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## Human muscle structure after exposure to extreme altitude

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*Summary.* Muscle structural changes during typical mountaineering expeditions to the Himalayas were assessed on muscle biopsies. A significant reduction in muscle fiber size (−20%) and a loss of muscle oxidative capacity (−25%) were observed. The capillary network was not affected by catabolism. It is concluded that the oxygen supply to muscle mitochondria after high altitude exposure is thus improved.
*Key words.* High altitude; hypoxia; muscle; computed tomography; capillaries; fiber size; human; exercise.

### *Introduction*

Participants in mountaineering expeditions to the Himalayas are exposed to chronic hypoxia at about 5000 m altitude (base camp) for several weeks, with occasional excursions (with or without supplementary oxygen) to altitudes in excess of 8000 m. The adaptational consequences of this type of exposure to high altitude for the cardiovascular system have been well studied (see reviews by Sutton et al.[15], Cerretelli and di Prampero[4] and Banchero[1]). However, little is known in humans about structural adaptations of skeletal muscle tissue as a consequence of high altitude exposure. From animal experimentation it would appear that chronic exposure to hypoxia leads to an increase in muscle tissue capillarity[9] and oxidative capacity[7]. These generally held assertions have been questioned, mainly on the grounds that there were technical limitations, and confounding variables such as simultaneous exposition to hypoxia and cold, in some of the older studies[1, 13]. Banchero[1] comes to the conclusion that chronic normothermic hypoxia has no influence on skeletal muscle capillarity in sedentary laboratory animals, and that exercise or cold exposure must further challenge the oxygen delivery system before measurable structural adaptations can take place in muscle tissue.

With regard to human muscle adaptations to high altitude, experimental data are rather scarce. Short exposure to 4300 m (18 days) has no effect on oxidative and glycolytic enzyme activities measured in biopsies of M. vastus lateralis[16]. However, there is an almost complete lack of structural data on adaptations of human skeletal muscle tissue to continued exposure to the stresses of high altitude.

### *Methods*

$\dot{V}_{O_2}$max tests, computed tomographies and muscle biopsies were obtained before and 10–15 days after the return of expeditions to the Himalayas, one in 1981 and one in

1984, which were typical of this type of expedition with respect to acclimation procedures. The subjects were rather varied with respect to their training background and mountaineering expertise; they included both experienced high-altitude mountaineers and less experienced scientific staff. However, all participants spent a minimum of six weeks at the base camp at 5200 m, with some exposures to altitudes in excess of 8000 m. $\dot{V}_{O_2}max$ was estimated with an incremental bicycling exercise test and muscle biopsies were obtained and morphometrically analyzed with the electron microscope as previously described in detail[8]. The cross-sectional area of the thigh muscles was estimated planimetrically on CT-scans taken at 2/3 of the distance between the patella and the trochanter major of the femur. Absolute values of mitochondrial and myofibrillar volumes, as well as absolute capillary lengths, were obtained by multiplying the density estimates for the skeletal muscle tissue components by the muscle volume (calculated for a slice of muscle of 1 cm thickness). This procedure has been described in detail by Conley et al.[5]. For statistical comparisons of group means (before and after the expeditions) Student's t-test for paired samples was used; the level of statistical significance was set at 5%.

## *Results and discussion*

### *Body composition and $\dot{V}_{O_2}max$*

The characteristics of the two expeditions were rather similar and it was decided to analyze members of both expeditions jointly. Despite this, the number of subjects was too small to allow for a meaningful division of experimental subjects into subgroups according to their training background or mountaineering expertise.

The participants lost close to 5% of their body mass and maximal oxygen uptake capacity (fig. 1). Measurements done at the base camp indicated that the weight loss was already partially compensated by the time our 2nd set of measurements could be obtained. Weight loss after a prolonged sojourn at high altitude is commonly reported[2,6]. It has been recognized that the loss in body mass is due both to a loss of muscle mass and a loss of total body fat[3]. These findings are supported by the computer tomographic data of the current analysis. Thigh muscle cross-sectional area was significantly reduced, by close to 10%, after the expeditions.

### *Fiber size*

As would be expected from the loss in total muscle cross-sectional area, the fiber cross-sectional area of M. vastus lateralis was significantly reduced (fig. 2). This decrease was of the order of 20%. We performed no histochemical analysis and therefore have no information on whether all fiber types were affected to a similar degree by high altitude exposure. Fiber type-specific size reductions after hypoxia exposure have been reported for rats and guinea pigs[10,12].

### *Capillarity*

The capillary-to-fiber ratio was found to be significantly reduced (fig. 2). This result is at variance with the bulk of data gained from comparable animal experimentation in which the capillary-to-fiber ratio is found to be unchanged[12–14]. However, because of the relatively larger decrease in muscle fiber area than in the capillary-to-fiber ratio, the capillary density was still increased significantly (fig. 2). From this it becomes evident that the apparent increase in capillary density in the muscles of our subjects could be solely a result of the decrease in muscle fiber cross-sectional area, and did not represent new formation of capillaries. In fact, the decrease in capillary-to-fiber ratio would indicate that some capillaries were lost. As a consequence of the decrease in fiber size and the increase in capillary density we found that the fiber area supplied by one capillary was also significantly reduced.

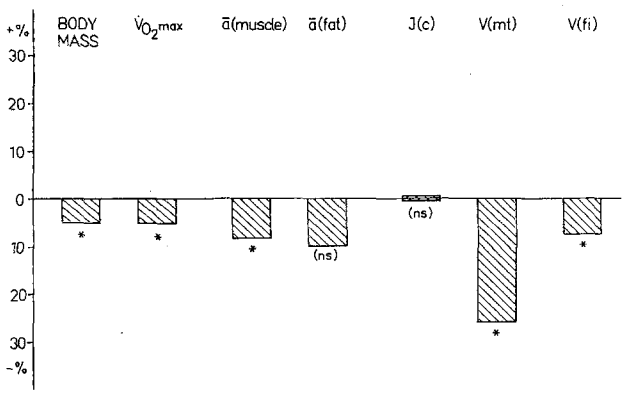


Figure 1. Relative changes of body mass, $V_{O_2}max$, muscle cross-sectional area ā (muscle), fat tissue cross-sectional area ā (fat), capillary length J (c), mitochondrial volume V (mt) and myofibrillar volume V (fi) with high altitude exposure (asterisk indicates significant, $p \leqq 0.05$).

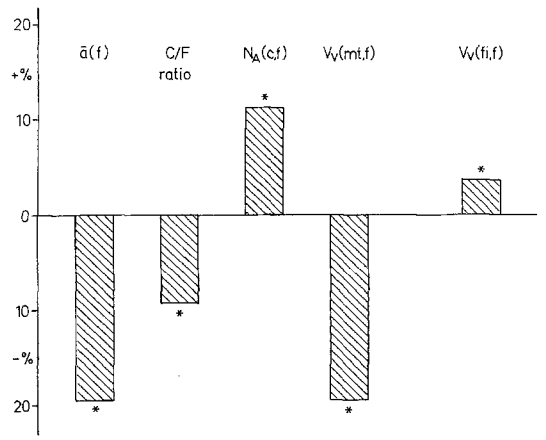


Figure 2. Relative changes of muscle fiber area ā (f), C/F ratio, capillary density $N_A$ (c,f), mitochondrial volume density $V_V$ (mt,f) and volume density of myofibrils $V_V$ (fi,f) with high altitude exposure (asterisk indicates significant, $p \leqq 0.05$).

*Muscle ultrastructure*

The volume density of total mitochondria (volume of mitochondria per unit volume of muscle fiber) was significantly reduced by almost 20% after exposure to high altitude (fig. 2). The decrease observed in the volume density of mitochondria was due to a relatively larger decrease in the smaller fraction of subsarcolemmal mitochondria (−43%) than in the larger fraction of interfibrillar mitochondria (−13%). In contrast to exercise training, in which the intracellular lipid content of muscle fibers is usually increased, this variable remained unchanged in the current study (results not shown). The small but significant increase in volume density of myofibrils is due to the drop in volume density of mitochondria; all other components of the muscle cell remained a constant fraction of the total cell volume.

Comparing the morphometric estimates of muscle tissue components after high altitude exposure obtained in the present investigation with values previously obtained with identical techniques on a group of six world-class high-altitude climbers[11], we find a remarkable match between the two sets of data. In both cases mitochondrial volume densities are in the range found in untrained people, whereas fiber cross-sectional areas are reduced significantly. As a consequence of the decrease in fiber size with a 'normal' capillary to fiber ratio we find a significantly increased capillary density in both cases. The data on world-class climbers were obtained between 2 and 12 months after their last high-altitude exposure. From this it could be speculated that possibly not all of the acute structural changes observed in the current study are completely reversible.

*Absolute changes in structural components of muscle tissue*

Figure 2 reports morphometric data obtained with reference to a unit volume of muscle tissue. It is important to consider that owing to the decrease in body mass, and in particular to muscle wastage, resulting from the prolonged high altitude exposure, the muscle volume decreased significantly by 10%. The total quantity of muscle tissue constituents available to the subjects was therefore likewise globally reduced. By multiplying the volume density of tissue component with the organ volume, absolute values for structural quantities can be calculated. Figure 1 reports data on absolute myofibrillar and mitochondrial volume in 1-cm-thick slices of the thigh of our subjects. It is evident that despite the significant increase in volume density of myofibrils, the absolute quantity of contractile protein was significantly reduced by close to 10%, owing to the overriding effect of the loss of muscle mass. Likewise, the decrease in absolute volume of mitochondria of nearly 30% is due to the multiplicative effects of the loss in volume density and muscle mass. The total capillary length and hence also the total capillary volume and surface area (assuming constant capillary diameters and tortuosity) were found to be unchanged with high altitude exposure. A constant capillary length or volume thus supplied a greatly reduced quantity of skeletal muscle mitochondria. In that sense we can state that the capillary supply of the remaining mitochondria is improved; this is not because of an adaptation of the capillary network, but because of a reduction of the mitochondrial mass.

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