (84.4 ($\pm$ 6.0)%). The rate of Sto₂ recovery after vascular occlusion (Sto₂ upslope) was significantly reduced at 4900 m (2.4 ($\pm$ 0.4)%/sec) and 5600 m (2.4 ($\pm$ 0.8)%/sec) compared to sea level (3.7 ($\pm$ 1.3)%/sec) ($p=0.021$ and $p=0.032$, respectively). There was no change from sea level in the rate of desaturation during occlusion (Sto₂ downslope) at either altitude. The findings suggest that in resting skeletal muscle of acclimatizing healthy volunteers at high altitude, microvascular reactivity is reduced (Sto₂ upslope after a short period of ischemia) but that oxygen consumption remains unchanged (Sto₂ downslope).

Key Words; altitude; hypoxia; ischemia; microcirculation; near infrared spectroscopy; oxygen consumption; skeletal muscle.

Introduction

WITH INCREASING ALTITUDE, THE PARTIAL PRESSURE of atmospheric oxygen declines as a consequence of the reduction in atmospheric pressure. Humans possess the capacity to adapt to this hypobaric hypoxia through the process of acclimatization, classically characterized by the augmentation of systemic convective oxygen transport mediated through increases in minute ventilation, heart rate, and hemoglobin concentration (Hornbein and Schoene, 2001; West et al., 2007). In addition, innate physiological alterations within the tissue microcirculation might help match local tissue oxygen demands with supply. However, pathophysiological microcirculatory dysregulation could uncouple the oxygen supply-demand relationship, leading to tissue hyp-

oxia and cellular metabolic failure (Ince, 2005). Such influences have yet to be characterized and clarified: a reduction in microcirculatory flow appears to be a dominant feature in both animal models (Saldivar et al., 2003) and human volunteers ascending to altitude (Martin et al., 2009a, 2010), although whether this represents a beneficial or detrimental adaptation remains unclear.

Skeletal muscle oxygenation can be measured by near infrared spectroscopy (NIRS) and, in combination with a non-invasive vascular occlusion test (VOT), provides a dynamic assessment of resting oxygen consumption and microvascular reactivity (Gerovasili et al., 2010). We hypothesized that adaptation to hypobaric hypoxia at high altitude (acclimatization) would result in i) reduced skeletal muscle oxygen consumption, and ii) impairment of the microcirculation, as

¹Centre for Altitude, Space, and Extreme Environment Medicine (CASE Medicine), Portex Unit, Institute of Child Health, ²Division of Surgery and Interventional Science, and ³Institute of Human Health and Performance, University College London, London, United Kingdom.

⁴Department of Translational Physiology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands.

⁵Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, and ⁶Anaesthesia and Critical Care Research Unit, Faculty of Medicine, University of Southampton, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom.

TABLE 1. SUBJECT BASELINE CHARACTERISTICS

Number of subjects	12
Number of males (%)	8 (66.6)
Mean ($\pm$ SD) age	35.4 ($\pm$ 7.8) years
Mean ($\pm$ SD) weight	72.6 ($\pm$ 10.3) kg
Mean ($\pm$ SD) height	1.77 ($\pm$ 0.09) m
Mean ($\pm$ SD) BMI	23.0 ($\pm$ 1.4)

BMI, body mass index; SD, Standard deviation.

assessed (respectively) by the decline in muscle oxygenation during a brief period of ischemia, and its rate of recovery upon cessation of the ischemic challenge.

Methods

Study setting and subjects

Approval for this study was obtained from the University College London Committee on the Ethics of Non-National Health Service (NHS) Human Research, and all participants gave written informed consent. Subjects were recruited from a medical research expedition to Cho Oyu (8201 m); the expedition has been previously described (Martin et al., 2009a). They were 12 non-smoking, healthy volunteers (8 males) whose baseline characteristics are shown in Table 1. Measurements were taken at sea level (75 m) where the barometric pressure was 100.5 kPa, prior to departure, and again after 7 and 17 days at 4900 m (57.2 kPa) and 5600 m (51.8 kPa), respectively. Peripheral arterial oxygen saturation (SpO₂) was measured at the time of investigation using a pulse oximeter (Onyx 9500, Nonin, USA) on the index finger of the opposite hand.

Measurement of thenar eminence muscle oxygen saturation

Local oxygenation in skeletal muscle can be monitored by NIRS, which calculates tissue oxygen saturation (StO₂) from

the ratio of oxygenated to total hemoglobin beneath a light-emitting optode. The absolute concentrations of oxy- and deoxyhemoglobin cannot be calculated by NIRS unless the path-length of the light through the tissue of interest is known (Delpy and Cope, 1997). NIRS also detects other chromophores in blood and tissue, and myoglobin and other species can comprise up to 80% of the overall optical signal in human skeletal muscle (Marcinek et al., 2007). However, the deoxygenation signal in skeletal muscle is primarily ($\approx$ 80%) derived from hemoglobin (Mancini et al., 1994). Static StO₂ values therefore vary widely between individuals, whereas dynamic physiological challenges evoke changes in StO₂, the rate of which reliably reflects changes in tissue oxygen tension. The NIRS-VOT consists of a short period of skeletal muscle ischemia induced by an occlusive cuff proximal to the site of NIRS probe, and has been used to assess skeletal muscle microcirculatory function in both healthy volunteers and patients (Bezemer et al., 2009; Creteur et al., 2007; De Blasi et al., 1993, 2005). The procedure typically involves placing a blood pressure cuff around the upper limb, rapidly inflating it above systolic blood pressure for a period of 3–5 min, and then releasing the cuff. During the protocol, StO₂ is measured continuously by NIRS, distal to the cuff, and the measurements plotted to generate a StO₂-time curve (Fig. 1). Temporary arterial, and venous, occlusion throughout cuff inflation results in muscle ischemia, and a steady decline in StO₂. This reaches a nadir prior to cuff release, which is followed by rapid reperfusion, re-oxygenation, and a reactive hyperemia (marked by a period of StO₂ raised above baseline). There is then a slow return of StO₂ back to baseline. The decline in muscle StO₂ during occlusion (StO₂ downslope) has been used as a measure of skeletal muscle oxygen consumption (Cheatle et al., 1991; De Blasi et al., 1993), whilst the rate of increase in StO₂ after cuff release (StO₂ upslope) is facilitated by a well-functioning microcirculation (Neviere et al., 1996).

Skeletal muscle in the thenar eminence was selected for the site of NIRS-VOT in this study as the thenar eminence is minimally susceptible to the confounding effects of excessive

FIG. 1. A typical StO₂-time curve generated during a near-infrared spectroscopy vascular occlusion test. AUC, Area under curve.

adipose accumulation and tissue edema (Gerovasili et al., 2010). StO_2 was measured using a tissue spectrometer (Inspectra Model 325, Hutchinson Technology, MN, USA), fitted with a probe of 15 mm optode spacing, and was defined as the ratio of oxygenated to total haemoglobin concentration. The device used light at 680 nm, 720 nm, 760 nm, and 800 nm and measured StO_2 every 3 sec. Data were recorded onto a laptop computer for later analysis.

Subjects rested for a minimum of 10 min in a sitting position prior to the commencement of recordings. Their dominant arm was placed at the height of the heart and a manual blood pressure cuff placed around the upper arm. A NIRS probe was attached to the thenar eminence and taped around its edges to reduce any effect that excessive ambient light might produce. Subjects were advised that they must not move their arm during any part of the investigation. After a 3 min period of stabilization, baseline StO_2 recordings were commenced. The blood pressure cuff was rapidly inflated to 250 mmHg for 3 min, then deflated. NIRS data collection continued for 3 min after cuff release. The exact times of occlusion and deflation were electronically marked on the NIRS tracing.

Data analysis

The electronic data were analyzed using the automated Inspectra StO_2 Researcher's Analysis Software version 4.01 (Hutchinson Technology). The following variables were derived: baseline, minimum and peak StO_2 (%), StO_2 downslope (% per minute) and StO_2 upslope (% per second). Downslope and upslope were calculated by the predetermined algorithms in the software using the slope of the least squares error linear equation. The downslope measurement was calculated from the point where StO_2 was 0.98 times the baseline StO_2 and the endpoint was 1 min later. The start point for upslope was determined when the recovery StO_2 first exceeded 1.05 times the minimum StO_2 reading, and the endpoint was when the recovery StO_2 reached 0.85 times the baseline StO_2 . All biological data reported were normally distributed and therefore treated as parametric data, and presented as mean ($\pm$ standard deviation (SD)). Values at the three different altitudes

displayed homoscedasticity and were compared using repeated measures ANOVA with Bonferroni correction for pairwise comparison (Norman and Streiner, 2000). The effect of gender on NIRS-VOT measurements was examined by the use of independent *t*-tests. Correlation between values was calculated using the Pearson's product-moment correlation coefficient. Calculations were performed using SPSS version 16.0 for Mac, and a *p* value of <0.05 was taken to indicate statistical significance.

Results

At sea level the mean ($\pm$ SD) SpO_2 was $97.9 (\pm 0.6)\%$, which was significantly reduced at 4900 m, $83.6 (\pm 5.4)\%$, and 5600 m, $77.6 (\pm 7.1)\%$, ($p < 0.001$). The mean temperature in the laboratories was $24.1 (\pm 1.0)^\circ\text{C}$ at sea level, $20.7 (\pm 2.9)^\circ\text{C}$ at 4900 m, and $17.6 (\pm 3.4)^\circ\text{C}$ at 5600 m. Individual StO_2 -time curves were generated for all participants at each of the three altitudes (Figs. 2 to 4) and analyzed using the Inspectra software. The mean values for all NIRS-VOT measurements are shown in Table 2. Mean baseline StO_2 was $84.4 (\pm 6.0)\%$ at sea level and declined to $69.3 (\pm 8.2)\%$ at 4900 m ($p = 0.001$) and $64.2 (\pm 6.1)\%$ at 5600 m ($p < 0.001$). The downslope during arterial occlusion remained unchanged between sea level and high altitude (Fig. 5) but the upslope, post cuff release, was significantly reduced at 4900 m ($2.4 (\pm 0.4)\%/sec$) and 5600 m ($2.4 (\pm 0.8)\%/sec$) when compared to sea level, ($3.7 (\pm 1.3)\%/sec$) ($p = 0.021$ and $p = 0.032$, respectively) (Fig. 6). There was no difference between upslope measurements at 4900 m and 5600 m ($p = 1.00$). There was also no difference between genders in this subject cohort for any of the NIRS-VOT measurements. The Inspectra software was not able to calculate area under the hyperaemia curve reliably in more than 30% of NIRS-VOT traces due to insufficient post-ischemic data. Analysis of the area under the hyperemic curve was therefore not performed.

At both of the high altitudes (4900 m and 5600 m), there was a significant inverse correlation between minimum StO_2 during the NIRS-VOT and subsequent StO_2 upslope; $r^2 = 0.348$ and $p = 0.044$ at 4900 m, and $r^2 = 0.608$ and $p = 0.003$ at 5600 m.

FIG. 2. Individual StO_2 -time curves for subjects during a near-infrared spectroscopy vascular occlusion test at sea level. Arterial occlusion from 0 to 180 seconds.

FIG. 3. Individual StO_2 -time curves for subjects during a near-infrared spectroscopy vascular occlusion test at 4900 m above sea level. Arterial occlusion from 0 to 180 seconds.

This relationship was absent at sea level ($r^2=0.065$ and $p=0.424$). When data from both high altitudes (4900 m and 5600 m) were combined, there were weak but statistically significant correlations between SpO_2 and baseline StO_2 ($r^2=0.206$, $p=0.03$) and SpO_2 and peak recovery StO_2 ($r^2=0.523$ and $p<0.001$). There was no correlation between SpO_2 and either StO_2 minimum, downslope or upslope. However, there was also a correlation between the StO_2 downslope and StO_2 upslope in the combined altitude cohort ($r^2=0.555$ and $p<0.001$). This relationship was not present at sea level.

Discussion

This is the first reported use of NIRS with a VOT at high altitude, here applied to the thenar eminence. Ascent to alti-

tude was associated with systemic arterial hypoxemia and also with tissue hypoxia (mean thenar eminence StO_2 being lower at rest, and during and at peak after 3 min of complete arterial occlusion). Ascent also appeared associated with unaltered basal oxygen consumption (StO_2 downslope during occlusion) despite the presence of tissue hypoxia, but with impaired microcirculatory function (reduced StO_2 upslope, Fig. 6)— StO_2 upslope reflecting endothelium dependent vasodilation (Gerovasili et al., 2010).

That systemic hypoxemia was associated with a sustained reduction of resting baseline skeletal muscle StO_2 is, perhaps, to be expected: skeletal muscle hypoxia is demonstrable in the presence of hypoxemia (Ferrari et al., 1997; Subudhi et al., 2007), and thigh muscle StO_2 correlates with the oxygen saturation of its venous outflow when healthy volunteers breathe hypoxic gas mixtures (Costes et al., 1996). More im-

FIG. 4. Individual StO_2 -time curves for subjects during a near-infrared spectroscopy vascular occlusion test at 5600 m above sea level. Arterial occlusion from 0 to 180 seconds.

TABLE 2. MEAN ($\pm$ SD) SpO_2 AND StO_2 VALUES DURING A VASCULAR OCCLUSION TEST AT SEA LEVEL AND HIGH ALTITUDE

	Sea level	4900 m	5600 m
SpO_2 (%)	97.9 (± 0.6)	83.6 (± 5.4)*	77.6 (± 7.1)* Ψ
Baseline StO_2 (%)	84.4 (± 6.0)	69.3 (± 8.2)*	64.2 (± 6.1)*
Minimum StO_2 (%)	43.2 (± 12.1)	29.8 (± 12.6)*	22.4 (± 11.0)*
Peak StO_2 (%)	94.1 (± 1.4)	83.0 (± 5.6)*	76.4 (± 6.6)* Ψ
Overshoot StO_2 (%)	9.6 (± 6.4)	13.7 (± 5.0)	12.2 (± 6.1)
Downslope (%/min)	13.6 (± 3.3)	13.6 (± 3.0)	14.2 (± 4.4)
Upslope (%/sec)	3.7 (± 1.3)	2.4 (± 0.4)*	2.4 (± 0.8)*

SD, Standard deviation; *significantly different from sea level ($p < 0.05$); Ψ , significantly different between 4900 m and 5600 m ($p < 0.05$).

portantly, however, we showed altitude exposure to be associated with a sustained reduction in StO_2 upslope. This impact seemed independent of the absolute degree of arterial hypoxemia: despite SpO_2 falling from 83.6 % at 4900 m to 77.6 % at 5600 m ($p < 0.001$), there was no further reduction in absolute StO_2 measurements or the upslope (2.4%/sec at both altitudes). We also demonstrated weak correlation between SpO_2 and two of the absolute StO_2 measurements (baseline and peak recovery) at altitude, and between StO_2 up and downslopes at altitude.

The divorce between the degree of arterial hypoxemia and the magnitude of depression in StO_2 upslope is hard to explain with certainty. However, the responses we characterized will have resulted from a complex interaction of degree and magnitude of hypoxic exposure along with an unpredictable degree of acclimatization. Whilst the magnitude of hypoxia was greater at 5600 m, there was a period of 10 days between the two high altitude measurements. Absence of a further decline in StO_2 upslope may be explained by adaptive changes within skeletal muscle occurring over this time interval. Interactions

FIG. 5. StO_2 downslope measurements for subjects at sea level, 4900 m, and 5600 m. 4900 m = Day 7 at altitude; 5600 m = Day 17 at altitude.

FIG. 6. StO_2 upslope measurements for subjects at sea level, 4900 m, and 5600 m. 4900 m = Day 7 at altitude; 5600 m = Day 17 at altitude; NS = nonsignificant.

between exposure-duration and exposure-magnitude are difficult to unravel in the setting of a field study, however repeated recordings over time at each altitude might have provided additional insights into the mechanisms underlying these findings. Alternatively, the decrease in SpO_2 from 4900 m to 5600 m may have been insufficient to elicit additional alterations within the skeletal muscle microcirculation, or the upslope may have reached its minimum physiological rate.

StO_2 upslope represents removal of deoxyhemoglobin from the ischemic skeletal muscle by a rapid influx of oxyhemoglobin when arterial influx returns (Bezemer et al., 2009). However, NIRS-assessed StO_2 upslope is not a measure of blood flow per se, but a surrogate for a spectrum of endothelially-dependent changes in capillary blood flow (Poole et al., 2011) which occur following a period of ischemia. Vasodilatation begins during the ischemic occlusion phase such that when the cuff is released, there is a brief period of hyperemia, the magnitude of which is dependent of microcirculatory function (Neviere et al., 1996). Endothelial dysfunction thus results in slower reperfusion rates and therefore a reduced StO_2 upslope (Gerovasili et al., 2010). We have previously demonstrated that ascent to high altitude is associated with a reduction in sublingual microcirculatory flow index (MFI) measured by sidestream dark field (SDF) imaging (Martin et al., 2009a, 2010). However, it remains unclear as to whether this reduction in MFI and alteration of StO_2 upslope represents a pathological or beneficial adaptive response to hypoxemia. It is plausible that a reduced microcirculatory blood flow may aid tissue oxygenation through an increase in tissue transit time.

However, other factors may also have contributed to the observed changes in StO_2 upslope. Tissue diffusion limitation, the potential barrier to oxygen flux from erythrocytes to cells when arterial oxygenation falls, and the gradient of oxygen tension between them is diminished (Wagner, 1992), may have played such a role. In addition, metabolic mediators (such as adenosine, potassium, hydrogen ions, carbon dioxide, and prostaglandins) certainly play a central role in mediating exercise-induced hyperemia, (Delp and Laughlin, 1998) and may also influence the hyperemic response to

ischemia. Thus, the vasodilatory effect of hypoxemia could have exhausted skeletal muscle flow reserve prior to the ischemic stimulus commencing, giving the impression of a diminished vascular response after the VOT. Increased sympathetic/ catecholaminergic activity at altitude (Cunningham et al., 1965), detectable in skeletal muscle (Mazzeo et al., 1995; Saito et al., 1988), may also have affected the microcirculation and thus Sto_2 upslope. Polycythemia (Huff et al., 1951), endothelial dysfunction (Vallet, 1998), and changes in red blood cell deformability (Parthasarathi and Lipowsky, 1999) following acclimatization may also have impacted upon the microvascular flow response. Low ambient temperature could (through vasoconstriction) have affected Sto_2 upslope, although the reduction in ambient temperature in the high altitude laboratories was not particularly marked.

The relationship between Sto_2 up- and downslope also warrants further comment. Whilst these measures were unrelated at sea level, they correlated at altitude such that a reduced resting muscle oxygen consumption was associated with a less responsive microcirculation. This might represent evidence of the coupling of metabolic and circulatory responses. Perhaps present at sea level but only revealed in response to sustained hypoxia. The lack of change in Sto_2 downslope in the current study suggests that there was no overall change in resting muscle oxygen consumption at altitude.

The NIRS-VOT technique has been validated (Kragelj et al., 2000). Whilst data vary considerably between individuals (Figs. 2 to 4) (likely due to differences in subcutaneous adipose tissue depth and the inability of the Hutchinson spectrometer to generate a truly quantitative measurement), intra-individual variability remains low. In the present study, 3 minutes of arterial occlusion allowed adequate time for useful readings to be measured without causing undue discomfort, and its use has been reliably applied and reported by others investigators (Gerovasili et al., 2010). Active limb movement during measurements will increase muscle oxygen consumption. The need for passive immobility was, however, stressed to all subjects, and any unseen movement is unlikely to have introduced systematic bias.

The literature is divided as to whether cuff inflation should be for a specific time period (Creteur et al., 2007) or to a predefined minimum Sto_2 (Gomez et al., 2008). We selected the time-limited methodology so as to have a body of clinical data to draw comparison with and to avoid confounding from the inter-individual differences in absolute Sto_2 that occur on ascent to altitude (Martin et al., 2009b).

The Inspectra NIRS device measured Sto_2 at 3 second intervals. The analysis software generated Sto_2 curves by extrapolating between measurement points and the accuracy of data relating to periods of rapid change (such as VOT recovery) may thus have been blunted. Furthermore, the NIRS-VOT measurements were calculated by commercially written software that contained predetermined algorithms. Such factors are unlikely to introduce any altitude-related bias, but may limit comparison with studies using different analysis techniques. These technical differences might account for lower baseline Sto_2 upslope values in our study when compared to those reported by Creteur et al. (2007) and Doerschug et al. (2007) (3.7%/sec vs. 4.8%/sec and 4.7%/sec, respectively). The inability of the Inspectra software to calculate the hyperemic area under the curve in all cases was due

to insufficient measurement time post cuff release. In retrospect, a longer period of data capture post cuff release may have avoided this data loss.

Some degree of tissue edema is not uncommon upon ascent to altitude (Gunga et al., 1995; Maggiorini et al., 1990). If present within the skeletal muscle or overlying subcutaneous tissue, this might have attenuated the NIR light signal and falsely lowered recorded Sto_2 values. However, altitude-related accumulation of interstitial edema at the thenar eminence (our site of measurement) is uncommon (Mancini et al., 1994; Poeze, 2006).

We observed no difference between genders in the NIRS-VOT measurements studied, however, imbalance in the gender distribution amongst the subjects (four females, eight males) may account for this negative finding, and a type 2 error cannot be excluded.

Conclusion

Ascent to high altitude resulted in hypoxemia that was associated with a reduction in skeletal muscle absolute Sto_2 values. Basal oxygen consumption, as assessed by Sto_2 downslope during vascular occlusion, was unaffected by hypoxemia at altitude. However, the recovery rate after occlusion had been released (St -o_2 upslope) was significantly reduced. These observations may reflect alterations in microvascular reactivity, but whether these are physiological or pathophysiological remains unknown. The results of this study may have implications for critically ill patients exposed to sustained hypoxemia secondary to pathophysiology.

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No competing financial interests exist.

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Address correspondence to:

Dr. Daniel Martin

University College London

Division of Surgery and Interventional Science

9th Floor, Royal Free Hospital

London, NW3 2QG

United Kingdom

E-mail: daniel.martin@ucl.ac.uk

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