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Systemic oxygen extraction during exercise at high altitude

D. S. Martin[1*], A. Cobb[1], P. Meale[1], K. Mitchell[1,2,3,4], M. Edsell[1,5], M. G. Mythen[1] and M. P. W. Grocott[1,2,3,4], for the Xtreme Alps Research Group

[1] UCLH NIHR Biomedical Research Centre, Institute of Sport and Exercise Health, University College London Centre for Altitude Space and Extreme Environment Medicine, 170 Tottenham Court Road, London W1 T 7HA, UK
[2] Integrative Physiology and Critical Illness Group, Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Mailpoint 810, Sir Henry Wellcome Laboratories, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, UK
[3] Anaesthesia and Critical Care Research Unit, GICU, Mailpoint 27, Level D, Centre Block, University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, UK
[4] NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK
[5] Department of Anaesthesia, St George's Hospital, London, UK

* Corresponding author. E-mail: daniel.martin@ucl.ac.uk

Editor's key points

- Five healthy subjects were studied at sea level and at altitude (4559 m).
- Systemic oxygen extraction after peak exercise was measured.
- Hypoxaemia was seen but no change in the oxygen extraction ratio.
- The lack of increased tissue oxygen extraction despite hypoxaemia is not known.

Background. Classic teaching suggests that diminished availability of oxygen leads to increased tissue oxygen extraction yet evidence to support this notion in the context of hypoxaemia, as opposed to anaemia or cardiac failure, is limited.

Methods. At 75 m above sea level, and after 7–8 days of acclimatization to 4559 m, systemic oxygen extraction [$C(a-v)O_2$] was calculated in five participants at rest and at peak exercise. Absolute [$C(a-v)O_2$] was calculated by subtracting central venous oxygen content ($CcvO_2$) from arterial oxygen content (Ca_{O_2}) in blood sampled from central venous and peripheral arterial catheters, respectively. Oxygen uptake ($\dot{V}O_2$) was determined from expired gas analysis during exercise.

Results. Ascent to altitude resulted in significant hypoxaemia; median (range) Sp_{O_2} 87.1 (82.5–90.7)% and Pa_{O_2} 6.6 (5.7–6.8) kPa. While absolute $C(a-v)O_2$ was reduced at maximum exercise at 4559 m [83.9 (67.5–120.9) ml litre^{-1} *vs* 99.6 (88.0–151.3) ml litre^{-1} at 75 m, $P=0.043$], there was no change in oxygen extraction ratio (OER) [$C(a-v)O_2/CaO_2$] between the two altitudes [0.52 (0.48–0.71) at 4559 m and 0.53 (0.49–0.73) at 75 m, $P=0.500$]. Comparison of $C(a-v)O_2$ at peak $\dot{V}O_2$ at 4559 m and the equivalent $\dot{V}O_2$ at sea level for each participant also revealed no significant difference [83.9 (67.5–120.9) ml litre^{1} *vs* 81.2 (73.0–120.7) ml litre^{-1}, respectively, $P=0.225$].

Conclusion. In acclimatized individuals at 4559 m, there was a decline in maximum absolute $C(a-v)O_2$ during exercise but no alteration in OER calculated using central venous oxygen measurements. This suggests that oxygen extraction may have become limited after exposure to 7–8 days of hypoxaemia.

Keywords: altitude; blood gas analysis; exercise; hypoxia; oxygen; physiology

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Exposure to hypobaric hypoxia at high altitude presents a significant physiological challenge to oxygen transport processes within the body. This environmental stress is heightened during exercise by the additional demand of increased oxygen consumption from exercising skeletal muscles. Intuitively, one would expect that when hypoxaemic, whole body oxygen extraction would be increased to match the heightened demand for oxygen. However, during a simulated ascent of Mount Everest in a hypobaric chamber study, Operation Everest II (OE II), no such augmentation of oxygen extraction was observed either at rest or during exercise.[1] Using a mathematical modelling approach based on data from OE II it was suggested that oxygen conductance within the muscle was one of the most likely factors to limit exercise at high altitude (tissue diffusion limitation).[2]

Whole body oxygen extraction is difficult to measure directly but can be inferred from the difference between the influent and effluent oxygen contents of an organ, or for the entire body. As proposed by Adolf Fick, comparison of blood sampled from the pulmonary vein and artery provides a measure of whole body oxygen extraction that can be used to calculate cardiac output and oxygen consumption. Estimations of these

measures can be obtained in humans by obtaining simultaneous peripheral arterial and central venous blood samples.

Based on previous data, we hypothesized that absolute whole body oxygen content extraction [$C(a-v)O_2$] derived from arterial and central venous blood samples, and relative oxygen extraction ratio (OER) [$C(a-v)O_2/CaO_2$], would be reduced at rest and during peak exercise at high altitude when compared with sea level values.

Methods

Study design and participants

Approval for this study was obtained from the University College London Committee on the Ethics of non-NHS Human Research and all participants gave written informed consent. Participants were five individuals enrolled from the Xtreme Alps 2010 expedition,[3] three females and two males; median age was 37.4 years. The participants were studied at sea level in London (75 m) and then at 4559 m in the Margherita Hut high altitude research laboratory. Ascent was initially by road to Alagna (1200 m) and then, on the same day, by cable car to Punta Indren (3200 m) and on foot to the Gnifetti Hut (3647 m). After two nights spent at 3647 m, participants ascended to 4559 m. Study measurements were made on Days 5 and 6 after arriving at 4559 m (Days 7 and 8 at high altitude). Subjectively, participants were well acclimatized to high altitude with no evidence of acute high altitude illness at the time of the study and had no contraindications to undertake a maximal exercise capacity test. The median barometric pressure during the studies was 101.7 kPa at sea level and 58.1 kPa at 4559 m.

Vascular catheter insertion

All catheters were placed under full sterile conditions, local anaesthetic infiltration with 1% lidocaine. A 20 G arterial catheter (Vygon, UK) was inserted into the radial artery of the non-dominant arm. An 11 cm 18-G single lumen central venous catheter (Vygon, UK) was inserted as caudally as possible into the right internal jugular vein using ultrasound (Micromaxx, SonoSite, Inc., Bothell, WA, USA) to identify the vein. A modified Seldinger technique (without skin incision or dilatation of the vein) was used to insert the catheter. Both catheters were then connected to a pressure transducer system (Edwards Lifesciences, CA, USA) using 0.9% sodium chloride as the flushing fluid. Transducers were attached to a monitoring system (GE Marquette Dash 3000, GE Healthcare, Chalfont St Giles, UK), zeroed at the height of the right atrium and attached firmly to the participant. After completion of the exercise protocols and 30 min of recovery, vascular catheters were removed using a sterile technique.

Table 1 Median (range) resting oxygen extraction values at sea level and 4559 m. [Hb], haemoglobin concentration; * Significant difference between 75 and 4559 m ($P<0.05$)

	75 m	4559 m
[Hb] (g dl^{-1})	14.2 (13.2–15.2)	14.7 (12.4–16.3)
Pa_{O_2} (*kPa*)	13.8 (11.7–14.4)	6.6 (5.8–7.1)*
Sa_{O_2} (%)	97.9 (96.7–98.2)	87.1 (82.5–90.7)*
Scv_{O_2} (%)	62.6 (53.8–64.6)	57.7 (52.8–59.9)*
CaO_2 (ml $litre^{-1}$)	193.5 (183.0–210.7)	175.2 (157.9–193.8)*
$CcvO_2$ (ml $litre^{-1}$)	118.3 (111.6–137.5)	116.6 (100.5–125.5)*
$C(a-v)O_2$ (ml $litre^{-1}$)	69.2 (64.7–92.9)	63.5 (57.4–68.3)*
OER	0.36 (0.35–0.45)	0.35 (0.33–0.38)
$\dot{V}O_2$ (ml min^{-1})	381 (248–391)	384 (255–455)

Exercise protocol

Exercise was performed on an electronically braked cycle ergometer (Lode Corival; Lode, Groningen, Netherlands) and cardiopulmonary exercise testing system (Metamax 3b; Cortex, Leipzig, Germany) previously validated at altitude.[4] At sea level a ramp increment was selected depending on the sex, age, height, weight and physical fitness of each participant, in order to obtain a test duration of ~10 min. The same ramp increment was used at altitude. After 3 min of resting data collection, a 3 min period of unloaded pedalling preceded a ramp protocol to exhaustion. Pedalling cadence was maintained at 60 rpm. The load was removed from the ergometer when participants were no longer able to maintain a steady pedalling cadence of 60 rpm. Oxygen uptake ($\dot{V}O_2$) was determined breath-by-breath from expired breath analysis. Peak $\dot{V}O_2$ was recorded as the highest average $\dot{V}O_2$ achieved during the final 20 s of exercise.

Measurements

Measurement of blood gas partial pressures, pH, and haemoglobin concentration was performed using the Rapidlab 348 analyser (Siemens Medical Solutions Diagnostics, UK) and a handheld photometric device (Hemocue® Whole Blood Hemoglobin System, HemoCue AB, Angelhoim, Sweden). We have previously validated this Siemens blood gas analyser for use at high altitude and this is described elsewhere.[5] At rest and during exercise, 1 ml blood samples were obtained simultaneously from the arterial and venous catheters. Sampling was performed at the end of 3 min of unloaded cycling and then every minute during exercise until exhaustion. A final sample was obtained 1 min after cessation of exercise. Measurements comprised arterial partial pressure of oxygen (Pa_{O_2}), arterial partial pressure of carbon dioxide (Pa_{CO_2}), and pH; arterial oxygen saturation (Sa_{O_2}) was calculated by the blood gas analyser according to a standard algorithm[6] as pulse oximetry is unreliable when Sa_{O_2} falls to <80%.[7]

Calculations and statistical analysis

Arterial oxygen content was estimated as the product of haemoglobin concentration, Sa_{O_2} and the volume of oxygen carried by 1 g of haemoglobin [1.39 ml g^{-1}] plus the product of the Pa_{O_2} and the solubility coefficient for oxygen (0.225). Absolute oxygen extraction $C(a-v)O_2$ was calculated by subtracting central venous oxygen content ($CcvO_2$) from CaO_2 in blood sampled simultaneously from central venous

and peripheral arterial catheters, respectively. The OER was calculated by dividing $C(a-v)O_2$ by CaO_2.

Data were treated as non-parametric and presented as median (range). Data at altitude and sea level were compared using the Wilcoxon signed-rank test, with statistical significance set at $P<0.05$. Analyses were performed using SPSS version 21.0 and Graphpad Prism 5.0.

Results

Data collection was successful in all five participants and no complications or adverse events occurred.

Median Pa_{O_2} and Sa_{O_2} at rest were higher at sea level compared with 4559 m (Table 1). Resting absolute oxygen extraction declined after ascent, however, OER remained unchanged at 4559 m (Table 1).

After exercise, median peak $\dot{V}O_2$ was lower at 4559 m than at 75 m (Table 2). In keeping with this, the maximum work rate achieved during exercise was reduced at 4559 m [239 (139–315) W], when compared with 75 m [286 (189–405) W; $P=0.042$]. During exercise at altitude Pa_{O_2} and Sa_{O_2} declined steadily for each individual as work rate increased during exercise while $C(a-v)O_2$ increased to reach a maximum value at peak $\dot{V}O_2$ (Fig. 1). At peak $\dot{V}O_2$ the absolute $C(a-v)O_2$ declined from 99.6 (88.0–151.3) ml litre^{-1} at sea level to 83.9 (67.5–120.9) ml litre^{-1} at 4559 m while OER remained unchanged, 0.53 (0.49–0.73) and 0.52 (0.48–0.71), respectively. As the maximum work rate for each participant was significantly reduced at high altitude, the $C(a-v)O_2$ at $\dot{V}O_2$ peak for 4559 m was compared with the equivalent work rate at sea level during the ramped protocol to exhaustion (Table 3). The median difference between $C(a-v)O_2$ calculations at these two comparable work rates was 2.6 (−5.5–15.0) ml litre^{-1}, $P=0.225$.

Discussion

Despite a significant reduction in Pa_{O_2}, Sa_{O_2} and CaO_2 at rest after ascent to 4559 m [calculated inspired P_{O_2} (PI_{O_2}) of 10.9 kPa], there was no increase in systemic oxygen extraction either at rest or at peak exercise. In absolute terms there was a significant decrease in systemic oxygen extraction both at rest and at peak exercise at altitude; however, in relative terms OER remained unchanged. In view of the reduced work rate at maximum exertion at high altitude a comparison was made between mean $C(a-v)O_2$ for peak exertion at high altitude and the equivalent $\dot{V}O_2$ at sea level; no difference in oxygen extraction was detected.

Table 2 Median (range) oxygen extraction values during peak exercise at sea level and 4559 m. * Significant difference between 75 and 4559 m ($P<0.05$)

	75 m	4559 m
Pa_{O_2} (kPa)	13.0 (12.3–15.8)	6.0 (5.7–6.8)*
Sa_{O_2} (%)	97.0 (96.0–97.6)	82.5 (75.1–85.1)*
Scv_{O_2} (%)	45.4 (26.8–49.1)	36.2 (24.6–42.0)
CaO_2 (ml litre^{-1})	193.4 (179.0–208.7)	165.8 (139.8–192.7)*
$CcvO_2$ (ml litre^{-1})	86.7 (57.4–94.5)	73.6 (49.0–81.9)*
$C(a-v)O_2$ (ml litre^{-1})	99.6 (88.0–151.3)	83.9 (67.5–120.9)*
OER	0.53 (0.49–0.73)	0.52 (0.48–0.71)
$\dot{V}O_2$ (ml min^{-1})	3646 (2156–4537)	2701 (1609–3355)*

The absence of an increase in whole body OER at 4559 m from the value at 75 m is consistent with data from a previous hypobaric chamber study[1] and field data collected at high altitude.[8 9] Others have specifically measured limb oxygen extraction during maximal exercise at high altitude, and also found no change from the sea level value.[10] The consistent finding that sub-acute exposure to hypoxia is not associated with an increase in systemic oxygen extraction is surprising in view of the reduced arterial oxygen content noted in all of these studies, and goes against the traditional teaching that when oxygen delivery declines, tissues respond by extracting more oxygen from arterial blood, resulting in a lower mixed venous oxygen saturation and content.[11] At rest, with only a modest reduction in CaO_2, it is conceivable that there is sufficient oxygen delivery to meet tissue demands in various organs such that overall oxygen extraction is unaltered. However, the lack of an increase in oxygen extraction during exercise at altitude is less easy to explain if viewed from the perspective of balancing oxygen supply and demand. In a classic animal model study, reducing systemic oxygen delivery through isovolaemic haemodilution led to a demonstrable increase in tissue oxygen extraction in order to maintain oxygen uptake in the face of diminishing oxygen availability.[12] In this experimental setting Pa_{O_2} was constant throughout and it was anaemic hypoxia that impeded systemic oxygen transport. Oxygen extraction increased (in accordance with the Fick equation) until a critical level of oxygen delivery, after which oxygen uptake began to decline as oxygen extraction had reached its upper limit. It is conceivable that this process of increased oxygen extraction may not be possible (or is less effective) during a hypoxic challenge. Factors that may contribute to this lack of increase in overall whole body oxygen extraction at altitude include:

- Tissue diffusion limitation of oxygen because of the reduction in partial pressure gradient from the capillary to the mitochondria that is exacerbated during exercise by a reduced capillary transit time within skeletal muscle.[13 14]
- Localized mismatch between tissue oxygen demand and microcirculatory blood flow because of heterogenous flow patterns.
- Redistribution of blood flow away from actively exercising muscle in order to 'protect' vital organs, a significant reduction in blood flow to other less vital organs such as the gastrointestinal tract, or both.[15] Redistribution of flow may therefore result in no overall increase in systemic oxygen extraction.
- Altered cellular metabolism with reduced oxygen consumption at a mitochondrial level. Oxygen consumption is determined primarily by mitochondrial oxygen metabolism rather than oxygen delivery, and at altitude

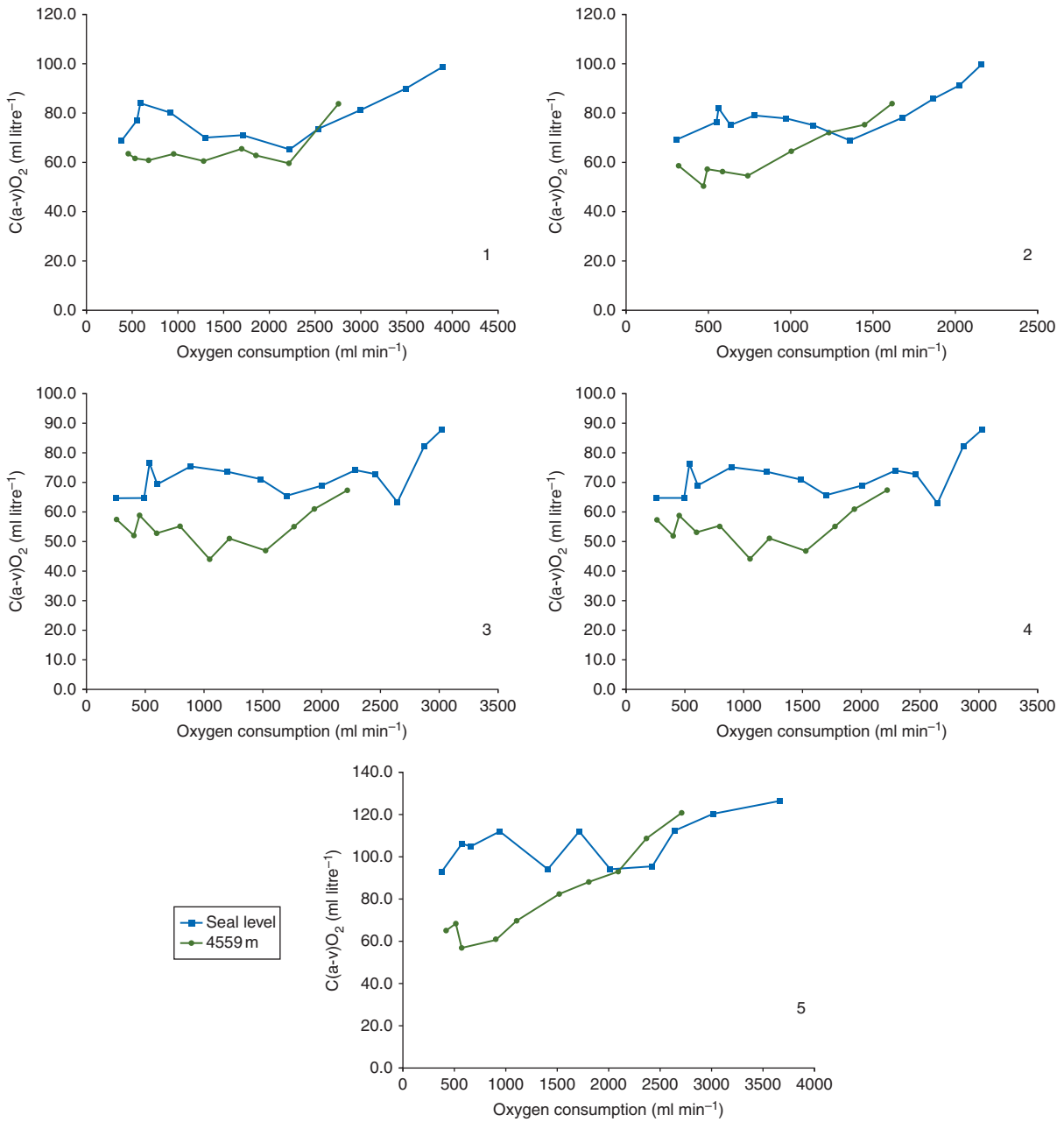

Fig 1 Individual participant oxygen extraction [C(a−v)O_2] data plotted against oxygen consumption ($\dot{V}O_2$) during exercise at sea level and at 4559 m.

alterations in mitochondrial function may limit peak oxygen consumption.[16]

Using the Fick equation, it is possible to calculate the cardiac output [$\dot{V}O_2$/C(a − v)O_2] for the group, at rest and maximal exercise. Using this method the sea level values for cardiac output were 5.5 litre min^{-1} at rest and 36.6 litre min^{-1} at maximum exercise; at altitude the respective figures were 6.0 and 32.2 litre min^{-1}. This is in keeping with previously published data when volunteers were acutely exposed to simulated high altitude.[17] Thus despite a reduced cardiac output at maximum exertion at altitude in our study, there was still no demonstrable increase in whole body oxygen extraction.

Of interest we observed that the altitude-related reduction in peak work rate was proportionally smaller than that of $\dot{V}O_2$ peak, despite the work rate incrementation having been standardized for each subject. This is apparent as a reduction in the slope of the $\dot{V}O_2$–work rate relationship, which has previously been observed in subjects performing ramp-incremental exercise with acute inhalation hypoxia ($F_{I_{O_2}}$ 0.14).[18] This may reflect an inability of oxygen transport to meet metabolic demands in the presence of

Table 3 Oxygen extraction values for peak exercise at 4559 m and the equivalent work rate at sea level (SL). *The $C(a-v)O_2$ for equivalent $\dot{V}O_2$ for each individual at SL (ml litre^{-1})

Subject	$C(a-v)O_2$ at peak VO_2 (ml litre^{-1}): 4559 m	$C(a-v)O_2$ for equivalent work rate (ml litre^{-1}): SL*	$C(a-v)O_2$ (ml litre^{-1}) difference (4559 m—SL)
1	83.8	81.2	2.6
2	83.9	78.1	5.9
3	67.5	73.0	−5.5
4	119.1	104.1	15.0
5	120.9	120.7	0.3
Median (range)	83.9 (67.5–120.9)	81.2 (73.0–120.7)	2.6 (−5.5–15.0)

reduced oxygen content,[18] a change in the efficiency of oxygen utilization or altered oxygen uptake kinetics with hypoxia.

A limitation of our study was that no sample size calculation was performed before commencing the study and the number of participants was low, therefore it is possible that the lack of difference in OER between sea level and high altitude was the result of a type II error. However, the significant reduction in absolute oxygen extraction strongly suggests that there is no true increase in OER and the likelihood is that extraction is actually reduced. Another limitation of this study is the use of central venous catheters rather than pulmonary artery catheters to measure mixed venous oxygen saturation (Sv_{O_2}). This method measures central mixed venous oxygen saturation (Scv_{O_2}) and is commonly used as a surrogate for Sv_{O_2} clinically. While the two values are strongly correlated, Scv_{O_2} tends to be lower than Sv_{O_2} in healthy volunteers at rest because of the flow of well-saturated venous blood from the renal circulation that returns to the heart via the inferior vena cava; oxygen extraction is lower in the kidneys than in most other organs.[19 20] We chose not to insert pulmonary artery catheters in participants as it is technically more challenging than central venous catheter insertion and is associated with significant risk of adverse events. The tip of a correctly place central venous catheter should lie in the superior vena cava just above the entrance to the right atrium. The distance from the entry site of the catheter and the superior vena cava-atrial junction is ~16 cm in adults,[21] although this depends upon the height of entry within the internal jugular vein and individual participant characteristics. The catheters used in this study were 11 cm in length but it was possible to use a 'low' insertion technique with ultrasound guidance in order to minimize the distance between the tip of the catheter and the right atrium. It is possible that the stresses induced by both exercise and hypobaric hypoxia may have led to disparity between measured Scv_{O_2} and true Sv_{O_2}. However, it is likely that this would have resulted in a relative under-estimation of oxygen extraction while resting at sea level; both exercise and hypoxia may have resulted in a relative over-estimation of oxygen extraction. That said, as an identical sampling technique was used at sea level and altitude one would expect to detect relative changes in OER if they were present, even if the absolute values of Scv_{O_2} were not truly representative of Sv_{O_2}.

The clinical implication of this high altitude field study is that increased tissue oxygen extraction may not be an innate physiological response to sub-acute hypoxaemia as it is in other situations of reduced oxygen delivery such as haemorrhage. Thus under conditions of hypoxaemia, strategies to maintain oxygen homeostasis at a cellular level may differ from those used in anaemia or cardiovascular failure. Simple arithmetic rebalancing of the oxygen delivery equation (the product of CaO_2 and cardiac output) may well restore values back to those we associate with normal physiology but fail to address the underlying biological abnormality.

Using $C(a-v)O_2$ derived from peripheral arterial and central venous blood samples, we have shown a decrease in absolute whole body oxygen extraction at rest and peak exercise after ascent to high altitude (4559 m) while OER remained unchanged. The cause for this lack of increase in oxygen extraction remains uncertain but may be attributable to diminished diffusion of oxygen from the microcirculation to mitochondria because of a reduced Pa_{O_2} gradient.

Authors' contributions

A.C.: study conduct, and manuscript preparation; D.S.M.: study design, study conduct, data analysis, and manuscript preparation; P.M.: study conduct and manuscript preparation; K.M.: study conduct and manuscript preparation; M.E.: study conduct and manuscript preparation; M.G.M.: study design, data analysis, and manuscript preparation; M.P.W.G.: study design, data analysis, and manuscript preparation.

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