King of the Mountains: Tibetan and Sherpa Physiological Adaptations for Life at High Altitude

Anecdotal evidence surrounding Tibetans’ and Sherpas’ exceptional tolerance to hypobaric hypoxia has been recorded since the beginning of high-altitude exploration. These populations have successfully lived and reproduced at high altitude for hundreds of generations with hypoxia as a constant evolutionary pressure. Consequently, they are likely to have undergone natural selection toward a genotype (and phenotype) tending to offer beneficial adaptation to sustained hypoxia. With the advent of translational human hypoxic research, in which genotype/phenotype studies of healthy individuals at high altitude may be of benefit to hypoxic critically ill patients in a hospital setting, high-altitude natives may provide a valuable and intriguing model. The aim of this review is to provide a comprehensive summary of the scientific literature encompassing Tibetan and Sherpa physiological adaptations to a high-altitude residence. The review demonstrates the extent to which evolutionary pressure has refined the physiology of this high-altitude population. Furthermore, although many physiological differences between highlanders and lowlanders have been found, it also suggests many more potential avenues of investigation.

Although many places on the planet have resident populations above 3,000 m, the elevation at which the majority of people demonstrate physiological changes to hypobaric hypoxia, three main regions host populations over 4,000 m. These are the Tibetan plateau and Himalayan valleys, the South American Andes, and the Ethiopian Highlands (158). Covering some 1.5 million square miles of central Asia, the Qinghai-Tibetan plateau is both the largest and the highest. Although archaeological evidence suggests that this plateau has been inhabited since the Neolithic ages (4, 172), a debate fuelled by conflicting genetic, historical, linguistic, and archaeological records exists as to the origin of todays high-altitude resident Tibetans. Thought to have migrated in the early to mid-16th century from the eastern Tibet Kham region, they initially settled in the relatively uninhabited Solukhumbu district of Nepal (119). Since then, although the ancestral land of the Sherpas remains in the northern side of the Solukhumbu district, many have since migrated along the eastern hill districts of Nepal and further west in the Rolwaling valley and lowland regions north of Kathmandu. Sherpas are one of many tribes originating from Tibet, and for the purpose of this review we discuss Tibetans and Sherpas as one entity.

Since the early expeditions to Mount Everest in the 1920s, tales of Sherpas’ extraordinary tolerance to hypoxia at high altitude have been commonplace. Stories of their superior exercise and endurance abilities, and the ease at which they outperform their Western counterparts have become legendary. With anecdotal evidence suggesting such clear advantages at altitude, for the myths to be true one would expect discernible physiological differences between Sherpas and lowlanders. Undoubtedly, their genome has adapted through natural selection over the last 500 generations in response to the hypoxic environmental stressor; however, evidence of phenotypic differences is limited.
The purpose of this literature review is therefore to summarize the physiological differences between Sherpas/Tibetans and lowlanders. We provide an up-to-date and comprehensive appraisal of the literature encompassing their adaptations to a life up high. We use the term “adaptation” as meaning a process or change occurring by means of natural selection, by which a species becomes more suited to its environment, thus giving it an evolutionary advantage. This review does not aim to compare Tibetans with Sherpas. Nor do we comprehensively review comparisons between Tibetans/Sherpas with other high-altitude populations. A few such differences are, however, alluded to where they are of particular relevance.

**Search Strategy**

A sensitive search strategy was constructed to locate publications relevant to Tibetan and Sherpa physiology. We used the key words Tibetan, Sherpa, high altitude, altitude, hypoxia, epidemiology, and physiology to search the following databases: Medline (OVID), EMBASE (OVID), PUBMED, and Google Scholar. For the OVID searches, articles were limited to “human” from years 1950 to the present day. Having reviewed each article located through the above search stratagem, we inspected their reference lists for other publications of significance and subsequently referred to these.

Results from the systematic search are presented broadly according to phenotype. We have attempted to follow the oxygen cascade, from ventilation through to cardiac output, and for themes not directly encompassed in this, we have used an integrative physiological functional approach.

**Summary of Search Findings**

Our search revealed 542 hits. After screening titles and abstracts, and reviewing references, we found 169 relevant papers. Split physiologically, the number in each category can be seen in Table 1. Results are then discussed in further detail below and summarized in Table 2.

**Ventilation and Hypoxic Ventilatory Response**

The hypoxic ventilatory response (HVR) is an innate increase in ventilation following exposure to hypoxia controlled by the carotid bodies. It varies widely between individuals and has been used to quantitatively assess control of ventilation (13). Early reports suggested Tibetans and Sherpas exhibited a “blunted” HVR, a relative lack of sensitivity to hypoxia (34, 85, 86, 97, 131). It was reasoned that this was an entirely appropriate adaptation to hypoxia given that hyperventilation wasted energy (133). Although this may be plausible, current consensus is that their HVR is actually in keeping with acclimatized lowlanders (12, 24, 28, 36, 56, 82, 102, 103, 146, 165, 176).

Figure 3 of Ref. 176 illustrates this situation elegantly using a Rahn/Otis O2/CO2 diagram. The points for Himalayan populations (attained from the numerous references cited), fall on the line for acclimatized lowlanders, whereas the Andean populations mostly fall between that and the line for unacclimatized lowlanders. The discrepancy relating to early studies has since been attributed to using inconsistent methods for measuring HVR and to small study numbers with insufficient attention being paid to previous altitude exposure in lowlanders (102, 107, 176).

Although HVR is independent of age and time spent at altitude, intra-population ventilatory differences have been demonstrated, and these are dependent on elevation of residence. Tibetans living at moderate altitude (2,000–3,000 m) have a greater maximal exercise ventilation and HVR compared with those living at higher altitudes (4,000–4,700 m) (34, 47). These different ventilation phenotypes seem to be attributable to both genetic and environmental influences, since 35% of Tibetan’s resting ventilation variance and 31% of Tibetan’s HVR have been attributed to genetic differences (24). The optimum HVR is probably that seen in acclimatized lowlanders and Himalayan highlanders; however, there are distinct advantages to both a “brisk” and a “blunted” response. A brisk response results in hyperventilation and improved oxygenation, and has been suggested to relate to performance at high altitudes (94, 135).

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**Table 1. Summary of search findings**

<table>
<thead>
<tr>
<th>Physiological System</th>
<th>Number of Studies</th>
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<tbody>
<tr>
<td>Ventilation and hypoxic ventilatory response</td>
<td>21</td>
</tr>
<tr>
<td>Lung volumes, diffusing capacity, and gas exchange</td>
<td>9</td>
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<tr>
<td>Hypoxic pulmonary vasoconstriction</td>
<td>6</td>
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<td>Hemoglobin</td>
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<td>The heart and cardiac metabolism</td>
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<td>Cerebral function</td>
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<tr>
<td>Pregnancy and utero-placental blood flow</td>
<td>12</td>
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<tr>
<td>Skeletal muscle structure and metabolism</td>
<td>14</td>
</tr>
<tr>
<td>Exercise capacity, efficiency, and economy</td>
<td>22</td>
</tr>
<tr>
<td>Growth, body weight, and basal metabolic rate</td>
<td>20</td>
</tr>
<tr>
<td>Nitric oxide metabolism</td>
<td>10</td>
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<tr>
<td>Genetics and epigenetics</td>
<td>25</td>
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Some papers discuss more than one phenotype and are thus included in multiple physiological systems.
This, however, comes at the cost of increased energy utilization through increased ventilation and a reduction in $P_{ACO_2}$, which may impair cerebral function by reducing cerebral blood flow (71). Conversely, a blunted or low HVR conserves energy but results in lower $P_{O_2}$ and therefore increases the risk of hypoxia related pathology.

Regarding ventilatory control, compared with Caucasian lowlanders, Himalayan residents demonstrated lower ventilatory recruitment thresholds, and decreased central and minimal peripheral chemoreflex sensitivity to carbon dioxide ($CO_2$) (141). The authors suggested that the decreased ventilatory recruitment threshold exhibited without the concurrent increase in the sensitivity to $CO_2$ (as would normally be apparent in lowlanders at altitude) suggested Tibetan ventilation was controlled by one of two mechanisms, either a $CO_2$-independent oxygen-sensing mechanism regulated by the peripheral chemoreceptors or an increased central chemoreceptor drive secondary to hypoxia-induced central lactic acidosis. The study did, however, compare unacclimatized lowlanders with acclimatized Tibetans, so differences in the $CO_2$ response may be attributed to the effects of acclimatization rather than to long-term adaptation mechanisms. Intriguingly, when 70% oxygen was administered to Tibetans and lowlanders at high altitude, whereas lowlanders decreased their ventilatory rate as expected, Tibetans paradoxically increased theirs (176).

**Lung Volumes, Diffusing Capacity, and Gas Exchange**

Matched for age, height, weight, and smoking history, Tibetans demonstrate significantly larger chest circumferences, total lung capacity, vital capacity, residual volumes, and tidal volumes than Han Chinese lowlanders (33, 38, 79, 146). Additionally, compared with age- and sex-matched lowlanders, Sherpas also demonstrate greater peak expiratory flow rates, forced expiratory volume in 1 s (FEV$_1$), forced vital capacity (FVC), and FEV$_1$-to-FVC ratio (58, 163).

Years spent residing at high altitude may well have adapted Tibetan morphology and respiratory mechanics to allow for increased respiratory volumes (79), and it has been suggested that larger lung volumes might also provide a mechanism for improving lung diffusing capacity (38). Pugh et al. (128) suggested over 50 years ago that Sherpas’ greater maximum oxygen uptake ($VO_2_{max}$) was in part due to a more efficient gas exchange process secondary to a larger diffusing capacity. A greater diffusing capacity compared with lowlanders has since been demonstrated, as has a consequential
lower alveolar-arterial oxygen gradient (30, 33, 72, 177).

**Hypoxic Pulmonary Vasoconstriction**

Hypoxic pulmonary vasoconstriction (HPV) facilitates ventilation-perfusion matching. At sea level, localized alveolar hypoxia secondary to pathology increases local pulmonary artery resistance, thereby diverting blood flow to more oxygenated regions and maintaining maximal arterial oxygenation. At altitude, HPV occurs globally since the lung is uniformly hypoxic, and this manifests as pulmonary hypertension. This is commonly seen in lowlanders at altitude (124), yet Tibetans demonstrate minimal pulmonary hypertension (both at rest and on exercise), at altitude (53), and (in subjects who had spent a least 6 years at altitude) at sea level (126). Signs of attenuated HPV have also been demonstrated histologically. At autopsy, thickened pulmonary arteries and structural alterations in the peripheral pulmonary arterial tree suggestive of pulmonary hypertension was evident in Andeans (8, 59, 60, 150). Tibetans by contrast exhibited small muscular thin-walled pulmonary arteries, with no medial hypertrophy or muscularization of the arterioles (54). Decreased HPV consequently minimizes right ventricular afterload, and this has been hypothesized as a reason permitting Tibetans to achieve a greater rise in cardiac output on exercising compared with acclimatized lowlanders (107). Parenthetically, a recent study in Ethiopian highlanders shows what may be a third type of pulmonary vascular response to hypoxia, i.e., a rise in pulmonary pressure without a rise in vascular resistance, perhaps due to increased blood flow (66).

**Hemoglobin**

Early manuscripts reporting hematological data from high-altitude populations do not describe patterns suggestive of beneficial adaptive mechanisms (95, 96, 114). These studies predominantly investigated “classical” characteristics such as blood groups, ultimately features that are thought to have no major influence on high-altitude adaptation (28). Later, it was subsequently demonstrated that Tibetan mean hemoglobin concentrations ([Hb]) at altitude seemed to lie within two standard deviations of Caucasian sea-level values (22). Other data support this (1, 2, 22, 132, 166); however, Tibetans still do demonstrate a steady rise in [Hb] at altitude, albeit not to the same extent as lowlanders such as Han Chinese (166) (FIGURE 1).

This divergence from the normal lowlander acclimatization response only becomes evident from the age of 13 years (45) and possibly suggests that relative anemia at altitude provides an advantageous mechanism for coping with hypoxia (22). Evidently, the phenotype is not uniform among all high-altitude populations; Tibetans demonstrate lower [Hb], hematocrit (Hct), and immunoreactive erythropoietin concentrations than Andeans (161, 162, 165), and both populations display significant genetic variance for hemoglobin levels (11, 13, 17). It seems, therefore, that the two populations have, by natural selection, pursued different paths. Although this relative anemia in Tibetans may on first thought seem detrimental, the “two-edged sword” analogy of polycythemia provides a possible explanation (162). Undoubtedly, increased [Hb] augments systemic oxygen content; however, elevated Hct levels increase blood viscosity, alter its rheology, and decrease cardiac output and
oxygen delivery (162). In addition, since elevated Hct leads to an increased prevalence of chronic mountain sickness and embolic/thrombotic events (100), it seems Tibetans accordingly favor a blunted erythropoietic response with those best adapted having the lowest [Hb] (100, 161). They must therefore rely on alternative physiological means to achieve their advantageous high-altitude adaptation.

Genetic studies support this theory because it has been demonstrated that Tibetans have recalibrated the set point for hypoxia-induced erythropoiesis (143) through regulatory changes in endothelial PAS domain protein 1 (EPAS1). This gene region encodes hypoxia inducible factor 2α (HIF-2α), a subunit of the protein complex HIF, which is in part responsible for determining the set point for hypoxic induction of erythropoietin (EPO). Intrapopulation genetic variance in [Hb] is also seen, and individuals possessing the major allele homozygote of EPAS1 have a [Hb] 0.8 g/dl lower than heterozygotes (18). Additionally, correlation between hemoglobin concentration and haplotype variation at other gene regions (EGLN1 and PPARA) has also been demonstrated (140).

**Oxygen Saturations**

Evidence related to Tibetan oxygen saturations is inconsistent. Numerous studies have demonstrated arterial oxygen saturations (SaO₂) at rest and during submaximal and/or maximal exercise to be greater in Tibetans and Sherpas compared with lowlanders (29, 33, 48, 56, 82, 146, 164, 176, 177). This is evident from birth (117). Others report no difference between various high- and lowland populations (83, 118, 131, 154, 163), or even that SaO₂ are lower in Tibetans (15). A review of the literature in 2007 concerning these discordances concluded there to be no significant difference in SaO₂ and the discrepancies could be attributed to variances in sample size, subject health, instruments, saturation probe location, and measurement protocols (154).

Among Tibetans, analysis of SaO₂ reveals a bimodal distribution (16), and the presence of a major gene conferring higher SaO₂ in those with the dominant “high-SaO₂” allele has been demonstrated (mean SaO₂: aa, 83.6%; Aa, 87.6%; AA, 88.3%) (25). The significance of this gene bestowing a selective advantage at altitude is clearly highlighted in the demonstration that offspring mortality in Tibetans at 4,000 m is markedly lower in those mothers carrying the high-SaO₂ genotype compared with those with the low-SaO₂ genotype (0.48 vs. 2.53 deaths, respectively) (23).

Directly related to SaO₂, Tibetans’ and Sherpas’ hemoglobin’s affinity for oxygen is not significantly different from that observed in sea-level residents. A rise in the 2,3-DPG concentration-to-[Hb] ratio compensates for the hypoxia-induced respiratory alkalosis encountered at altitude, and consequently the P50 is unchanged (113, 132, 160, 161).

**The Heart and Cardiac Metabolism**

At altitude, exercising Tibetans and Sherpas are able to generate a greater maximum heart rate (HR) compared with lowlanders (128, 129, 146, 164). This trait persists even after migration to lower altitudes (92). Among Tibetans, maximal exercising HR varies depending on their elevation of habitation, with a lower maximal HR demonstrated by those living higher (35, 47). When exercising against an increasing workload, Tibetans were also able to increase their cardiac output (CO) and HR, maintain their stroke volume (SV), and decrease their pre-ejection period (PEP)-to-left ventricular ejection time (LVET) ratio (PEP/LVET ratio). Conversely, Han Chinese subjects in the same study demonstrated an increased PEP/LVET ratio, limited HR increase, and decreased SV and CO (33, 46, 164).

An enhanced cardiac capacity may facilitate superior work ability at altitude; however, is it detrimental to their heart? Assuming right ventricular hypertrophy (RVH) to be an adverse sign, the answer, it seems, is no, since a far higher prevalence was demonstrated on electrocardiograms (ECGs) in adult Han Chinese compared with Tibetans (29% vs. 17%, respectively) (57). Moreover, this study also demonstrated a direct correlation between time spent at altitude and the degree of RVH in lowland subjects, a finding in keeping with the observation that young Han and Tibetan children have similar degrees of RVH (74).

Preservation of cardiac function in chronic hypoxia may also lie, at least in part, with a metabolic adaptation that drives an altered substrate preference. Positron emission tomography demonstrated that Sherpas had elevated myocardial glucose uptake rates after an overnight fast compared with those of lowland natives (67). These persisted after 3 wk of de-acclimatization. Given the significant energy demand of the heart, the preferred respiratory fuel of the resting cardiac muscle in the fasted state is normally fatty acids. This is due to the greater degree of reduction and thus superior adenosine triphosphate (ATP) yield per carbon compared with glucose. Under hypoxic conditions, a switch in substrate preference toward glucose makes sense given that the ATP yield per oxygen molecule is 25–50% higher with glucose than with free fatty acids; indeed, there appears to be a similar preference for carbohydrate substrates in skeletal muscle (115). The cost of a switch toward glucose, and thus a diminished oxygen demand, could, however, be a reduced overall...
capacity for ATP synthesis and thus a decreased energetic reserve. The concentration ratio of phosphocreatine (PCr) to ATP measured in the Sherpa heart at low altitude using 31P-magnetic resonance spectroscopy was found to be approximately half that of lowlanders (62). Strikingly, PCr/ATP was not further depressed in the Sherpa heart following sustained inhalation of a hypoxic gas mixture, perhaps suggesting a metabolic optimization for hypoxic conditions (62). Interestingly, in lowlanders returning from high altitude, myocardial PCr/ATP was also found to be depressed, perhaps reflecting an adaptive response in substrate preference following hypoxic exposure that is analogous to the metabolic adaptation of high-altitude natives (68). In lowlanders, however, cardiac PCr/ATP recovered following de-acclimatization (68), whereas, in the Sherpa heart, 27 days of residence at low altitude saw no rise in cardiac energetic reserves (62).

Regarding cardiac innervation, lowlanders exhibit sympathetic nervous system (SNS) stimulation on acute exposure to hypoxia that diminishes over time due to downregulation of beta-adrenergic receptors (158). In a similar manner to these latter changes, Tibetans express a significant vagal component of autonomic response to hypoxia (158). A mechanism of adaptation that may support this difference could relate to superior cerebral autoregulation and/or increasing oxygen delivery to the hypoxic brain. Up to a “transitional zone” of 3,658 m, Tibetans and Sherpas maintain autoregulation of cerebral blood flow (75, 76), and compared with lowlanders below this altitude they exhibit greater internal carotid artery (ICA) blood flow velocity (73). This increased velocity seen in cerebral vessels may well increase cerebral oxygen delivery and satisfy greater cerebral oxygen demands; however, to endorse this assumption, vessel diameter needs assessment (159).

A further adaptive mechanism utilized when oxygen availability is limited could be to mimic hypoxia-tolerant vertebrates by minimizing ATP utilization and reducing oxygen consumption. Although cerebral hypometabolism sounds plausible, it does not seem to be the case, as positron emission tomography (PET) of cerebral glucose metabolism demonstrates that Sherpas maintain “normal” values similar lowland controls (63). Perhaps, therefore, their increased cerebral blood flow velocity sufficiently compensates against the environmental hypoxia and they have no necessity to reduce cerebral metabolism.

**Pregnancy and Utero-Placental Blood Flow**

Chronic hypoxia diminishes the rise in cardiac output, blood volume, growth, and remodeling of both uterine and placental vessels normally experienced in pregnancy at sea level (104). As a consequence, low-altitude populations experience a progressive reduction in birth weight as they ascend, with a mean decline in weight of 100 g/1,000-m altitude gain (107). Tibetans and Sherpas, much like their Andean counterparts, do not demonstrate this reduction in birth weight at altitude (105–108) nor as they ascend. Mean birth weights were similar in Sherpa women living at low (1,330 m) and high (3,930 m) altitudes (142).

Assuming maternal arterial oxygenation is a fundamental determinant of fetal growth and Tibetans do not demonstrate greater levels of oxygen content than other populations, another mechanism of adaptation must allow for this discrepancy. As with the brain, the answer at least in part lies in increasing regional oxygen delivery. An increase in the proportion of common iliac blood flow into the uterine arteries accordingly raises utero-placental oxygen delivery. This in turn allows greater placental volumes to be attained (174) and subsequently less intrauterine growth retardation (IUGR) to be experienced (109, 112, 171). This mechanism is likely one of many compensatory means (109), and further factors such as those relating to substrate (oxygen, glucose) delivery and/or metabolism, mechanical elements protecting fragile fetal villi, or improved placental oxygen transfer need to be further evaluated (106). Compared with lowlanders and other high-altitude populations, Tibetans also encounter less gestational hypertension and pre-eclampsia, fewer premature births, and a three-fold decrease in pre- and postnatal mortality (98, 110, 148, 171). There is, however, no significant difference in the frequency of postpartum hemorrhages (98).

**Skeletal Muscle Structure and Metabolism**

Sherpas possess a significantly greater number of capillaries per cross-sectional area of muscle compared with sedentary unacclimatized lowlanders (80). They also demonstrate a lower muscle fiber cross-sectional area. This effectively increases their capillary density-to-muscle fiber ratio (80) and could serve to optimize convective and diffusive oxygen flow to the working muscles. At the mitochondrial level, despite a 25% lesser muscle mitochondrial volume density compared with lowland
populations, Tibetans seemingly demonstrate a larger maximal oxygen consumption-to-mitochondrial volume ratio (80). In theory, a low mitochondrial volume density could lead to a decreased oxidative potential of the muscle, therefore compensatory mechanisms such as changes in substrate preference, enhanced efficiency of the respiratory chain, or tighter coupling between ATP supply and demand pathways must exist to counter this (70). The former notion has been substantiated since Sherpas demonstrate a predilection toward carbohydrate oxidation with less reliance on intramyocellular lipids (IMCLs) and lipid substrates. This consequently increases the amount of ATP produced per volume of oxygen consumed and thus favors a high yield of muscle work-to-O\textsubscript{2} ratio (64, 69).

Myoglobin is a protein that contributes to oxygen storage and diffusion in both skeletal and cardiac muscle. Through its complex links with the regulation of nitric oxide (NO) concentration, myoglobin alters the efficiency of the oxygen inflow and consumption in skeletal muscles and may therefore serve a role in hypoxic adaptation (91). Although the Tibetan genome does not indicate selection for specific myoglobin alleles (111), myoglobin concentration and levels of a potent ROS scavenger, glutathione-S-transferase (GST P1-1), were higher in Tibetan skeletal muscle compared with lowlanders (49). Given that oxidative stress and ROS overproduction is thought to be responsible for the muscle deterioration encountered by lowlanders at altitude (115), an increase in GST P1-1 concentration might indicate a protective role for increased cellular detoxification. Evidence of minimal lipofuscin accumulation in Tibetan muscle at altitude, suggesting protection against oxidative stress in mitochondria, seems to confirm this (49).

Regarding muscle fiber type, Sherpas’ and Tibetans’ vastus lateralis muscle exhibited a broadly similar distribution to that of lowlanders, but with a slight dominance in type I fibers (60% cf. 50% in lowlanders) (80, 81). This increased prevalence of slow-twitch muscle fibers has been theorized as a mechanism to explain the “Lactate Paradox”—the lower than expected rise in postexercise blood lactate levels seen in those acclimatized to high altitude (157). Unlike that seen in unacclimatized lowlanders, where exercising fast-twitch fibers accumulate lactate, Tibetans’ predominance of slow type I fibers favors improved coupling between ATP demand and adenosine diphosphate (ADP) supply and thus limits lactate accumulation. With less intracellular pH instability, perhaps this improves exercise endurance under submaximal conditions (5, 48, 61, 69, 93).

**Exercise Capacity, Efficiency, and Economy**

Numerous means and methods have been used to portray Sherpas’ apparent superior exercise ability at altitude (9, 99). \(\text{VO}_{2}\text{max}\) has long been considered the gold-standard measure of exercise capacity and fitness at sea level, and may provide an important index of functional adaptation to high altitude (28). Whether or not Sherpas have a greater \(\text{VO}_{2}\text{max}\) compared with lowlanders at the same altitude remains a subject of much debate. The majority of papers describe a greater \(\text{VO}_{2}\text{max}\) in Sherpas and Tibetans (33, 43, 46, 86, 128, 129, 146, 165, 177), a characteristic retained both after migration to sea level upon acute exposure to hypoxia (175) and in second-generation Tibetans born and raised at low altitude (92). Other manuscripts, however, describe similar or even lower values obtained (48, 82, 118). Notably in these latter studies, although lesser \(\text{VO}_{2}\text{max}\) values were attained by Tibetan subjects, they did demonstrate greater workloads, higher anaerobic thresholds, and lower postexercise lactate levels, suggesting that maximum work had not been reached. A review of the literature in 2006 concluded that mean peak \(\text{VO}_{2}\) (\(\text{VO}_{2}\text{peak}\)), as opposed to \(\text{VO}_{2}\text{max}\) was marginally but not significantly higher in Tibetans at altitude compared with acclimatized lowlanders (91). The authors concluded that Tibetans’ better performance was due to increased submaximal exercise performance secondary to enhanced efficiency of the muscle oxidative metabolic machinery. A subsequent review in 2008 looked at \(\text{VO}_{2}\text{max}\) and concluded that high-altitude natives achieved a higher mean \(\text{VO}_{2}\text{max}\) at altitude and smaller \(\text{VO}_{2}\text{max}\) decrement with increasing hypoxia (30).

Aside from exercise capacity, work efficiency and work economy have also been studied. To clarify the somewhat confusing nomenclature, work efficiency may be defined as the ratio of total work done (internal and external) to total energy expenditure (aerobic, anaerobic, and contributions to the phosphagen system). In contrast, work economy is defined as the oxygen cost for a specific activity, and the external measures are not necessary (30). As is the case with exercise capacity, conflicting evidence exists relating to Tibetan and Sherpa work efficiency. Some studies state no differences are apparent compared with lowlanders (82, 84, 86), whereas others report significantly higher work efficiency (48, 118). Intrapopulation differences also exist, and Tibetans living at high altitude (4,400 m) demonstrate a greater work performance for given oxygen uptake compared with those at lower altitudes (3,658 m) (35).

Two studies demonstrated superior work economy. One demonstrated smaller mass-specific cost of carrying between Nepalese and lowlanders (9),
and the other a lower mass-specific \( \dot{V}O_2 \) during walking and running in Tibetans vs. lowlanders (93).

Work economy, independent of muscle-metabolic efficiency, could explain Tibetans’ anecdotal superior work performance at altitude; however, reviews of both studies have since stated that there is insufficient information to conclude that Tibetans have an enhanced work economy, and differences could be explained by other means.

\( \dot{V}O_2 \) has been studied in highland Tibetans who had been brought down to 1,300 m (93). Although Tibetan net \( \dot{V}O_2 \) and blood lactate remained consistently below Nepali lowlander controls (signifying lower aerobic energy expenditure) compared with their own high-altitude levels, Tibetans only demonstrated a minimal increase in \( \dot{V}O_2 \) peak. The authors concluded that metabolic adaptations, not differences in mechanical power output or compensatory anaerobic glycolysis, were responsible for Tibetans’ lower aerobic energy expenditure. It was also theorized that Tibetans’ minimal gain in \( \dot{V}O_2 \) peak was due to their low muscle mitochondrial density (91). Upon sudden re-oxygenation, such as on descent, the reduced number of mitochondria turn into the bottleneck of the aerobic pathway, henceforth limiting the expected gain in \( \dot{V}O_2 \) peak.

**Growth, Body Weight, and Basal Metabolic Rate**

Tibetan adults living at high altitude are both shorter and lighter than those living at low altitude (123, 149). This growth stunting in adulthood is uniform throughout the world’s multiple high-altitude populations (10, 14, 55). In childhood, Tibetans compared with Andeans and other high-altitude populations are initially smaller and lighter (10, 123), and as altitude increases relative size and weight decrease, with a moderate reduction in linear growth being evident (7, 156). Although poor nutrition has been indicated as being responsible, the growth and development delays seem to be independent of nutritional and socioeconomic factors (155), and thus impute a genetic (or epigenetic) influence on hypoxia per se (37, 122). One theory attributed the high levels of NO exhibited by Tibetans in response to hypoxia to act as a potent inhibitor of steroidogenesis. This in turn produces a population with both shorter stature and lesser musculature (120).

On ascent to high altitude, lowlanders increase their basal metabolic rate (BMR) (31, 50), and this response is independent of temperature (116). In contrast, at levels below 6,000 m, Tibetans’ BMR lies within the limits considered normal for healthy adults at sea level (19, 127). This finding is further supported by the observation that Tibetans, unlike lowlanders, do not seem to encounter weight loss at altitude (27, 167, 168). Moreover, it was demonstrated on the Chinese Mt. Anymaqin expedition that, although all the lowland members of the expedition displayed evidence of anorexia and weight loss, the Tibetans even gained weight at altitude. Weight loss is the most objectively assessed symptom of high-altitude deterioration (153), so perhaps this resistance to weight loss demonstrated by Tibetans may be interpreted as resilience to high-altitude deterioration per se.

**NO Metabolism**

The gaseous signaling molecule NO serves many roles. It is involved in inhibition of platelet aggregation, an antioxidant, a regulator of intermediary metabolism and cellular energy production by mitochondria, and one of the primary endothelial factors regulating macro- and microvascular resistance and consequently blood flow (6, 87). Its potential role in adaptation to hypoxia has been highlighted in a number of studies. In 2001, the superior ability of Sherpas over lowlanders to maximize blood flow velocity after a 2-min period of induced leg occlusion and muscle ischemia was demonstrated (134). The authors concluded disparities were likely due to differences in conduit vessel function and theorized this could be due to NO. Subsequent blood flow-related research demonstrated Tibetans, compared with a sea-level population, had more than double the forearm blood flow with more than 10 times the concentration of circulating concentrations of bioactive NO products (41). The authors inferred that the metabolic pathways controlling formation of NO products are regulated differently in Tibetans and concluded that NO-linked microcirculatory factors augment global convective oxygen delivery to permit adaptation to hypobaric hypoxia. The concept of increased microcirculatory flow was supported by Patitucci et al. (121) when they demonstrated that Sherpas have increased basal levels of angiogenic and lymphangiogenic factors [vascular endothelial growth factor A (VEGF-A), interlukin (IL-8), and VEGF-C, respectively].

Data regarding gas-phase measurements of NO, as opposed to circulating nitrogen oxides, have also been obtained from Tibetans. On hypoxic exposure at 4,200 m, Tibetans exhibit twofold greater levels of exhaled NO (eNO) compared with lowlanders (21). Interestingly, at 4,700 m, Tibetan vital capacity levels of NO were lower than at 4,200 m, and on reversal of hypoxia using supplementary oxygen Tibetans further increased eNO (21). This suggests that greater NO production is due to higher levels of oxygen-dependent NO synthesis, and maximal production of NO is restricted by oxygen availability (20). The functional benefits of higher levels of NO were further exhibited, for, although Tibetans demonstrated lower levels of
eNO compared with lowlanders at 4,200 m, they had a higher rate of NO transfer out of the airway wall by sevenfold (65). This is associated with vasodilation in pulmonary blood vessels, decreased pulmonary artery pressures, and consequently greater oxygen delivery to working tissues.

Concerning metabolism of NO, the endothelial NO synthase 3 gene (NOS3) is one of three NOS isoenzymes used in catalyzing the synthesis of NO. Tibetans and Sherpas display a significant overrepresentation of two alleles of this gene and G894T (Glu 298Asp) and 4B/4A (3, 40). Although no significant correlation between overrepresentation of NOS3 and elevated levels of exhaled NO have yet to be demonstrated, an association may still be determined given the presence of the other two NOS genes (13).

**Genetics**

Although numerous adaptive responses relating to the Tibetan and Sherpa phenotype have been documented over the last 50 years, it has only been in light of recent technological advances that attempts have been made to explore their genotype. To date, however, it must be noted that these discoveries relate to gene regions as opposed to specific genes, and intronic areas that may affect gene function and the functional effects stemming from the genetic variation observed still remain uncertain. Furthermore, although natural selection provides an explanation for the suggested advantageous Sherpa and Tibetan phenotype, the effects of nurture and its influence on the epigenome must also be considered. The potential implications of epigenetics in this area are difficult to overemphasize, but we were unable to identify any data linking epigenetics and Tibetan/Sherpa populations in the literature.

The multi-gene transcription protein hypoxia-inducible factor (HIF) family is one of many significant genetic components known to regulate oxygen homeostasis. With their ability to control the expression of VEGF, endothelin (ET), and erythropoietin (EPO), they have been described as the master regulator of cell hypoxic signaling (32) and systemic oxygen homeostasis (13, 143). In times of diminished oxygen supply to cells, HIF levels have been shown to increase almost immediately. This permits transcription of subsequent genes that counteract this hypoxic threat by increasing oxygen delivery or modifying metabolism (13, 136–139). Consequently, the possibility that HIF-pathway gene selection may be beneficial in hypoxia has been the focus of much attention (108).

Initial early reports of Sherpas possessing a novel dinucleotide repeat polymorphism on *intron 13 of HIF-1α* (147) were disputed as a means of genetic hypoxic adaptation (42). Since then, “adaptation” alleles reflecting natural selection have been identified through the evaluation of single nucleotide polymorphisms (SNPs) in Tibetan and Sherpa genomes. A human genome scan using polymorphic DNA markers on eight unrelated Sherpas concluded the DNA markers D6S1697, D14S274, and D17S1795 were likely to include genes involved in adaptation to hypobaric hypoxia (90). Genomewide allelic differentiation scans (GWADS) have reported high allele frequencies across SNP loci in two gene regions involved in oxygen homeostasis, namely transcription factor EPAS1, the gene encoding transcription factor HIF-2α, and oxygen sensor EGLN1 (18, 26, 125, 140, 169, 170). Interestingly, these two genes highlight the distinct patterns of genetic adaptation found among high-altitude populations. Although EGLN1 demonstrated evidence of positive selection in both Tibetans and Andeans, EPAS1 proved to be the best supported candidate gene in the Tibetan population, and PRKAA and NOS2A in Andeans (26). Notably, HIF-1α and HIF-2α are both isoforms of HIF, and both their function and their expression vary (130). HIF-1α displays significant involvement in hypoxia-inducible genes, and its frequency is not altered in the Tibetan population. HIF-2α mediates many of the same genes and is also involved in glucose sensing (GLUT1, GLUT4) and insulin sensing (IRS3). Its frequency is altered in Tibetans (89, 151, 152).

Aside from HIF, other gene regions have been studied. The insertion allele (I) of the ACE gene is associated with low serum levels of ACE and has been described as a marker of successful adaptation to hypoxia (144). Although it therefore seems plausible that the I allele’s presence is essential in the genotype of those thriving at high altitude (39, 101), no allele overrepresentation was seen in the Tibetan population. HIF-2α mediates many of the same genes and is also involved in glucose sensing (GLUT1, GLUT4) and insulin sensing (IRS3). Its frequency is altered in Tibetans (89, 151, 152).

Discussion of Findings

Tibetans and Sherpas have resided at high altitude for hundreds of generations. Through the process of natural selection, it seems plausible that only those most adapted to the hypoxic environment have survived. Stories describing their incredible feats and unremitting endurance on mountains support this notion. However, these tales of remarkable performance must also be remembered as what they so often are, anecdotes rather than scientific fact. Subjects of the accounts are often elite high-altitude climbing Sherpas but are com-
pared with Western trekking clients, a comparison confounded by many factors. Whether these discrepancies in performance would be apparent from the direct comparison of elite climbers from both populations remains to be answered (52). Nonetheless, as is evident from this review, much research has involved Tibetan and Sherpa subjects, and evidently Darwinian evolution has sanctioned numerous adaptive changes to their genotype and phenotype (FIGURE 2). Undoubtedly, of these many adaptations, there is not one sole mechanism that allows for their suggested hypoxia tolerance. Nor perhaps is their way the only way to achieve successful adaptation. Compared with Andeans, these two geographically discrete and somewhat isolated populations have evolved multiple distinct, yet evidently effective, phenotypic and genetic adaptive mechanisms to cope with the same environmental stressor. Three dissimilar quantitative traits used in the oxygen delivery process highlight this: resting ventilation and HVR are higher in Tibetans (24), whereas [Hb] is greater in Andeans (11).

So, although disparities exist between high-altitude populations’ adaptive mechanisms, can any of the aforementioned adaptations be considered more important or useful than others? Clearly, enhanced exercise performance will confer an evolutionary advantage under conditions where either an augmented or prolonged capacity for physical activity confers a survival advantage, such as a hunter-gatherer existence, escaping from predation, or where physical conflict is frequent. Thus

FIGURE 2. Key physiological differences between Sherpas/Tibetans and lowlanders
alterations in the DNA are obviously of utmost importance. Nonetheless, in terms of translational medicine, such as that practiced by CASE Medicine (51, 88), it is the downstream physiological effects that we may be able to therapeutically replicate to improve care for critically ill hypoxic patients.

In lowlanders at altitude, increasing oxygen flux to the metabolizing tissues through raising cardiac output, minute ventilation, and hemoglobin is demonstrated on acclimatization. In the medical setting, counteracting hypoxia associated with various pathologies often involves similar processes, and increasing [Hb] through blood transfusions is commonplace. Elevated [Hb] is not, however, evident in Tibetans, and their arterial oxygen content at altitude is similar to lowlanders at sea level. Hardly likely to be undercompensation, perhaps oxygen content is not the cardinal feature of successful adaptation to hypoxia. Additionally, these aforementioned processes used to increase oxygen flux are themselves energy consuming and not always sustainable. Although in the short term they serve as a crisis mechanism to restore normal oxygen delivery, it seems alternative mechanisms need to be sought for long-term adaption to hypoxia.

Supply and demand of oxygen is pivotal to any aerobic organism’s survival. Assuming the size and characteristics of the capillary-tissue barrier and the mitochondrial volume density and respiratory function represent an end point for human adaptability, fine tuning metabolic efficiency through tissue and cellular adaptation may be the key in long-term adaptation. Augmenting oxygen delivery to the metabolizing mitochondria through enhanced microcirculatory blood flow could provide the answer, since too many alterations in essential regulatory pathways such as the nitrate-nitrite-nitric oxide axis. Research involving Tibetans implies the presence of adaptations in this triad, the microcirculatory-mitochondrial unit and its regulator NO. Tibetan and Sherpa capillary density in skeletal muscle was larger, forearm and lower limb blood flow were greater, levels of circulating NO were 10-fold higher, and numerous cellular energetic changes (mitochondrial adaptation) exist. Admittedly, these candidate mechanisms cast doubt on conventional scientific opinion that pulmonary and hematological systems permit adaptation to hypobaric hypoxia but rather support the notion that factors far further down the oxygen cascade are essential for long-term hypoxia tolerance. Of course, the two areas of improvement in oxygen delivery are not mutually exclusive.

To clarify matters and aid further identification of the beneficial mechanisms of adaptation to hypoxia, future studies must be conducted on this and other indigenous high-altitude populations. Studies focused on the microcirculatory-mitochondrial unit and NO may produce useful insights into hypoxia tolerance in other circumstances such as clinical disease. Explaining the wide interindividual variability in performance that occurs as a consequence of hypoxia will also allow us to prove or refute Tibetans’ and Sherpas’ mythical claim to be “king of the mountains.” Time, however, is of the essence, and the clock is ticking on Earth’s natural hypobaric hypoxic laboratory. In this instance, with the recent migration of the Han Chinese from lowland plateaus up into the highland plateaus of Tibet and the descent of Sherpas from the Solukhumbu valley into lower regions of Nepal, 20,000 years of relative isolation for Tibetan-Sherpa genetics is coming to an end, and distinct physiological phenotypes are at risk of being attenuated. Interbreeding between Tibetan and Han populations is already commonplace, and as this continues the time left to conduct studies on this unique population is ever diminishing. The intriguing finding that admixture-mediated adaptation may contribute to the Tibetan/Sherpa genetic makeup challenges both this long-held assumption of genetic isolation and the related assumption that selection on new mutations and standing variation were the dominant drivers of environmental adaptation in the Tibetan-Sherpa population (77).

In conclusion, the unique Tibetan and Sherpa genotype:phenotype potentially provides us with an insight into the secrets of successful hypobaric hypoxic adaptation. Admittedly, much of the evidence relating to their superior performance at altitude relates to anecdotal stories. However, this population, much like their Andean and Ethiopian counterparts, are likely to have undergone natural selection to cope with persistent hypoxia. It seems plausible, if this is the case, that no one sole mechanism is responsible for their apparent tolerance to hypoxia but rather a dynamic interrelationship between a multitude of physiological and biochemical factors. With the initiation of translational hypoxic research, from mountainside to bedside, studies into indigenous high-altitude populations’ genotype:phenotype may benefit critically ill hypoxic patients in the clinical setting.

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