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REVIEW | *Hypoxia 2017*

Regulation of blood volume in lowlanders exposed to high altitude

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Siebenmann C, Robach P, Lundby C. Regulation of blood volume in lowlanders exposed to high altitude. *J Appl Physiol* 123: 957–966, 2017. First published June 1, 2017; doi:10.1152/japplphysiol.00118.2017.—Humans ascending to high altitude (HA) experience a reduction in arterial oxyhemoglobin saturation and, as a result, arterial O_2 content (Ca_{O_2}). As HA exposure extends, this reduction in Ca_{O_2} is counteracted by an increase in arterial hemoglobin concentration. Initially, hemoconcentration is exclusively related to a reduction in plasma volume (PV), whereas after several weeks a progressive expansion in total red blood cell volume (RCV) contributes, although often to a modest extent. Since the decrease in PV is more rapid and usually more pronounced than the expansion in RCV, at least during the first weeks of exposure, a reduction in circulating blood volume is common at HA. Although the regulation of hematological responses to HA has been investigated for decades, it remains incompletely understood. This is not only related to the large number of mechanisms that could be involved and the complexity of their interplay but also to the difficulty of conducting comprehensive experiments in the often secluded HA environment. In this review, we present our understanding of the kinetics, the mechanisms and the physiological relevance of the HA-induced reduction in PV and expansion in RCV.

erythropoietin; hemoglobin mass; hypoxia; plasma volume; red blood cell volume

HIGH ALTITUDE (HA) can constitute a hostile and inaccessible environment with cold temperatures, dry air, and increased solar radiation. The cardinal challenge for humans is, however, the progressive decrease in barometric pressure and hence atmospheric O_2 partial pressure (P_{O_2}) with increasing altitude, which despite compensatory increases in pulmonary ventilation leads to a reduction in alveolar P_{O_2} (99). Since O_2 diffusion from the alveoli into the pulmonary capillaries is driven by the P_{O_2} gradient, the lower alveolar P_{O_2} translates into a reduction in arterial P_{O_2}. Due the sigmoidal shape of the oxyhemoglobin saturation curve, the reductions in arterial O_2 saturation (Sa_{O_2}) and hence arterial O_2 content (Ca_{O_2}) arising from decreases in arterial P_{O_2} to levels >60 mmHg are mild, although they can already affect aerobic exercise capacity (100). At altitudes exceeding ~3,000 m, arterial P_{O_2} reaches the steeply descending portion of the oxyhemoglobin saturation curve so that more substantial reductions in Sa_{O_2} and Ca_{O_2} occur (19). During acute HA exposure, a compensatory increase in cardiac output is hence required in addition to the higher pulmonary ventilation for a given systemic O_2 delivery (96). However, as exposure extends, different acclimatization processes restore Ca_{O_2} to levels that often surpass sea level (SL) values and cardiac output at rest and at a given exercise workload normalizes (51). The main component responsible for restoring Ca_{O_2} is an increase in arterial hemoglobin concentration ([Hb]), which stems from a reduction in plasma volume (PV) and, often to a lesser extent, from an increase in total red blood cell volume (RCV) (83). As the magnitude of the reduction in PV usually exceeds that of the increase in RCV, at least during the first weeks at HA, a reduction in total blood volume (BV) occurs (1, 35, 78, 83).

The interest in the effects of HA on intravascular volumes is not limited to environmental physiology. Since chronic hypoxia is a feature of diseases such as anemia or chronic obstructive pulmonary disease, the resulting changes in intravascular volumes and their physiological consequences are relevant from a clinical perspective. In addition, the popularity of altitude training as a potential mean to increase RCV and thereby aerobic endurance performance (29) fuels an ongoing interest in the erythropoietic effect of HA. In this review, we summarize our understanding of the time course, the mechanisms, and the physiological relevance of the reduction in PV and increase in RCV at HA. We focus on studies exposing healthy human lowlanders to continuous HA/hypoxia without concomitant exercise training. The reason for the latter is that exercise training may affect both PV and RCV (81) so that the effect of HA per se is difficult to isolate. Similarly, given the acute effects of exercise on PV as well as autonomic and humoral control, we focus on observations made at rest.

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The large majority of subjects in the presented studies were males, and it needs to be considered whether the findings can be expanded to females. In support, a recent study reported similar increases in RCV in males and females exposed to 5,260 m (79). Furthermore, although a blunted RCV expansion could be expected in females due to lower iron availability, no correlation was found between iron availability and RCV expansion in women exposed to 4,300 m (36). With regards to the reduction in PV, a recent meta-analysis detected no differences between males and females throughout the first week of exposure to various altitudes (8). Another consideration is that in most studies subjects were exposed to a constant altitude. In contrast, mountaineering expeditions involve progressively increasing altitude, where each new ascent may again offset O_2 homeostasis so that larger intravascular volume adaptations might occur. These speculations are supported by the pronounced PV reduction and RCV expansion observed during progressive decompression to the simulated altitude of the summit of Mt. Everest (77).

Reduction in PV

While the erythropoietic effect of HA is widely appreciated, knowledge and understanding of the reduction in PV seem limited to researchers with a specific interest in HA physiology. As outlined below, this uneven awareness contrasts the often greater relevance of the reduction in PV for the restoration of Ca_{O_2}.

Time course and magnitude of the PV reduction. Figure 1*A* summarizes 21 studies monitoring changes in PV at altitudes ranging from 2,900 to 5,000 m (1, 26, 32, 36, 37, 39, 44, 46, 50, 55, 62, 70, 74, 77, 78, 83, 86, 87, 89, 92, 105). It is evident that the PV reduction commences early during HA exposure. Indeed, PV reductions of >10% can already occur within the first 24 h at ~4,000 m (8, 36, 50). Figure 1*A* furthermore illustrates that PV decreases steeply throughout the first 1–2 wk, where after it plateaus 10–30% below initial levels. Finally, Fig. 1*A* supports earlier reviews claiming that the final magnitude of the reduction in PV depends of the severity of HA (7, 8, 81). Since the rate of the initial, rapid decrease in PV appears similar across altitudes, the larger final reduction at higher altitudes may be primarily explained by a later plateauing. Whether the reduction in PV persists throughout HA sojourns exceeding 1 mo is barely explored. In 10 lowlanders exposed to 4,540 m (74), PV was reduced by ~20% after the first month, where after it slowly recovered, potentially in response to progressive RCV expansion, reaching initial levels after 1 yr. This is in contrast to observations made at higher altitudes (4,650 – 5800 m), where the initial reduction in PV changed little throughout 33 wk (71).

Figure 1*B* illustrates the decrease in BV that arises from the reduction in PV (1, 20, 32, 46, 50, 55, 62, 70, 74, 77, 78, 83, 87, 89, 92, 105), which, as expected, is also more pronounced at higher altitude. In the majority of subjects BV was reduced for about 3 wk, where after it often normalized or even increased beyond initial levels. It should, however, be noted that the data points illustrating notable BV increases stem from very early studies (20, 62, 74, 89), some of which failed to detect a reduction in PV at HA (74, 89). Based on more recent data (70, 77–79, 83), we would expect BV to recover more slowly at HA than suggested by Fig. 1*B*.

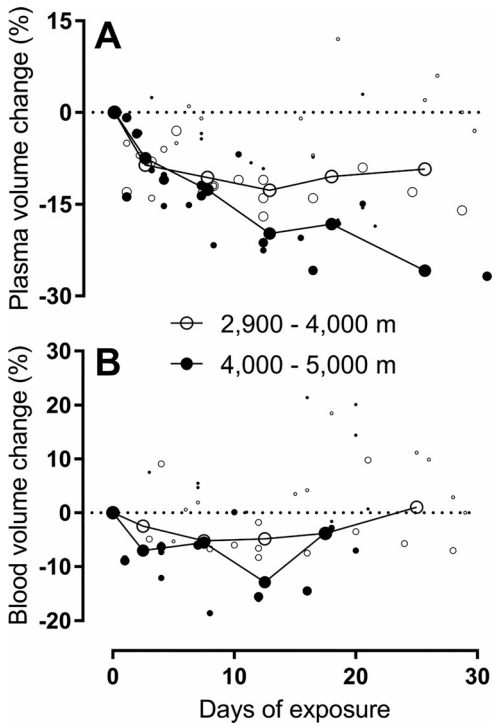

Fig. 1. Changes in plasma (*A*) and total blood volume (*B*) throughout exposure to different altitudes. *A*: data from 21 peer-reviewed articles (see text for references). All studies were conducted at fixed altitude except for the following: In 2 studies (32, 105), 1 night was spent at 1,950 m before ascent to the final altitude of 4,300 m. In another study ascent to the final altitude of 3,350 m took 4 days (89). Finally, in one study subjects were exposed to a progressive ascent to 6,000 m over the course of 16 days and we used a time-weighted average (5,000 m) to present that data point (77). *B*: data from 16 peer-reviewed articles (see text for references). All studies were conducted at fixed altitude with the same exceptions as in *A*. Small, middle-sized and large data points illustrate results collected in 1–3, 4–7, and 8–10 subjects, respectively. Points connected by straight lines represent the weighted average for the two altitude categories calculated over 1–5, 6–10, 11–15, 16–20, and 21–30 days, respectively. In *B*, no weighted average is presented for 21–30 days at 4,000–5,000 m due to the limited available data.

The minimal altitude inducing reductions in PV is unclear. Studies determining PV changes at altitudes <2,500 m usually include athletes, where variations in PV may reflect changes in training routine (31). One exception is a study exposing seven normal individuals for 10 days to 1,850 m, which did not reduce PV (94). Further insights can be obtained from variations in hematocrit and/or [Hb] as these may serve as markers for changes in PV throughout the first 4 days at HA, where RCV is unlikely to increase (see below). No changes in hematocrit or [Hb] were noted in 15 subjects exposed for 48 h to 1,700 m (103), whereas an increase was observed at 2,210 m (10). Keeping individual variability in mind, these observations support that an altitude of ~2,000 m represents the threshold above which reductions in PV occur if *1*) altitude is well tolerated (see *Mechanisms of the PV reduction*), *2*) exposure time is sufficient, and *3*) no significant increase in physical activity occurs.

Upon return from HA, PV recovers rapidly, reaching initial levels within the first week after descent from high (78, 83) or even extreme altitude (77).

Mechanisms of the PV reduction. Reductions in PV occur when body water loss exceeds intake and/or when intravascular

fluid is shifted to the extravascular compartment. Since total body water content (TBW) decreases in the first but not in the latter situation, TBW may serve as a marker to distinguish between these two pathways, although the PV loss at HA is usually <1 liter (see Fig. 1*A*), which constitutes only ~2% of TBW and may be hard to detect. During mountaineering and/or trekking expeditions, strenuous exercise, limited access to drinking water, or dietary restrictions as well as digestive disorders may lead to reductions in TBW so that the effect of hypoxia is difficult to isolate. At research stations that allow maintaining habitual fluid/food intake and physical activity, a decrease in TBW has in some (46, 55, 88, 101) but not in all cases (33, 57, 82, 102) been observed, suggesting that a mismatch between water uptake and water loss can occur as a result of hypoxia per se. Hypoxia may reduce voluntary water uptake by blunting the sensation of thirst as suggested by animal experiments (48). Reductions in voluntary water consumption in humans exposed to increasing simulated altitude, however, closely reflected reductions in water loss, arguing against blunted sensation of thirst (101). Water loss may somewhat increase at HA due to the higher respiratory fluid loss resulting from the dry air and the enhanced pulmonary ventilation at rest and particularly during exercise. Nevertheless, the main component of TBW loss at HA is increased diuresis (93, 109), which may be governed by several hormones: a variety of studies have reported a decrease in circulating aldosterone starting during the first hours of HA/hypoxic exposure (15, 60) and persisting throughout several days (42, 63, 83) or even weeks (83, 109), although the latter is not a universal finding (63, 78). This decrease in aldosterone may not only reflect reduced renin activity (42, 78, 83, 109) but also diminished availability of angiotensin-converting enzyme (63) or a direct effect of hypoxia on aldosterone secreting cells in the adrenal cortex (72). In fact, the effect of HA on renin is somewhat controversial, since renin activity has been reported to increase (66), decrease (60), or remain unchanged (15, 22) during the first hours exposure, whereas a reduction is common after more than 1 day (42, 78, 83, 109). The mechanisms reducing renin activity at HA are unclear but increased circulating erythropoietin likely contributes (67). Conversely, renin activity is presumably stimulated at HA by increased sympathetic activity, so that the net response may depend on the balance between the renin suppressing mechanism and sympathoactivation. Interestingly, the above-mentioned studies reporting increased or unchanged renin activity (15, 22, 66) were conducted at altitudes higher than those were renin activity decreased (42, 78, 83, 109), so that sympathoactivation was likely more pronounced. Unchanged or even increased renin activity might be characteristic for rapid ascent to severe HA and the associated development of acute mountain sickness, which often manifests in individuals who do not experience diuresis (57). Conversely, withdrawal of the renin-angiotensin-aldosterone axis presumably facilitates HA diuresis if sufficient time for acclimatization is provided. Atrial natriuretic peptide (ANP) has been observed to increase in acute hypoxia, supporting that it is involved in the regulation of diuresis (22, 97). This ANP response could be related to a direct effect of hypoxia on the heart as indicated by in vitro experiments (6). Alternatively, hypoxia-induced sympathoactivation (34) may augment central blood volume through constriction of peripheral capacitance vessels, which could increase cardiac preload and hence ANP release. This is supported by a close correlation between the hypoxia-induced increases in arterial pressure and circulating ANP (22). After more extended HA exposure (3–4 days), a reduction in circulating ANP below normal levels occurs that persists throughout week-long exposure (83, 109). Reduced ANP during extended HA exposure may reflect the diminished end-diastolic volume of the heart (91), which is likely a consequence of the reduced PV (84). Increased ANP may hence contribute to the rapid decrease in PV in the initial phase of HA exposure, whereas reduced ANP could, at least in part, explain why PV eventually plateaus despite persisting withdrawal of the renin-angiotensin-aldosterone axis. With regards to antidiuretic hormone (ADH), an increase (18, 57), a decrease (14, 57), or no change (14) has all been observed throughout the first hours of exposure to HA/hypoxia. The observations that ADH decreases during acute exposure to moderate but not severe hypoxia (14), as well as that a decrease occurs in subjects that tolerate hypoxia well, whereas subjects developing acute mountain sickness present with an increase (57), supports that ADH, similar to the renin-angiotensin-aldosterone axis, decreases and promotes diuresis only if the ascent to HA is not too rapid.

Intriguingly, the role of all these hormones has been somewhat challenged by a study that did not detect a correlation between the HA-induced hormonal and diuretic responses (93). Since the diuretic response, however, correlated with the sensitivity of the chemoreflex, the authors proposed that hypoxic chemoreflex activation may trigger diuresis either through a direct neuronal pathway to the kidneys or through an unknown diuretic factor. To make the story even more complicated, hypoxia-induced increases in pulmonary ventilation can induce diuresis in itself as well as by promoting hypocapnia, which enhances renal excretion of bicarbonate and hence fluid (41). In that study, 90 min of hypoxia increased urine flow by 229%, whereas isocapnic hyperpnea and isocapnic hypoxia increased urine flow by 86 and 129%, respectively. The difference between these two responses may reflect the isolated effect of hypoxemia, which would account for merely about one-fifth (43% out of 229%) of the increase in urine flow seen during poikilocapnic hypoxia.

As indicated earlier, and in contrast to the studies above, some investigators have observed maintained or even increased TBW at HA (33, 57, 82, 102). While in most cases this reflected acute mountain sickness-related fluid retention (33, 57, 102), Sawka et al. (82) observed a maintained TBW in individuals that tolerated HA well. In that study, PV decreased secondary to transvascular leakage of plasma proteins leading to oncotically driven redistribution of intravascular fluid into the extravascular compartment. An elevated capillary permeability for albumin has indeed been observed during early HA exposure (39), although this is not a universal finding (53). Increased vascular permeability could result from the systemic inflammatory response to hypoxia that may occur even in subjects that tolerate the exposure well (49, 52). Arguing against transvascular protein leakage as a mechanism for the reduction in PV at HA are studies, in which total circulating protein mass remained unchanged when the reduction in PV occurred, so that plasma protein concentration (36, 83) and oncotic pressure (36) increased. An explanation for the conflicting outcomes could be that the subjects in the study by Sawka et al. (82) participated in strenuous mountaineering

training. The physical exercise may have activated the renin-angiotensin-aldosterone and ADH systems (16), hence requiring the recruitment of an alternative mechanism to reduce PV.

Since reductions in physical activity can facilitate PV contraction, confinement to research facilities may contribute to the decrease in PV at HA. Nevertheless, this potential contribution is likely minor since a recent meta-analysis reported a similar or even more pronounced PV reduction than that presented in Fig. 1*A* in subjects who maintained physical activity at HA by exercise testing, walking and cycling (8).

Taken together, the mechanism facilitating the reduction in PV at HA seems multifactorial and may depend on water availability, altitude tolerance, physical activity, and potentially many other factors. It has to be emphasized, however, that our current understanding is almost exclusively based on correlative evidence and that mechanistic interventions to quantify the individual contributions of the proposed mechanisms are lacking.

Physiological consequences of the PV reduction. PV reduction constitutes a rapid mechanism to increase [Hb] and hence Ca_{O_2} at HA. We have recently observed that the ~10% decrease in Ca_{O_2} associated with exposure to 3,454 m was restored within only 3 days, which was to ~85% related to the reduction in PV (83). Even after 3 wk of exposure, where Sa_{O_2} was increased by ~4% and RCV had expanded by 4.5%, PV reduction still accounted for 55% of the increase Ca_{O_2} compared with acute exposure. The importance of PV reduction for HA tolerance is highlighted by the aforementioned correlation between fluid retention and acute mountain sickness (57).

Nevertheless, the reduction in PV might also have negative consequences. The resulting decrease in BV might attenuate blood flow to the skin and hence impair thermoregulatory capacity during exercise in hot conditions. Furthermore, the reduced BV contributes (although to a small extent) to the persistent activation of the sympathetic nervous system at HA (38), presumably by diminishing cardiac stroke volume and hence arterial baroreflex activation (84). The elevated sympathetic nervous tone could negatively affect exercise tolerance by increasing the contribution of anaerobic metabolism (107) and the perception of effort (80). Restoration of PV at HA by Dextran infusion indeed tended to increase stroke volume and decrease circulating norepinephrine during submaximal exercise, although these effects did not reach statistical significance (13). During maximal exercise at HA, the impact of the reduced PV is controversial since PV expansion improved performance in one (77) but not in another study (13). A further potentially adverse effect of the reduced PV (and, at some point, the larger RCV) could be an increase in blood viscosity and hence cardiac afterload (69). Nevertheless, this is not supported by the aforementioned study (13), where mean arterial pressure during exercise at HA was unaffected by hemodilution. Taken together, although the reduction in PV might theoretically have negative effects on exercise capacity, there is at present no solid evidence for this.

Expansion of RCV

A clear increase in RCV was detected almost a century ago in lowlanders residing for several weeks at 3,350 m (89), and the erythropoietic effect of HA exposure has subsequently been confirmed on numerous occasions. Nevertheless, controversy persists regarding the "dose" of HA required to robustly increase RCV. This controversy is fueled by some recent altitude training studies reporting increases in RCV or (depending on the measurement method) total hemoglobin mass (Hb_{mass}) considerably outweighing those in classical HA studies. Indeed, while a review of classical HA studies concluded that "studies of lowlanders acclimatizing for up to 3 wk at elevations below 4,000 m consistently fail to demonstrate altered erythrocyte volume" (81), a meta-analysis concluded that only 2 wk of altitude training (live high-train low or live high-train high), including exposure to altitudes of 2,500–3,000 m, "will quite likely increase Hb_{mass}" (29). A potential explanation for this controversy could be that rigorous endurance training enhances the erythropoietic effect of HA. Nevertheless, since the scope of this review is the effect of HA per se, studies involving concomitant endurance training are excluded unless otherwise noted.

Time course and magnitude of the RCV expansion. Studies determining changes in RCV and/or Hb_{mass} at HA usually include too few measurement points for a close assessment of their time course. To overcome this, we measured Hb_{mass} of nine normally trained lowlanders on every fourth day of a 4 wk sojourn at 3,454 m (83) and observed that expansion followed a sigmoidal shape, with a notable onset after 12 days and a plateau after 20–24 days. The delayed onset likely reflected the time required for the formation of new erythrocytes in response to the erythropoietic stimulus (104). The final increase in Hb_{mass} was 5.3 ± 3.0%, but individual results ranged from 2.5 to 11.1%, which should be kept in mind when applying these findings to a general population. Furthermore, since both the rate and magnitude of Hb_{mass} expansion depend on the severity of HA (73), observations made at 3,454 m are not representative for other altitudes. To obtain more generalizable results, we have conducted a meta-analysis of 66 papers reporting intravascular volume and/or Hb_{mass} changes at HA in a total of 447 subjects (73) (Fig. 2). In this meta-analysis we did not

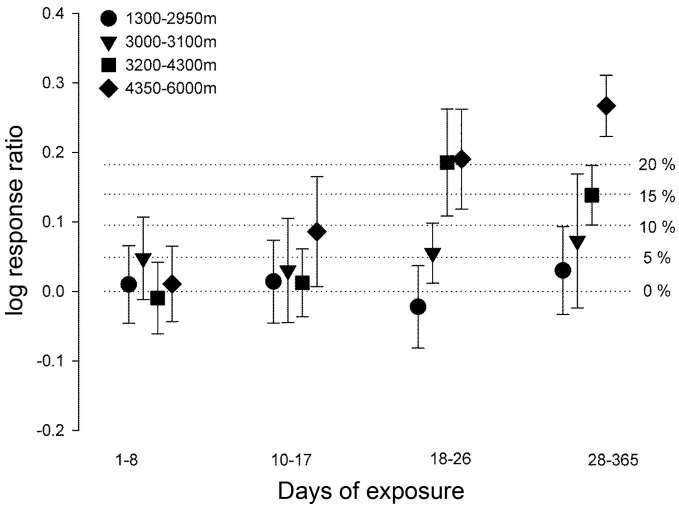

Fig. 2. Total red blood cell volume expansion throughout exposure to different altitudes. The figure is modified from Rasmussen and colleagues (73) and presents the data from 66 peer-reviewed articles with a total of 447 subjects. The data are distributed into altitude and exposure quartiles to yield a similar number of subjects in each data point. Data are weighted log-response ratios with error bars indicating 95% confidence intervals. Reference lines for a 0, 5, 10, 15, and 20% increase are given for simplicity.

observe a significant effect of concomitant exercise so that altitude training studies were included. The meta-analysis yielded that the average increase rate in RCV across all altitudes is ~50 ml/wk, which corresponds to the estimated maximal rate of erythropoiesis that recombinant erythropoietin treatment facilitates in healthy individuals (81). This average increase rate was associated with a tremendous standard deviation (±240 ml/wk), which could be explained as follows: first, it presumably reflects the interindividual variability in the erythropoietic response to HA. For instance, one included study reported an expansion of RCV throughout the first 18 days at 4,300 m that was approximately four times higher than the average rate (105), although the high measurement error in that study might have contributed to this extreme increase. Second, stratification by exposure time indicated that the expansion rate is slower over the first 10 days than over the first 28 days, which is line with the sigmoidal response curve mentioned above (83). Finally, categorization of the data according to the severity of HA illustrated that the expansion rate of RCV increases with the severity of HA (see Fig. 2). Indeed, in a recent study conducting repeated measurements of Hb_{mass} at 5,260 m (79), a much more rapid expansion than in our study at 3,454 m (83) was observed. Of note, the erythropoietic rate observed at 5,260 m (79) also exceeded that associated with erythropoietin treatment (81), which supports that other factors than erythropoietin might contribute to the erythropoietic response to HA (see below).

Evaluating the final magnitude of the increase in RCV requires that measurements are obtained after a plateau has been reached. Figure 2 supports that a plateau is reached within 4 wk of exposure to <4,300 m, whereas longer time may be required at higher altitudes. Indeed, studies conducted >4,500 m reported ongoing RCV expansion even after 160 days (71, 74). The reason for this maintained erythropoiesis at higher altitudes is unclear, since even at 5,260 m Ca_{O_2} surpassed SL values within 1 mo (38). Potentially, the more pronounced and persisting reduction in arterial P_{O_2} facilitate longer lasting erythropoiesis (see *Mechanisms of the RCV expansion*).

After descent from HA, RCV rapidly returns to initial values. For instance, the 5.3% increase in Hb_{mass} associated with 4 wk at 3,454 m reverted within 2 wk after descent (83), whereas the 7.6% increase that developed during 16 days at 5,260 m even reverted within 1 wk (79). Whether the more pronounced polycythemia that may occur during more extended exposure to severe HA persists longer is unknown.

Mechanisms of the RCV expansion. In comparison to the regulation of PV at HA, the mechanism underlying the expansion in RCV seems straightforward, at least at first sight. Upon ascent to HA, the reduced arterial oxygenation in combination with an unchanged (28) or even decreased (68) renal blood flow diminishes renal O_2 delivery. The consequent reduction in renal tissue P_{O_2} facilitates the stabilization of the hypoxia-inducible factor 2 system in peritubular cells, which triggers the release of erythropoietin (47). As a result, circulating erythropoietin starts to increase within the first 2 h of hypoxic exposure (54). The magnitude of the increase in erythropoietin seems to depend on the severity of hypoxia but is subject to massive interindividual variability (28). Although other organs, most importantly the liver, possess the ability to secret erythropoietin, the circulating erythropoietin at HA is predominantly of renal origin (58). Erythropoietin then accelerates erythropoietic activity in the bone marrow, resulting in higher circulating reticulocyte levels after 2–3 days (83). Circulating erythropoietin reaches a peak after ~4 days at HA, whereafter it returns to levels slightly above normal (9, 83). This response may reflect reductions in renal tissue P_{O_2}, which are presumably most pronounced throughout the first days at HA, i.e., before ventilatory acclimatization and, most importantly, the reduction in PV restore Ca_{O_2}. Why erythropoietin remains mildly elevated thereafter is not clear, but it indicates that the reduced Ca_{O_2} is not the only trigger for renal erythropoietin release. This is further illustrated by the finding that autologous blood transfusion attenuated the reduction in Ca_{O_2} but not the increase in erythropoietin resulting from ascent to 4,300 m (82). Ongoing renal erythropoietin release after restoration of Ca_{O_2} may reflect that renal P_{O_2} remains somewhat attenuated due to the persisting reduction in arterial P_{O_2} (12, 85, 105). Furthermore, the reduction in BV that arises from the decrease in PV (see Fig. 1*B*) may reduce central venous pressure in the upright body position, which can stimulate renal erythropoietin release independent of O_2 availability (64). Since the link between the increases in erythropoietin and RCV at HA is so obvious, potential other mechanisms have received little attention. However, HA exposure facilitates other autonomic and humoral responses that might accelerate erythropoiesis. Sympathetic activity is chronically increased at HA, even after restoration of Ca_{O_2} (38), and the elevated catecholamines levels (61) might activate erythropoietic progenitors in the bone marrow through β-adrenergic transmission (17). Nevertheless, the increase in RCV at 4,300 m was not attenuated by β-adrenergic antagonism (32), arguing against a significant contribution of this mechanism. Hypoxia may also lead to an increase in endogenous glucocorticoids (26) and upregulation of glucocorticoid receptors (56), which together could induce erythropoiesis (65). Other hormones that might increase at HA (although their responses vary greatly across studies) and facilitate erythropoiesis include insulin (108), growth hormone (5), and testosterone (43). Taken together, although the contributions of other factors to the erythropoiesis at HA are unclear, it may be an oversimplification to designate erythropoietin as the sole mechanism.

Sufficient iron stores are required to support accelerated erythropoiesis and heme synthesis. This is highlighted in anemic patients treated with recombinant erythropoietin, where adjunction of intravenous iron enhances the erythropoietic response (59). Accordingly, low iron stores could be a limiting factor for erythropoiesis at HA. This is supported by a retrospective analysis indicating that iron supplementation during moderate HA exposure may enhance Hb_{mass} production in athletes with low prealtitude iron stores (30). In contrast, other studies have shown that *1*) non-iron-supplemented women presenting with low initial ferritin levels increase Hb_{mass} at HA (79), and *2*) iron supplementation does not boost the Hb_{mass} response to moderate HA (27). Accordingly, further prospective and controlled studies are required for a full understanding of the contribution of iron availability on RCV expansion at HA.

Similarly to PV, RCV can decrease in response to reductions in physical activity so that confinement to research facilities might counteract the erythropoietic response to HA. Neverthe-

less, in our meta-analysis (73), the RCV response to HA was unchanged by exercise training arguing against a major effect of changes in physical activity on the RCV response described above.

The regulation of the return of RCV to initial levels after descent from HA is subject of debate. Active downregulation may occur through the selective destruction of newly formed erythrocytes in a process called neocytolysis (3). The trigger for neocytolysis could be suppression of circulating erythropoietin below normal levels, which may activate phagocytes to destroy newly formed erythrocytes (2). Furthermore, erythrocytes formed at HA seem to have a limited antioxidant capacity and may hence undergo apoptosis in the face of increased levels of reactive oxygen species upon return to SL (90). Whatever the mechanism, neocytolysis could explain why RCV decreases despite maintained circulating reticulocyte levels (75, 83). In one of these studies (83), the decrease in RCV was accompanied by a ~65% increase in venous carboxyhemoglobin, which supports accelerated lysis of red blood cells (25). Nevertheless, it should also be kept in mind that under homeostatic conditions ~1% of the erythrocytes are phagocytized and replaced every day (40). A decrease in RCV may hence be facilitated by a modest attenuation of the reticulocyte production rate that could be hard to detect in small subject groups.

Physiological consequences of the RCV expansion. Compared with the reduction in PV, the RCV expansion is of surprisingly little importance for the recovery of Ca_{O_2}, at least at altitudes up to 4,350 m, where full restoration of Ca_{O_2} occurs before expansion of RCV takes place (78, 83). Indeed, when RCV expansion at 3,454 m was prevented by repeated blood withdrawal, Ca_{O_2} still surpassed SL values after 3 wk of acclimatization (85). Finally, in another study at the same altitude, the ~5% expansion in Hb_{mass} resulting from 3 wk of acclimatization contributed merely 15% to the increase in Ca_{O_2} compared with acute exposure (83). Nevertheless, the larger increase in RCV that may occur with higher altitudes and/or longer exposure (Fig. 2) can obviously have a greater impact on Ca_{O_2}.

RCV is a main determinant of endurance performance at SL (45), where RCV expansion has an ergogenic effect (24). Accordingly, it might appear obvious that RCV expansion also improves endurance performance at HA. Surprisingly, however, autologous erythrocyte infusion had no effect on maximal O_2 uptake ($\dot{V}O_{2max}$) on the first or ninth day at 4,300 m (106). Similarly, reduction of RCV to SL values by isovolemic hemodilution did not affect $\dot{V}O_{2max}$ of acclimatized lowlanders at 5,260 m (12). Interestingly, RCV expansion induced by recombinant erythropoietin treatment enhanced $\dot{V}O_{2max}$ at altitudes $<$ 3,500 m but not at 4,500 m (76), supporting an ergogenic effect at moderate HA. During whole-body exercise in the severe hypoxia at higher altitudes, alveolar-capillary and capillary-muscular O_2 diffusion limitation (98), blood flow redistribution toward nonexercising tissues (11), and fatigue originating within the central nervous system (4) may counteract the ergogenic effect of an increased convective O_2 transport capacity.

A negative consequence can occur if excessive erythropoiesis increases [Hb] to levels exceeding 21 g/dl in men or 19 g/dl in women, leading to a condition termed chronic mountain sickness or Monge's disease (95). Since this condition is, however, only a concern for HA natives or individuals dwelling for several years at HA, it is beyond the scope of this review.

Interaction Between the Plasma and RCV Responses

Above, the PV reduction and RCV expansion were primarily discussed as isolated responses, although we have pointed out some potential interactions, namely that PV reduction may be involved in the control of renal erythropoietin release through its effects on Ca_{O_2} and central venous pressure, whereas erythropoietin may in turn contribute to the reduction in PV by suppressing renin activity. Further interactions are suggested by the critmeter theory, which holds that renal EPO production is finely regulated by tissue P_{O_2} in the juxtamedullary region of the cortical labyrinth (21, 23). This P_{O_2} can be modulated by either changes in renal O_2 consumption, fundamentally dependent on tubular sodium reabsorption, or changes in renal O_2 delivery (21, 23). At HA, renal O_2 delivery decreases due to the lower Ca_{O_2}. Concomitantly, the fluid regulating hormones mediating diuresis decrease tubular sodium reabsorption, which, based on the critmeter theory, should reduce renal O_2 consumption and thereby blunt the erythropoietin response that is triggered by the reduced Ca_{O_2}. It has also been hypothesized that reduced renal O_2 consumption induced by fluid regulating hormones explains the return of erythropoietin toward normal levels after a few days at HA (67). We, however, consider this unlikely since the changes in fluid regulating hormones occur during the first hours at HA (15, 22, 60), whereas erythropoietin continues to increase for several days (9). A further interaction that arises from the critmeter theory is that the reduction in PV decreases glomerular filtration rate and thereby the O_2 consuming tubular sodium reabsorption (21, 23). The lower renal $\dot{V}O_2$ would then augment the increase in renal tissue P_{O_2} that arises from the restoration of Ca_{O_2}. In that manner, the critmeter function may indeed contribute to the partial normalization of circulating erythropoietin. Taken together the proposed critmeter function of the kidneys is expected to blunt the initial increase in erythropoietin at HA and contribute to the reduction of erythropoietin toward normal levels after the reduction in PV has occurred.

Summary and Conclusions

Figure 3 summarizes the mechanisms that may contribute to intravascular volume changes at HA. It has to be emphasized that the isolated contributions of the different components are difficult to quantify and that undiscovered hormonal or neural pathways might be involved. In Fig. 4, the potential interactions between the mechanisms mediating PV reduction and RCV expansion at HA are summarized.

In conclusion, HA acclimatization facilitates a reduction in PV over the first 1–2 wk, which is usually sufficient to restore Ca_{O_2}. Studies investigating the mechanisms of this reduction in PV have provided variable and often controversial results, which could reflect the confounding influence of acute mountain sickness as well as of changes, in, e.g., food and fluid intake, physical activity, and temperature. It is hence recommended for future studies to elaborate on the effect of hypoxia per se on PV by replicating experimental conditions between

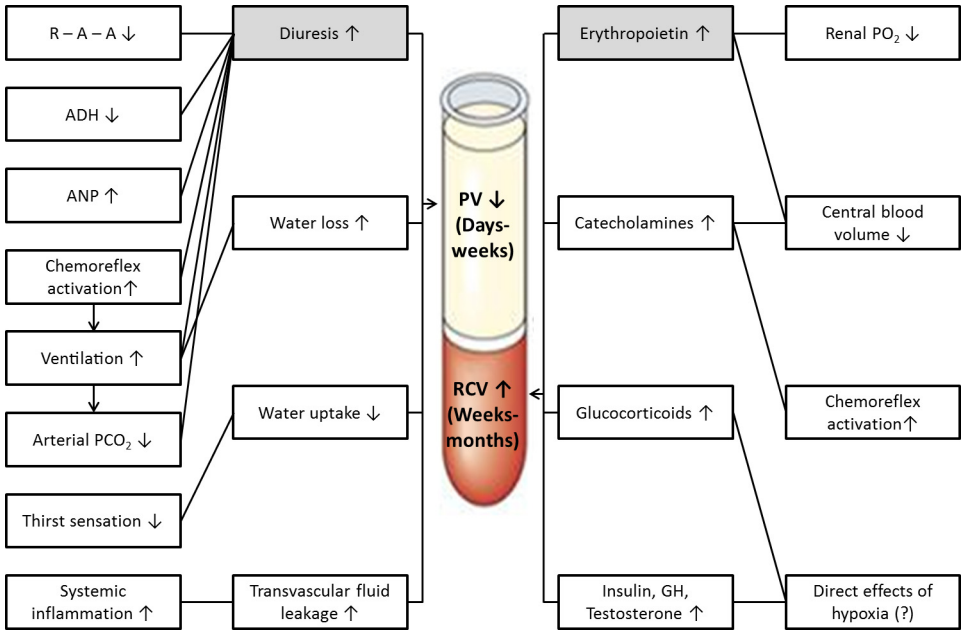

Fig. 3. Summary of intravascular volume changes at high altitude and potential underlying mechanisms. Note that the individual contributions of these mechanisms are unclear and that we cannot exclude the involvement of other mechanisms. Diuresis and erythropoietin are highlighted since we consider them the cardinal mechanisms underlying plasma volume contraction and total red blood cell volume expansion, respectively. "Direct effects of hypoxia (?)" is named as trigger for increases in glucocorticoids, insulin, growth hormone (GH), and testosterone for lack of a more specific explanation. PV, plasma volume; RCV, total red blood cell volume; R-A-A, renin-angiotensin-aldosterone axis; ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; P_{CO_2}, CO_2 tension; P_{O_2}, O_2 tension.

SL and HA as far as possible. Furthermore, experimental interventions that isolate the individual contributions of the proposed mechanisms are warranted. With more extended HA exposure, a progressive RCV expansion occurs, the final magnitude and hence impact on Ca_{O_2} of which depend on the severity of HA and the acclimatization time. Why this RCV expansion occurs despite the early restoration of Ca_{O_2} remains to be conclusively answered, but it could reflect that the persistent reduction in arterial P_{O_2} translates into a blunted renal tissue P_{O_2}. Alternatively, and as illustrated in Fig. 3, mechanisms unrelated to renal oxygenation may increase renal erythropoietin formation and/or erythropoietic activity at HA. Apart from elaborating on these mechanisms, future studies should also investigate the determinants of the intraindividual variability in the erythropoietic response to HA.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

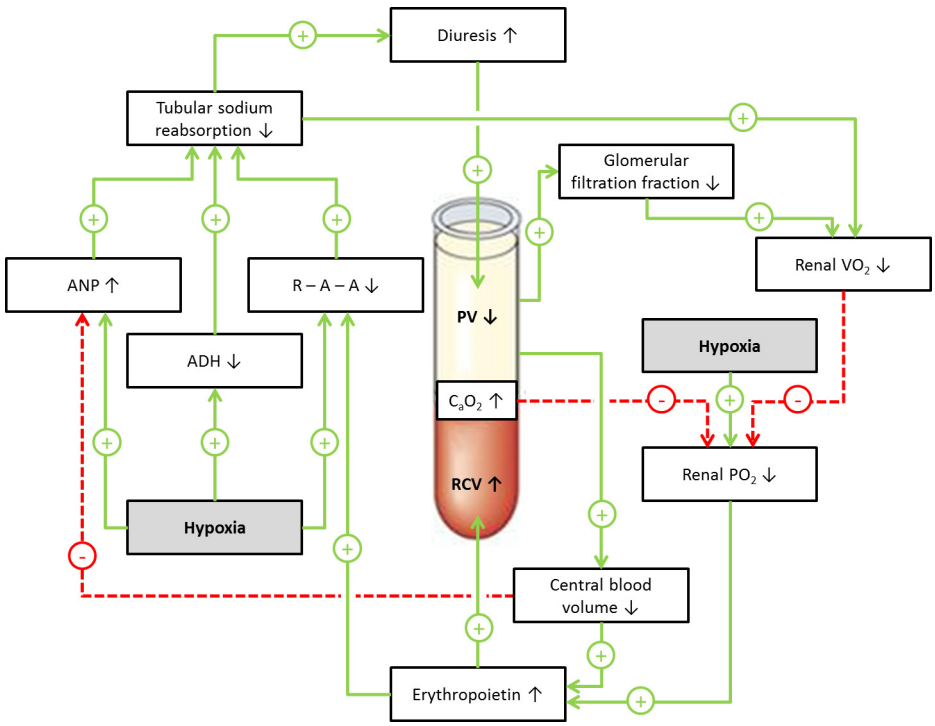

Fig. 4. Possible interactions between the plasma and total red blood cell volume responses to high altitude. Grey boxes should be used as starting points to read the figure. Green arrows marked with a plus symbol indicate that the response in the next box is promoted, whereas red arrows with a minus symbol indicate that the response in the next box is counteracted. PV, plasma volume; RCV, total red blood cell volume; Ca_{O_2}, arterial O_2 content; ANP, atrial natriuretic peptide; ADH, antidiuretic hormone; R-A-A, renin-angiotensin-aldosterone axis; $\dot{V}O_2$, oxygen uptake; P_{O_2}, O_2 tension.

AUTHOR CONTRIBUTIONS

C.S. prepared figures; C.S. drafted manuscript; C.S., P.R., and C.L. edited and revised manuscript; C.S., P.R., and C.L. approved final version of manuscript.

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