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Air to Muscle O_2 Delivery during Exercise at Altitude

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Abstract

Calbet, José, and Carsten Lundby. *High Alt. Med. & Biol.* 10.123–134, 2009.—Hypoxia-induced hyperventilation is critical to improve blood oxygenation, particularly when the arterial Po_2 lies in the steep region of the O_2 dissociation curve of the hemoglobin (ODC). Hyperventilation increases alveolar Po_2 and, by increasing pH, left shifts the ODC, increasing arterial saturation (Sao_2) 6 to 12 percentage units. Pulmonary gas exchange (PGE) is efficient at rest and, hence, the alveolar–arterial Po_2 difference (PAo_2-Pao_2) remains close to 0 to 5 mm Hg. The (PAo_2-Pao_2) increases with exercise duration and intensity and the level of hypoxia. During exercise in hypoxia, diffusion limitation explains most of the additional PAo_2-Pao_2. With altitude, acclimatization exercise (PAo_2-Pao_2) is reduced, but does not reach the low values observed in high altitude natives, who possess an exceptionally high DLo_2. Convective O_2 transport depends on arterial O_2 content (Cao_2), cardiac output (Q), and muscle blood flow (LBF). During whole-body exercise in severe acute hypoxia and in chronic hypoxia, peak Q and LBF are blunted, contributing to the limitation of maximal oxygen uptake (Vo_{2max}). During small-muscle exercise in hypoxia, PGE is less perturbed, Cao_2 is higher, and peak Q and LBF achieve values similar to normoxia. Although the Po_2 gradient driving O_2 diffusion into the muscles is reduced in hypoxia, similar levels of muscle O_2 diffusion are observed during small-mass exercise in chronic hypoxia and in normoxia, indicating that humans have a functional reserve in muscle O_2 diffusing capacity, which is likely utilized during exercise in hypoxia. In summary, hypoxia reduces Vo_{2max} because it limits O_2 diffusion in the lung.

Key Words: hypoxia, oxygen diffusion, pulmonary gas exchange, performance, altitude acclimatization

Introduction

A continuous transfer of O_2 from air to the muscle mitochondria is needed to maintain muscle metabolism. This process matches O_2 demand at rest. During exercise the O_2 demand increases in direct proportion to muscle work, stressing the O_2 transport system to its limits at maximal exercise. When the amount of O_2 arriving to the muscles is insufficient to satisfy the O_2 demand, anaerobic metabolism is activated and exercise capacity is reduced. Since at altitude the transfer of O_2 to the active muscles is reduced, particularly during whole-body exercise, fatigue occurs at lower work rates with lower peak oxygen consumption (Vo_2); that is, in hypoxia, muscle metabolism is even more limited by O_2 availability than at sea level. With acclimatization to altitude, arterial O_2 content (Cao_2) is restored at rest and almost restored to sea-level values during maximal exercise. However, maximal oxygen uptake (Vo_{2max}) improves little with altitude acclimatization. In this review we examine the effects of acute and chronic hypoxia on the transfer of O_2 from the air to the muscle mitochondria during submaximal and maximal exercise. We will also address the influence on O_2 transport of the level of altitude, altitude acclimatization, ancestry, and amount of muscle mass recruited during the exercise. In this review the term *severe acute hypoxia* will be used to refer to a level of hypoxia equivalent to altitudes above ~4500 m and the term *chronic hypoxia* is used for the situation created by permanent residence for at least 1 week at altitudes above 3000 m.

An optimal transfer of O_2 from the air to the mitochondria during exercise requires (1) a pulmonary ventilation high enough to maintain or elevate alveolar Po_2 to increase the rate of O_2 diffusion, (2) the diffusion of O_2 from the alveoli to the capillary blood in the lung, (3) the transport of O_2 from the lungs to the tissues, and (4) the diffusion of O_2 from the muscle capillaries to the muscle mitochondria.

Pulmonary Ventilation and Hypoxia

When resting PAo_2 (or Pao_2) drops below 60 mmHg, pulmonary ventilation (V_E) increases (Dempsey and Forster,

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1982). This response is primarily mediated by the peripheral chemoreceptors (Heymans and Bouckaert, 1930). The carotid body is composed of clusters of neuronlike glomus, or type I, cells enveloped by glialike sustentacular, or type II, cells. Oxygen sensing appears to be mediated by the inhibition of O_2-sensitive K^+ channels in glomus cells (Lopez-Barneo et al., 2008), which leads to cell depolarization, Ca^{2+} entry, and the release of transmitters, causing depolarization of nearby afferent nerve endings (Prabhakar and Peng, 2004). Carotid chemoreceptors are responsive to changes in Po_2, while aortic chemoreceptors are sensitive to changes in O_2 saturation (Sao_2) (Lahiri et al., 1981). Carotid-body denervation attenuates or abolishes the hypoxic ventilatory response (HVR) in bilateral (or unilateral) carotid-body-resected humans (Wade et al., 1970; Lugliani et al., 1971; 1992; Prabhakar and Peng, 2004). As depicted in Fig. 1A, the hypoxic ventilatory response is increased within a few minutes in hypoxia and develops progressively during 2 weeks before V_E stabilizes (Dempsey and Forster, 1982; Sato et al., 1992). After 2 to 3 days at altitude, the level of hyperventilation at rest is proportional to the degree of desaturation (Fig. 1B).

Ventilatory acclimatization is likely due to senzitation of the peripheral chemoreceptors, which respond more easily to both hypoxia and hypercapnia (Dempsey and Forster, 1982; Schoene et al., 1990; Sato et al., 1992). As a consequence of chronic hypoxia, the carotid bodies are enlarged in humans (Arias-Stella and Valcarcel, 1976; Heath et al., 1985). Ventilatory acclimatization does not occur in patients lacking carotid bodies (Roeggla et al., 1995; Prabhakar and Peng, 2004). Ancestry also influences HVR and V_E at rest (Brutsaert, 2007). Tibetans have elevated resting V_E and a high HVR, similar to altitude-acclimatized lowlanders (Brutsaert, 2007). In contrast, Andean natives born and living at sea level have lower isocapnic HVR than comparable humans of European ancestry also born and living at sea level (Sorensen and Severinghaus, 1968; Brutsaert et al., 2005).

The acute ventilatory response to hypoxia increases P_{AO_2} and Pao_2 slightly and may cause a small increase in arterial pH, particularly at high altitudes, facilitating hemoglobin (Hb) O_2 uploading in the lungs (Dempsey and Forster, 1982; Wagner et al., 2007).

During exercise at a given absolute intensity, V_E is exaggerated in acute hypoxia compared to normoxia, which is reflected in a higher V_E/Vo_2. Even if the viscosity of the air is reduced at altitude, the fraction of the whole-body Vo_2 that must be used to sustain V_E is greater at altitude than at sea level. Hypoxia-induced exercise hyperventilation improves blood oxygenation by two main mechanisms. First, hyperventilation augments P_{AO_2} by eliminating CO_2 and by renewing the alveolar gas, increasing somewhat P_{AO_2}. Second, and not less important, hyperventilation left-shifts the O_2 dissociation curve of the hemoglobin (ODC) and consequently, for a given P_{AO_2}, Sao_2 is greater (Lundby et al., 2006a). For example, during submaximal exercise ($\sim$120 W) in severe acute hypoxia equivalent to 5300 m ($F_{IO_2} = 0.105$), V_E was 72% higher in hypoxia than in normoxia (Calbet et al., 2003). As mentioned, hyperventilation in hypoxia allows P_{AO_2} to increase, thus improving Pao_2, despite the fact that the alveolar-to-arterial O_2 pressure difference $P_{AO_2}-Pao_2$ is increased during exercise. However, the improvement in P_{AO_2} that can be achieved through hyperventilation is limited by physiological dead space and the P_{IO_2}. Figure 2A depicts some of the values for the P_{IO_2}–P_{AO_2} gradients observed during exercise at sea level and at the barometric pressure equivalent to the summit of Mt. Everest (Sutton et al., 1988). At rest in normoxia, the P_{IO_2}–P_{AO_2} lies close to 50 mmHg and to 30 mmHg at peak exercise (Sutton et al., 1988; Calbet et al., 2003a). During exercise in severe acute hypoxia ($F_{IO_2} = 0.105$), the P_{IO_2}–P_{AO_2} difference is reduced to 19 mmHg (Calbet et al., 2003a). The minimum value reported for this gradient was observed during exercise at the barometric pressure equivalent to the summit of Mt. Everest, in the course of Operation Everest II, when it was 12 mmHg at rest, and re-

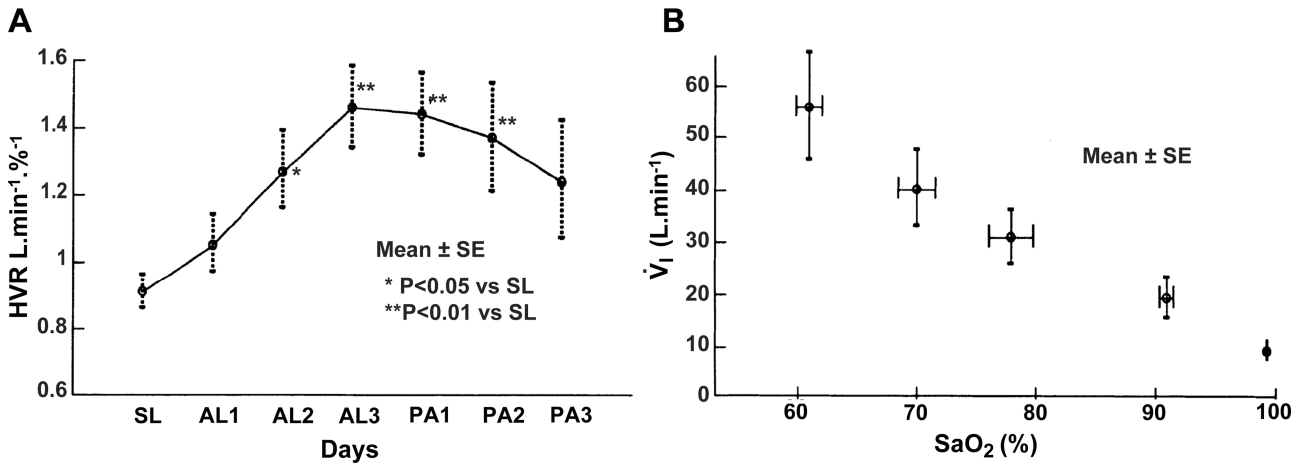

FIG. 1. (**A**) Hypoxic ventilatory response at 3810 m. Effect of time at altitude and return to sea level on hypoxic ventilatory response (HVR). SL, sea level; ALl, AL2, and AL3, 30 ± 18, 76 ± 19, and 115 ± 10 h, respectively, at 3810-m altitude; PAl, PA2, and PA3, days 1, 3, and 4 to 7, respectively, after altitude exposure. (**B**) Linearity of HVR. Relationship of isocapnic ventilation ($\dot{V}_I$) to four levels of steady-state hypoxia (5 min each) with 5 min of rest at inspired O_2 fraction >0.3 between tests in six subjects on days 2 to 3 at altitude. HVR, mean slope, is $\Delta V_I = -1.16 \times \Delta Sao_2$, where $\dot{V}_I$ is inspiratory flow and Sao_2 is arterial O_2 saturation (Sato et al., 1992).

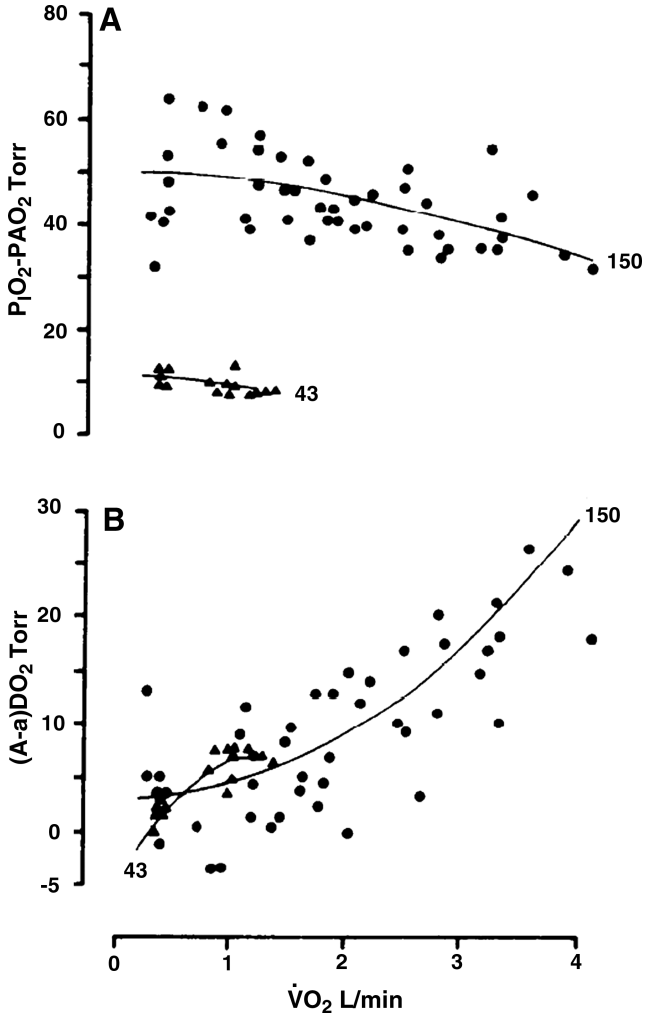

FIG. 2. Influence of $\dot{V}o_2$ on the level of hyperventilation and **[P-P]** at sea level and at the altitude equivalent to the summit of Mt. Everest. (**A**) O_2 pressure difference from inspired air to alveolus (P_{IO_2}–P_{AO_2}). (**B**) O_2 pressure difference from alveolus to arterial blood ($P_{AO_2}-Pa_{O_2}$) as a function of $\dot{V}o_2$. • Sea-level measurements ($P_{IO_2} = 150$ mmHg). ▾ Measurements at barometric pressure of 253 mmHg ($P_{IO_2} =$ 43 mmHg), equivalent to the summit of Mt. Everest (Sutton et al., 1988).

mained close to this value during maximal exercise (Fig. 2A) (Sutton et al., 1988).

Exercise V_E in chronic hypoxia

Compared to acute hypoxia, submaximal exercise V_E remains at the same level with altitude acclimatization, while peak exercise V_E is increased at moderate to high altitudes (Calbet et al., 2003b; Marconi et al., 2004) and reduced at 4000 m (Lundby et al., 2004a). However, peak exercise V_E in altitude- acclimatized lowlanders may be similar (Calbet et al., 2003b), higher (Marconi et al., 2004), or slightly lower than observed in normoxia (Lundby et al., 2004a).

The ventilatory response to exercise in hypoxia is blunted in altitude natives compared to lowlanders. This is also true when acclimatized lowlanders are compared with Andean altitude natives, both measured at altitude (Wagner et al., 2002; Lundby et al., 2004a). Unlike Caucasians, second-generation Tibetans living at 1300 m do not increase V_{Emax} in response to acclimatization to 5050 m above sea level (Marconi et al., 2004). Despite the lower V_{Emax}, low-altitude-residing Tibetans acclimatized to 5050 m during 26 to 28 days were able to attain almost the same Vo_{2max} as at sea level (only 8% less, not statistically significant), while Caucasians having a similar normoxic Vo_{2max} as the Tibetans only reached a Vo_{2max} 31% below that at 1300 m (Marconi et al., 2004). These differences are most likely determined by the genetic background in both Andeans (Brutsaert et al., 2005) and Tibetans (Marconi et al., 2004).

Thus, the extra-hyperventilation observed during exercise in hypoxia has a critical impact on blood oxygenation, particularly in severe acute hypoxia, when the arterial Po_2 lies in the steep region of the ODC. This is illustrated in Fig. 3 using the data from Calbet and colleagues (2003a) at maximal exercise in severe acute hypoxia ($F_{IO_2} = 0.105$). In that study, hyperventilation allowed for an elevation of P_{AO_2} and reduced $Paco_2$ and was associated with 0.1 higher pH at exhaustion in hypoxia than in normoxia. Consequently, the ODC was shifted to the left in hypoxia, improving by 8 percentage units the level of Sa_{O_2} at exhaustion compared with the Sa_{O_2} expected from the ODC corresponding to normoxia (Calbet et al., 2003a). The drop in Sa_{O_2} that occurs with exercise in hypoxia is inversely related to HVR, explaining why sojourners with high HVR may perform better at extreme altitude (Schoene et al., 1984). In addition, replacing the N_2–O_2 gas mixture by helium–O_2 (both with a $F_{IO_2} = 0.11$) allowed increases in V_{Emax} by 31%, Pa_{O_2} by 17%, Sa_{O_2} by 6%, and Vo_{2max} by 14% (Esposito and Ferretti, 1997), thus emphasizing the impact of hyperventilation on O_2 transport and exercise capacity in hypoxia.

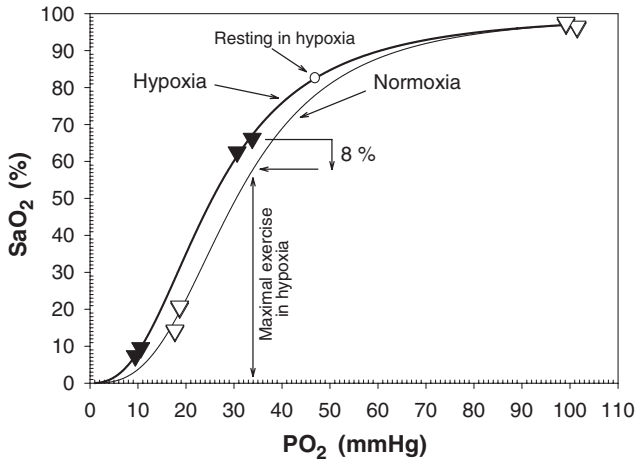

FIG. 3. Impact of hypoxia–hyperventilation on the hemoglobin dissociation curve. Effect of severe acute hypoxia ($F_{IO_2} = 0.105$) on the O_2 dissociation curve of the Hb during exercise in normoxia (white triangles; fine line) and hypoxia (black triangles; thick line). Note the left shift caused by hyperventilation and its impact on Sa_{O_2} at maximal exercise in hypoxia. Points on the graph represent the mean arterial or femoral venous values for each condition in nine subjects. (Po_2 values corrected for blood temperature) (Calbet et al., 2003a).

Pulmonary Gas Exchange

Pulmonary O_2 exchange is driven by the O_2 pressure gradient between the alveolar gas and the lung capillary blood (P_{AO_2}–$P_{mean}cO_2$, where $P_{mean}co_2$ is the mean Po_2 in the lung capillaries), but depends also on the factors that determine the O_2 diffusing capacity of the lungs (DLo_2) (Roughton and Forster, 1957), such that O_2 flow (Vo_2) is equal to the product of $DLo_2 \times (P_{AO_2}–P_{mean}cO_2)$. Since DLo_2 expresses the amount of O_2 that can diffuse in 1 min/mmHg of O_2 pressure gradient, this implies that the process of O_2 gas exchange is not instantaneous and may be limited if the transit time is too short (Wagner, 1977). In a lung without V_A/Q heterogeneity, in the absence of shunt, and with enough time for gas equilibration between the alveolar gas and capillary blood, P_{AO_2} and Pao_2 would reach the same value. Thus, the difference between P_{AO_2} and Pao_2 ($P_{AO_2}-Pao_2$) reflects the efficiency of the pulmonary gas exchange process.

The ($P_{AO_2}-Pao_2$) may be increased due to V_E perfusion (V_A/Q) inequality, right-to-left shunts (or postpulmonary venous admixture, i.e., Thebesian and bronchial venous drainage), intrapulmonary shunts, and alveolar–capillary diffusion limitation. Using the multiple inert gas elimination technique, intrapulmonary shunt always lies below 1% and averages 0.1% of cardiac output (Q) and could contribute less than 2 mmHg to the ($P_{AO_2}-Pao_2$) (Hopkins et al., 2008). Although Lovering and colleagues (2008) have shown that microbubbles cross the lung circulation, which is compatible with the existence of intrapulmonary arteriovenous shunt pathways opening at lower workloads in moderate acute hypoxia, quantitatively the amount of shunt is likely very small and part of it may be artifactual (Hopkins et al., 2008; Vogiatzis et al., 2008). Moreover, some gas exchange may also occur in these shunting pathways. Using the multiple inert gas elimination technique, Wagner and colleagues (Torre-Bueno et al., 1985; Wagner et al., 1986; Wagner et al., 1987) demonstrated that the contribution of ventilation–perfusion inequality to the ($P_{AO_2}-Pao_2$) is rather small in acute hypoxia, particularly at intensities between 60% and 90% of Vo_{2max}. Therefore, the main mechanism limiting pulmonary gas exchange during exercise at altitudes above 3000 m is diffusion limitation (Torre-Bueno et al., 1985; Wagner et al., 1987). The diffusion limitation is supposedly caused by too short transit times of the red blood cells through the pulmonary capillaries, which does not allow for a complete gas equilibration between the alveolar gas and the capillary blood (Wagner, 1977; Calbet et al., 2008). This reduction in mean transit time has been attributed to high values of Q based on the negative correlation that exists between pulmonary transit time and Q (Hopkins et al., 1996). During exercise in moderate hypoxia and normoxia, the $P_{AO_2}-Pao_2$ increases linearly with Q with a slope of approximately 2 mmHg L^{-1}/min^{-1} (Torre-Bueno et al., 1985; Holmberg and Calbet, 2007; Calbet et al., 2008). According to the model of Piiper and Scheid (1981) and to the data published by Wagner's group (Torre-Bueno et al., 1985; Wagner et al., 1986; Wagner et al., 1987), pulmonary gas exchange should be more sensitive to an elevation of Q in acute hypoxia than in normoxia. As illustrated in Fig. 4, the slope of the relationship between Q and $P_{AO_2}-Pao_2$ is not more pronounced in hypoxia than in normoxia, but, as expected, the $P_{AO_2}-Pao_2/Q$ relationship is shifted upward; that is, for a given Q, $P_{AO_2}-Pao_2$ is higher in hypoxia than in normoxia.

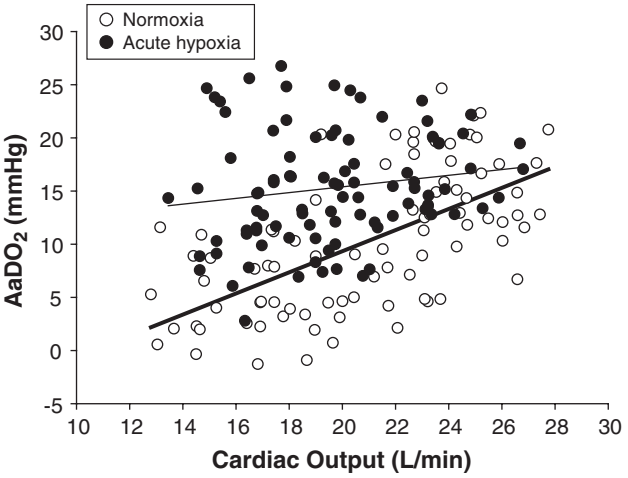

FIG. 4. Relationship between cardiac output and $P_{AO_2}-Pao_2$ (severe hypoxia >4000 m). $P_{AO_2}-Pao_2$ versus cardiac output during exercise in normoxia (open circles, thick line) and hypoxia (black circles, thin line). Own data from several studies (Calbet et al., 2003a; Calbet et al., 2006b; Robach et al., 2007). Slopes and intercepts of the linear regression were statistically different ($p < 0.05$) (Calbet et al., 2008).

Influence of active muscle mass on pulmonary gas exchange

We have recently examined the impact of the size of the active muscle mass on ($P_{AO_2}-Pao_2$) during exercise in normoxia, severe acute hypoxia, and chronic hypoxia (Calbet et al., 2009). While submaximal exercise on the cycle ergometer in severe acute hypoxia (~120 W), cardiac out was 16 L/min^{-1} and the ($P_{AO_2}-Pao_2$) was 23 mmHg (Calbet et al., 2003a), during peak knee-extension exercise in severe acute hypoxia, the corresponding values were 14 L/min^{-1} and 15 mmHg (Calbet et al., 2009). Thus, despite an almost similar Q and lower mean arterial pressure during exercise with a large-muscle mass, the ($P_{AO_2}-Pao_2$) was 53% higher. In subjects acclimatized to 5260 m during 9 to 10 weeks, peak leg-extension exercise elicited a Q of 12 L/min^{-1}, while the accompanying ($P_{AO_2}-Pao_2$) was only 2 mmHg; this condition can be compared with the values obtained during submaximal exercise on the cycle ergometer after acclimatization (~120 W), which elicited a Q of 14 L/min^{-1} and a ($P_{AO_2}-Pao_2$) of 15 mmHg. The 13-mmHg difference in ($P_{AO_2}-Pao_2$) between one-leg knee extension and cycle ergometer exercise is too large to be explained alone by the small difference in Q between these two conditions (Calbet et al., 2008; Calbet et al., 2009).

The same subjects were studied during submaximal exercise (~120 W) after altitude acclimatization with the Hb concentration ([Hb]) achieved after acclimatization and after isovolemic hemodilution to a [Hb] similar to that observed before altitude acclimatization (Calbet et al., 2002). During submaximal exercise the isovolemic hemodilution was compensated for by increasing mean Q from 14 to 16 L/min^{-1} without any significant effect on pulmonary gas exchange (Calbet et al., 2002). Similar results were obtained in another study when the Q was increased during submaximal exercise on the cycle ergometer in acute hypoxia by infusing adenosine into one femoral artery (Calbet et al., 2008).

Altogether these experiments indicate that, for mean Q values up to 14 to 16 L/min^{-1}, pulmonary gas exchange is not

limited by Q either in acute or chronic hypoxia (Calbet et al., 2008; Calbet et al., 2009). An explanation for these findings is that more lung capillaries are recruited in some circumstances when Q is increased, attenuating the effect of Q on mean transit times.

Effects of altitude acclimatization on pulmonary gas exchange

With altitude acclimatization, the impairment of pulmonary gas exchange is reduced when examined at the same absolute workload (Bebout et al., 1989; Calbet et al., 2003b; Calbet et al., 2008). This improvement in pulmonary gas exchange has been considered the outcome of a smaller diffusional limitation (Wagner, 1987; Bebout et al., 1989), due to the fact that for a given workload Q is reduced after altitude acclimatization (Wagner, 1987). Using data from Bebout et al. (1989), Fig. 5 shows the slope for the relationship between ($P_{AO_2}-Pa_{O_2}$)/Q. Since the slopes were similar in normoxia and acute hypoxia and after 2 weeks of acclimatization to 3800 m, this result could indicate that ($P_{AO_2}-Pa_{O_2}$) depends more on Q than on relative exercise intensity during exercise in normoxia and moderate hypoxia. However, at altitudes above 4500 m, for a given Q the ($P_{AO_2}-Pa_{O_2}$) is higher in acute than in chronic hypoxia, implying that the improvement in ($P_{AO_2}-Pa_{O_2}$) with acclimatization could also depend on other mechanisms (Calbet et al., 2003b; Calbet et al., 2008; Calbet et al., 2009).

Although maximal exercise ($P_{AO_2}-Pa_{O_2}$) is not significantly improved during the initial 2 weeks of acclimatization to 4100 m, it is improved after 8 weeks of acclimatization (Lundby et al., 2004a). At a higher altitude (5050 m), maximal exercise Sa_{O_2} was not improved from 2 to 4 days to either 14 to 16 or 26 to 28 days at altitude, also indicating lack of improvement of maximal exercise pulmonary gas exchange during the first month at altitude (Marconi et al., 2004). Improvement in maximal exercise ($P_{AO_2}-Pa_{O_2}$) could be explained by increased pulmonary capillarization, as shown in rats exposed to 2 weeks of chronic hypoxia equivalent to 5500 m (Howell et al., 2003). Alternatively, altitude acclimatization could allow for a greater recruitment of preexiting lung capillaries, reducing mean transit time and, hence, the limitation to O_2 diffusion (Capen and Wagner, 1982). In addition, acclimatization could reduce the diffusional limitation by, for example, reducing the level of interstitial edema.

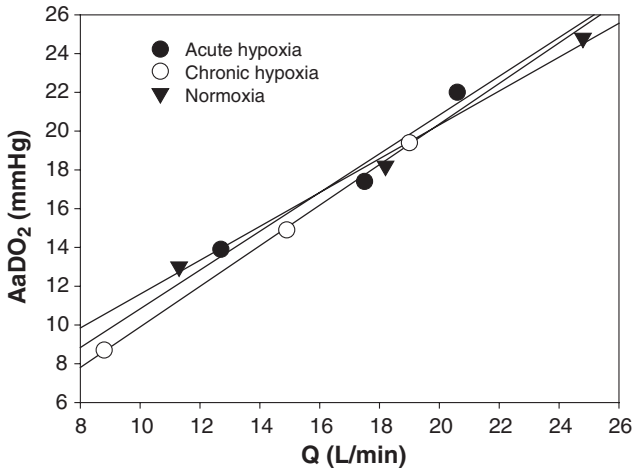

FIG. 5. Relationship between cardiac output and ($P_{AO_2}-Pa_{O_2}$) (moderate hypoxia <4000 m). Relationship between ($P_{AO_2}-Pa_{O_2}$) and cardiac output at sea level (black triangles) and acute hypoxia (black circles) and after 2 weeks at 3800 m above sea level (white circles). Each point represents the mean value of eight men (Bebout et al., 1989).

The $P_{AO_2}-Pa_{O_2}$ during submaximal and maximal exercise is lower in altitude natives than in lowlanders acclimatized to the same altitude where the natives live (Dempsey et al., 1971; Zhuang et al., 1996; Wagner et al., 2002; Lundby et al., 2004a; Brutsaert, 2007; Lundby and Calbet, 2009). The higher efficiency of the pulmonary gas exchange in altitude natives has been explained by their remarkably higher DL_{O_2} at maximal exercise compared with acclimatized lowlanders (Wagner et al., 2002). This increased DL_{O_2} is associated with larger total lung capacities in the altitude natives (Zhuang et al., 1996). This difference in lung structure may be in part the result of a developmental adaptation (i.e., structural organization of the lung during growth), since altitude natives born in Morococha (4540 m) had 38% larger residual lung volume than individuals of the same ethnicity but born and living at sea level. The vital capacity was approximately the same; as a result, total lung capacity was higher in the altitude natives (Hurtado, 1964). Exercise differences in pulmonary gas exchange between altitude natives and lowlanders are also the result of genetic selection over millennia, since second-generation Tibetan lowlanders acclimatize to high altitude more quickly than Caucasians (Marconi et al., 2004). Thus both genetic and developmental adaptations contribute to the enhanced pulmonary gas exchange efficiency in altitude natives, with a likely predominance of the genetic over the developmental component (Brutsaert et al., 2003; Marconi et al., 2004).

Oxygen Diffusing Capacity in the Lungs

By definition, $V_{O_{2max}}$ cannot be greater than the amount of O_2 that diffuses from the atmosphere to the capillary blood in the lungs, and this is the main mechanism accounting for the reduction of $V_{O_{2max}}$ during exercise at altitude in lowlanders (Blomqvist et al., 1969). The critical question is why this transfer of O_2 from the atmosphere to the lung capillaries is reduced at altitude. A main contributing factor is the reduction of P_{IO_2} and consequently of P_{AO_2}, resulting in a lower P_{O_2} gradient driving O_2 diffusion. Pulmonary O_2 diffusing capacity (DL_{O_2}) increases during exercise in normoxia and hypoxia (Steinacker et al., 1998). When the P_{O_2} gradient driving diffusion is small, as occurs during exercise in hypoxia, transfer of O_2 from the atmosphere to the lung capillaries becomes more sensitive to changes in DL_{O_2} (Blomqvist et al., 1969).

Pulmonary O_2 diffusing capacity is usually estimated by measuring carbon monoxide diffusing capacity (DLco) (Roughton and Forster, 1957). The resistance to the diffusion of O_2 ($1/DL_{O_2}$) can be divided into the resistances at the capillary membrane ($1/DM$) and the reaction rate of O_2 with Hb in the red blood cells ($1/\theta Vc$) such that $1/DL_{O_2} = 1/DM + 1/\theta Vc$, where DL_{O_2} is the overall diffusing capacity of the lung, DM is the diffusing capacity of the membrane separating the alveolar air from the blood, Vc is the total volume in milliliters of the blood in the lung capillaries exposed to alveolar air, and θ is the diffusing capacity of the red blood cells.

The DM component of the lung diffusing capacity may be reduced during exercise by interstitial edema; however, this reduction does not seem to affect O_2 transport (Hanel et al., 1994). Interstitial edema may occur more easily during

exercise in hypoxia, due to higher pulmonary artery pressures in hypoxia than in normoxia (Dehnert et al., 2006; Maggiorini, 2006). Pulmonary artery hypertension may be prevented during exercise in acute hypoxia with 5-phosphodiesterase inhibitors (sildenafil) (Ricart et al., 2005; Richalet et al., 2005). Administration of sildenafil prior to exercise in acute moderate and severe hypoxia results in higher arterial Hb O_2 saturation during submaximal (Hsu et al., 2006) and maximal exercise (Ghofrani et al., 2004; Ricart et al., 2005; Richalet et al., 2005; Faoro et al., 2007). However, in chronic hypoxia sildenafil may fail to improve Sao_2 at peak exercise despite reducing pulmonary hypertension (Faoro et al., 2007).

For a given Po_2, the O_2 transport capacity of blood is mainly determined by the [Hb] and Hb affinity usually assessed by determining the P_{50}. Factors that reduce and increase P_{50} may enhance and lower, respectively, the flow of O_2 from the alveolar gas to the capillary blood. In chronic hypoxia, the standard P_{50} (the value of Po_2 that causes Hb to be saturated by 50% when the O_2–Hb equilibration curve is determined at 37°C, pH = 7.40, $Pco_2 = 40$ mmHg) is increased with altitude acclimatization from 25 at sea level to 31 mmHg after 9 to 10 weeks at 5269 m (Calbet et al., 2003b), likely due to increased 2,3-diphosphoglycerate (Wagner et al., 2007). This right shift of the ODC implies that, for a given Po_2, less O_2 can react with Hb to form O_2Hb. This mechanism should reduce O_2 diffusion at the lungs due to the increased resistance to O_2 diffusion associated with the chemical reaction of O_2 with Hb ($1/\theta Vc$). In fact, during maximal exercise at 5260 m, the improvement in Sao_2 after acclimatization would have been 10% higher if the P_{50} had remained in the left-shifted position observed at the same level of hypoxia but under maximal exercise in acute conditions (Calbet et al., 2003a). However, the position of the ODC in the lung at Vo_{2max} in chronic hypoxia was similar to that observed in normoxia at sea level (Calbet et al., 2003a; Calbet et al., 2003b).

Although a theoretical analysis claims that the observed changes in P_{50} at altitude do not affect exercise capacity (Wagner et al., 2007), a recent experimental study shows otherwise (Calbet et al., 2009). As shown in Fig. 6, the drop in Vo_{2max} during exercise in severe acute hypoxia ($Fio_2 = 0.105$) is blunted during exercise with a small (one-leg, knee-extension exercise) compared with a large-muscle mass (two-leg, cycle ergometer exercise), in part due to better pulmonary gas exchange (lower ($PAo_2 - Pao_2$)) and less of a right shift of the ODC. During one-leg, knee-extension exercise in severe acute hypoxia, Sao_2 was 10 units higher compared with exercise on the cycle ergometer (76.5 ± 1.7 and 66.2 ± 2.7%, respectively). About 40% of the difference in Sao_2 could be accounted for by the higher arterial pH (+0.23) during one-leg, knee-extension exercise and 10% by the higher blood temperature (+0.35°C) during exercise on a cycle ergometer. Forty-five percent of the difference in Sao_2 could be accounted for by the impact of the 3.7-mmHg lower Pao_2 on Sao_2 during exercise on the cycle ergometer. As a result, at maximal exercise in severe acute hypoxia, Cao_2 was 17% higher during one-leg, knee- extension exercise than during exercise on the cycle ergometer. Similar results were obtained when the same conditions were compared after altitude acclimatization, that is, 20% higher Cao_2 at peak exercise during one-leg knee extension compared with the cycle ergometer bicycling exercise, due to better pulmonary gas exchange during small-muscle exercise (Calbet et al., 2009). Therefore, an attenuation of exercise-induced right shift of the ODC by, for example, reducing the level of exercise-induced hyperthermia or lactic acidosis should have a positive effect on exercise capacity by allowing a higher convective O_2 transport, particularly when the exercise is performed in hypoxia.

Convective Oxygen Transport (Cardiac Output and Leg Blood Flow)

During submaximal exercise at a given absolute workload, systemic O_2 transport ($Q \times Cao_2$) and muscle O_2 transport (muscle blood flow $\times Cao_2$) are adjusted to maintain steady levels of O_2 delivery in response to changes in Cao_2, particularly when Cao_2 is reduced (Calbet, 2000). Thus, during submaximal exercise in either acute hypoxia, chronic hypoxia, or acute isovolemic anemia, a mild reduction in Cao_2 (up to 20%) is counterbalanced by an increase in Q and leg blood flow (LBF) (Koskolou et al., 1997a; Koskolou et al., 1997b; Gonzalez-Alonso et al., 2001; Calbet et al., 2002; Calbet et al., 2006a). However, in severe acute hypoxia the compensatory increase in Q and muscle blood flow may not be sufficient to maintain convective O_2 transport and, hence, Vo_2 is reduced (Calbet et al., 2003a). A mismatch between O_2 delivery and O_2 demand accelerates the rate of fatigue development during exercise by several mechanisms (see Amann and Calbet, 2008, for a review).

During whole-body upright exercise at sea level, systemic O_2 transport is limited by the maximal pumping capacity of the heart (Calbet et al., 2004). However, during maximal exercise with a small muscle, only a fraction of the maximal pumping capacity of the heart is utilized (Roach et al., 1999). By combining small- and large-muscle-mass exercise with different levels of Fio_2, we expected to determine what roles Po_2 and Cao_2 might play in the regulation of Q and LBF

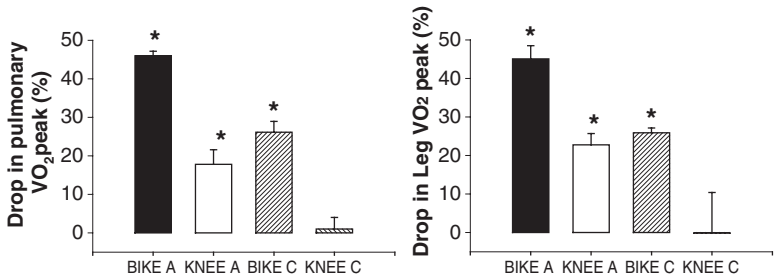

FIG. 6. Effect of hypoxia on peak pulmonary and leg Vo_2. Drop in pulmonary Vo_2 during peak exercise on cycle ergometer (Bike) and knee-extension ergometer (Knee) in severe acute hypoxia (A) and after 9 to 10 weeks of residence at 5260 m (C). *Significantly different from normoxia ($p < 0.05$) (Calbet et al., 2009).

(Calbet et al., 2009). During maximal exercise in acute hypoxia, peak Q and peak LBF are similar to those achieved in normoxia when the level of hypoxia stays below that equivalent to 4000 m. Above this altitude, peak Q and peak LBF are below normoxic values during exercise on a cycle ergometer (Calbet et al., 2003a; Calbet et al., 2003b), but are similar to normoxic values during knee-extension exercise (Calbet et al., 2009). In chronic hypoxia, peak Q and LBF are reduced during exercise on the cycle ergometer (Pugh, 1964; Calbet et al., 2003b; Lundby et al., 2006). These effects are already present at moderate altitude (Lundby et al., 2006) and may be more pronounced at higher altitudes (Reeves et al., 1987; Calbet et al., 2003b). However, during one-leg, knee-extension exercise in chronic hypoxia (5260 m), peak LBF was not reduced compared with normoxic conditions (Calbet et al., 2009). A detailed discussion on the mechanisms that could explain these blunted peak Q and LBF responses to exercise in severe acute and chronic hypoxia can be found in previous articles (Calbet et al., 2003a; Calbet et al., 2003b; Calbet et al., 2009).

Thus, during exercise in severe acute or chronic hypoxia with a small muscle, pulmonary gas exchange is less perturbed, Pao_2 is higher, and the ODC is less shifted to the right as compared to exercise with a large-muscle mass. In contrast with cycle ergometer exercise, knee-extension exercise in severe acute or chronic hypoxia does not reduce peak LBF. These mechanisms facilitate O_2 uploading in the lungs and, hence, Cao_2, permitting a relative larger O_2 delivery when exercise is performed with a small muscle.

Diffusive O_2 Transport

The last step in the transfer of O_2 from air to the muscle mitochondria requires the appropriate distribution of Q, with priority to the most active muscle fibers, which during whole-body exercise compete with the respiratory muscles, myocardium, and brain for the supply of O_2. This competition may lead to premature fatigue if the brain or the respiratory muscles do not receive enough O_2 to maintain their metabolic rate (Amann and Calbet, 2008). During whole-body exercise in severe acute hypoxia, the distribution of blood flow is somewhat similar to normoxia (Calbet et al., 2003a). In contrast, in chronic hypoxia a lower proportion of the available Q is diverted to irrigate the active leg muscles and, consequently, leg O_2 delivery increases less than it could (theoretically), limiting leg and whole-body Vo_{2max} (Calbet et al., 2003b). However, during exercise with a small muscle (one-leg, knee-extension exercise), peak LBF is not reduced, and the amount of blood available to perfuse the other competing vascular beds (brain, heart, and respiratory muscles) is greater than during whole-body exercise (Calbet et al., 2009). The latter is accompanied by a higher perfusion pressure during one-leg knee extension, which also contributes to securing O_2 delivery to the competing territories (Calbet et al., 2009).

Inside the muscle, the blood flow must be distributed to the most active muscle fibers; this is likely achieved by the combined action of an increased sympathetic activation (Calbet et al., 2006b; Lundby et al., 2008a), with selective sympatholysis near the muscle fibers consuming more O_2 (Remensnyder et al., 1962).

Once in the capillaries the O_2 must diffuse from the Hb to the mitochondria. This process depends on the pressure gradient between the capillaries (mean muscle capillary Po_2) and the mitochondrial Po_2, which lies close to 0 mmHg at maximal exercise (Gayeski and Honig, 1986; Severinghaus, 1994; Richardson et al., 1995). In hypoxia the Po_2 gradient driving this diffusion is reduced simply because Pao_2 is lower. This alone could contribute to limiting Vo_{2max} and exercise capacity in hypoxia. However, during maximal exercise on the cycle ergometer, the Po_2 in the femoral vein is reduced to a similar, if not to a lower, value than during normoxic exercise, implying that O_2 is extracted from the capillaries to the same limit during whole-body exercise in severe acute hypoxia as in normoxia (Calbet et al., 2003a; Calbet et al., 2009). However, some O_2 is left in the femoral vein (Fig. 7), part of which is an admixture with blood coming from less active muscle fibers, skin, adipose tissue, and bone marrow. The rest may represent a true limitation to O_2 diffusion. This limitation could be caused by a too short mean transit time (Hogan et al., 1994), low pressure gradient, and insufficient muscle O_2 diffusing capacity, which in part depends on the capillary density (see Calbet et al., 2005, and Richardson et al., 2006, for a review).

Effects of hypoxia on muscle intracellular oxygenation

Resting intracellular muscle Po_2 has been estimated by measuring, with proton nuclear magnetic resonance spectroscopy (^{1}H NMR), the fraction of myoglobin that is deoxygenated. By assuming a value for the myoglobin P_{50}, it is possible to calculate the intracellular Po_2 from the O_2–myoglobin dissociation curve (Jue and Anderson, 1990; Mole et al., 1999). At rest in normoxia the intracellular Po_2 remains close to 34 mmHg and is reduced to 23 mmHg in hypoxia ($FIo_2 = 0.10$) (Richardson et al., 2006). During small-muscle exercise either in normoxia or hypoxia ($FIo_2 = 0.12$), myoglobin desaturates rapidly to 50% and 60%, respectively, already at 50% of Vo_{2max} without further decrease with increasing exercise intensity (Richardson et al., 1995; Richardson et al., 2001). The latter corresponds to an intracellular Po_2 of 3 and 2 mmHg, respectively, meaning that there is a gradient between the mean capillary Po_2 and intracellular Po_2 (Richardson et al., 1995). The presence of this gradient has been interpreted as an indication of diffusion limitation from red cell to the sarcoplasma in human skeletal muscle (Richardson et al., 1995). Nevertheless, the presence of the gradient does not necessarily imply that muscle Vo_{2max} is limited by a diffusional limitation. In fact, we have shown that muscle Vo_{2max} may be increased without increasing the Po_2 gradient driving diffusion (Lundby et al., 2008c). It remains unknown if intracellular Po_2 is reduced below 2 mmHg during whole-body exercise, but looking at Fig. 7 it is clear that both mean capillary Po_2 and femoral vein Po_2 are lower during whole-body than during small-muscle exercise; hence, a change in the same direction for intracellular Po_2 is expected. However, mitocondrial respiration is not impaired until Po_2 falls below 0.1 to 0.5 mmHg (Chance and Quistorff, 1977; Richmond et al., 1997).

As shown in Fig. 7, when exercise in severe acute hypoxia is performed with a small muscle (one-leg, knee-extension exercise), the gradient driving the diffusion of O_2 ($P_{mean}cO_2$–$P_{mitochondrial}O_2$) is just a little greater than during whole-body exercise (Calbet et al., 2009); however, blood flow (mL/kg) of active muscle mass is also larger, implying a shorter transit time (Hogan et al., 1994; Richardson et al., 1995). Despite the shorter transit time during small-muscle exercise, leg Vo_{2max} is reduced much less during small-muscle than during whole-body exercise, implying that proportionally a remarkably greater amount of O_2 can diffuse from the capillaries to the muscle fiber during small-muscle exercise (Calbet et al.,

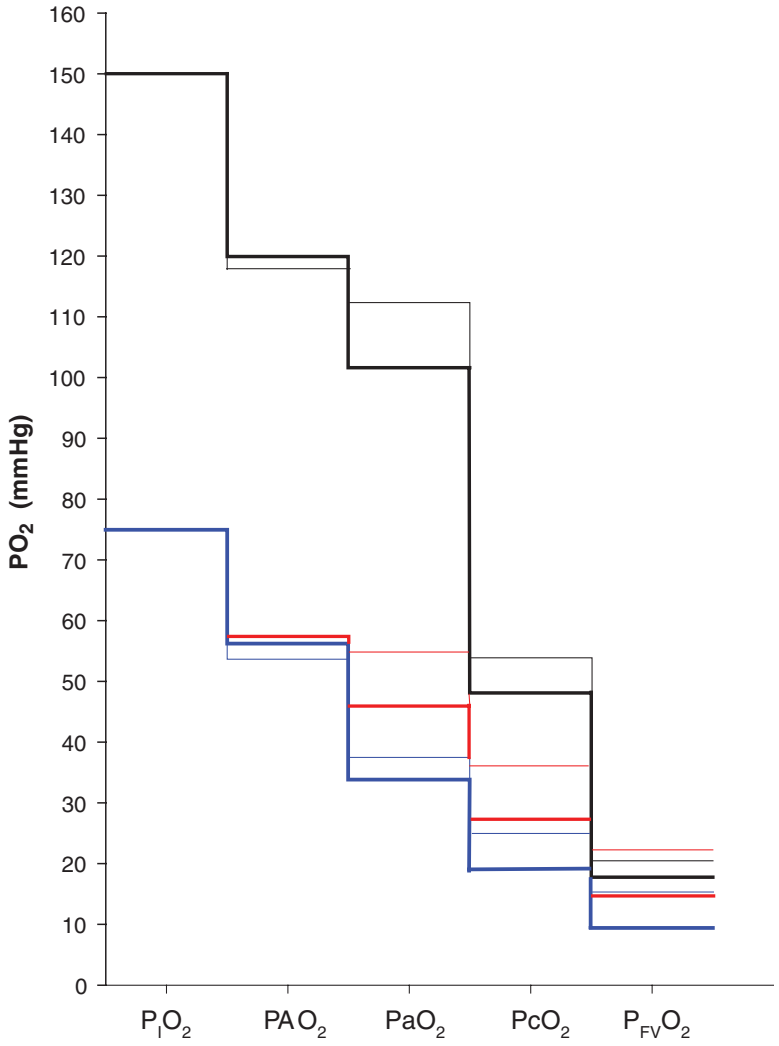

FIG. 7. Oxygen cascade from the atmosphere to the femoral vein. The values of inspiratory O_2 pressure (P_{IO_2}), alveolar P_{O_2} (P_{AO_2}), arterial P_{O_2} (P_{aO_2}), estimated mean capillary P_{O_2} (P_{cO_2}), and femoral vein P_{O_2} ($P_{FV}O_2$) are represented during exercise on the cycle ergometer (thick lines) and knee-extension exercise (thin lines) during normoxia (black lines), severe acute hypoxia (blue lines), and chronic hypoxia (red lines) (Calbet et al., 2009). Mean capillary P_{O_2} was calculated as previously described (Lundby et al., 2008c).

2009). The latter indicates that the main mechanism limiting $V_{O_{2max}}$ during exercise in hypoxia is O_2 delivery, while muscle O_2 diffusing capacity may have a secondary role (Calbet et al., 2009).

Effects of chronic hypoxia on muscle O_2 diffusing capacity

Other factors that could influence muscle diffusing capacity in chronic hypoxia, such as reduced mitochondrial oxidative capacity induced by chronic hypoxia (Cerretelli, 1976; Wagner, 2000), can be ruled out since (1) a moderate level of hyperoxia is able to reestablish sea-level $V_{O_{2max}}$ values (Calbet et al., 2003b; Lundby et al., 2006), (2) maximal mitochondrial respiration remains unaltered after 8 to 10 days of residence at 4559 m (Boushel et al., unpublished), and (3) neither citrate synthase nor 3-hidroxyacil-CoA-dehydrogenase activities are affected by 75 days of residence at 5250 m or higher in physically active or less active men (Mizuno et al., 2008). In the same way that increasing [Hb] facilitates the diffusion of O_2 from the alveolar space to the vascular space (Roughton and Forster, 1957), it could make more difficult the diffusion of O_2 from the red cells to the muscle mitochondria, since the O_2 may tend to remain bound to the hemoglobin, particularly without the *in vivo* right shift of P_{50}. However, muscle O_2 conductance (an estimation of muscle diffusing capacity) was not influenced by [Hb] during maximal exercise in chronic hypoxia (Calbet et al., 2002). In addition, increasing [Hb] with erythropoietin treatment allowed a higher diffusion of O_2 in the active muscle, despite no effect on capillarization or muscle oxidative enzymatic activity (Lundby et al., 2008b; Lundby et al., 2008c; Robach et al., 2008), indicating that not all the available muscle O_2 diffusing capacity is used during exercise in normoxia. We think that part of the functional reserve in muscle O_2 diffusing capacity is used during maximal exercise in hypoxia to compensate for the reduction in the O_2 pressure gradient.

In lowlanders acclimatizing to 4100 m during 8 weeks, maximal leg O_2 extraction values (~90%) remained unchanged (Lundby et al., 2006). In this study the standard P_{50} was

increased by 2 mmHg, reaching a value (28 mmHg) similar to that observed in natives living at the same altitude. However, the *in vivo* P_{50} was decreased from 44 mmHg in normoxia to 39 mmHg in acute hypoxia (a value similar to that observed in altitude natives) and remained at this level during the acclimatization period. This finding implies that the off-loading of O_2 from the Hb does not limit O_2 diffusion from the capillaries to the muscle fibers in altitude-acclimatized humans. However, peak exercise leg O_2 extraction in the natives was 7 percentage units lower than in the lowlanders, despite the fact that $V_{O_{2max}}$ in normoxia was comparable between both groups. The only structural difference that could explain this reduced O_2 extraction capacity in the altitude natives was that they had less capillaries per muscle fiber than the lowlanders (Lundby et al., 2004b; Lundby et al., 2006).

Conclusions

In summary, an optimal transfer of O_2 from the air to the mitochondria requires the coordinated increase of pulmonary V_E and efficient pulmonary exchange, the transport and distribution of O_2 to the tissues with the appropriate level of priority, and the diffusion of O_2 from the tissue capillaries to the mitochondria. The main effect of hypoxia is that P_{IO_2} is reduced and hence the gradients driving the transfer of O_2 from air to muscle are reduced. To preserve O_2 transport, particularly during high-intensity exercise, the organism responds with countermeasures aimed at enhancing the P_{O_2} gradients; that is, V_E is increased to elevate P_{AO_2}. In addition, the O_2-carrying capacity of blood is enhanced by shifting the ODC to the left. With chronic hypoxia, the Hb concentration is increased and the C_{aO_2} at peak exercise with a small muscle in chronic hypoxia tends to be more similar to that observed in normoxia at sea level. These responses allow the restoration of convective O_2 transport during exercise in chronic hypoxia with a small muscle, but not during whole-body exercise. Consequently, sea-level peak leg extension, but not cycling V_{O_2}, can be attained after 9 to 10 weeks of residence at 5260 m. The latter occurs despite much lower P_{O_2} gradients driving the diffusion of O_2 from the muscle capillaries to the mitochondria in chronic hypoxia than at sea level. During whole-body exercise in chronic hypoxia, peak LBF is reduced, not only because peak cardiac output is blunted, but also because a greater amount of flow is directed to perfuse other vascular territories to reduce the possibility of insufficient O_2 delivery to the respiratory muscles, myocardium, and brain. However, the price paid is a lower $V_{O_{2max}}$ and exercise capacity, despite the fact that systemic convective O_2 transport is only slightly reduced compared to that observed at sea level. Although the P_{O_2} gradient driving O_2 diffusion is reduced in hypoxia, similar levels of muscle O_2 diffusion are observed during small-mass exercise in chronic hypoxia and in normoxia, suggesting that humans have a functional reserve in muscle O_2 diffusing capacity that is likely to be recruited during exercise in hypoxia.

Disclosures

Authors Calbet and Lundby have no conflicts of interest or financial ties to disclose.

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