Blood volume: importance and adaptations to exercise training, environmental stresses, and trauma/sickness

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ABSTRACT

SAWKA, M. N., V. A. CONVERTINO, E. R. EICHNER, S. M. SCHNIEDER, and A. J. YOUNG. Blood volume: importance and adaptations to exercise training, environmental stresses, and trauma/sickness. *Med. Sci. Sports Exerc.,* Vol. 32, No. 2, pp. 332–348, 2000. This paper reviews the influence of several perturbations (physical exercise, heat stress, terrestrial altitude, microgravity, and trauma/sickness) on adaptations of blood volume (BV), erythrocyte volume (EV), and plasma volume (PV). Exercise training can induce BV expansion: PV expansion usually occurs immediately, but EV expansion takes weeks. EV and PV expansion contribute to aerobic power improvements associated with exercise training. Repeated heat exposure induces PV expansion but does not alter EV. PV expansion does not improve thermoregulation, but EV expansion improves thermoregulation during exercise in the heat. Dehydration decreases PV (and increases plasma tonicity) which elevates heat strain and reduces exercise performance. High altitude exposure causes rapid (hours) plasma loss. During initial weeks at altitude, EV is unaffected, but a gradual expansion occurs with extended acclimatization. BV adjustments contribute, but are not key, to altitude acclimatization. Microgravity decreases PV and EV which contribute to orthostatic intolerance and decreased exercise capacity in astronauts. PV decreases may result from lower set points for total body water and central venous pressure, while EV decreases may result from increased erythrocyte destruction. Trauma, renal disease, and chronic diseases cause anemia from hemorrhage and immune activation which suppresses erythropoiesis. The re-establishment of EV is associated with healing, improved life quality, and exercise capabilities for these injured/sick persons. **Key Words:** ERYTHROCYTE VOLUME, PHYSICAL EXERCISE, HEAT STRESS, HYPOXIA, MICROGRAVITY, PLASMA VOLUME, SPACE, VASCULAR VOLUMES

Blood volume changes are often credited as being important adaptations to the perturbations imposed by physical exercise, environmental stressors, trauma, and certain sicknesses. The relative contributions of plasma volume and erythrocyte volume for adaptations to these perturbations have not been systematically reviewed, despite many recent advances. Blood volume represents the sum of erythrocyte volume and plasma volume. Erythrocyte volume and plasma volume can change independent of each other to alter blood volume. Physical exercise, environmental stresses, and trauma/illness can influence each of these vascular volumes. Erythrocyte volume expansion usually occurs slowly over many weeks to months, whereas plasma volume expansion can occur rapidly over several hours to days (131). A principle factor regulating erythrocyte production is the hormone erythropoietin (EPO) (101). Reduced tissue oxygen tension (renal and hepatic) is a primary factor stimulating EPO synthesis; however, other factors such as central venous pressure, growth hormone stimulation, and nutrition may contribute (131). Plasma volume is regulated by the extracellular fluid (ECF) volume, as well as by changes in total circulating protein and pre- to postcapillary resistance ratios (131).

The purpose of this review is to examine critically the influence of several perturbations (physical exercise, environmental (heat, terrestrial altitude, and microgravity) stress, and trauma/sickness on blood volume. In addition, the relative importance of changes in erythrocyte volume and plasma volume on minimizing the adverse effects of these perturbations will be examined.
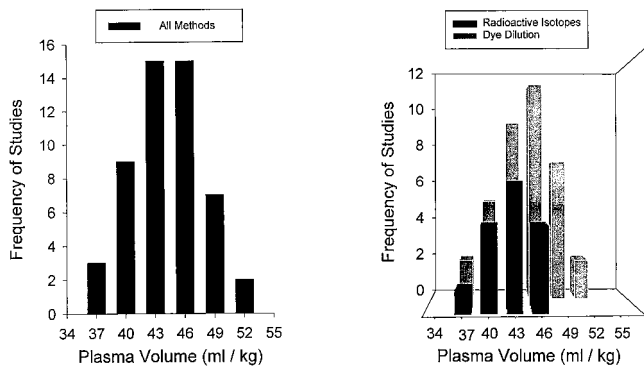
METHODOLOGY

Figure 1 presents the frequency distribution of the mean plasma volume values from studies reported in the literature (*left*) and the influence of measurement methodology (*right*) (131). Note that although considerable overlap occurs between the methodologies, dye dilution tends to yield higher mean values. Direct comparisons between methodologies of Evans blue and radioactive isotope labeled albumin demonstrate similar (5,62,92,161) values. It is unclear whether studies that reported the high plasma volumes with dye

Report Documentation Page

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1. REPORT DATE **01 FEB 2000**	2. REPORT TYPE **N/A**	3. DATES COVERED **-**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Blood volume: importance and adaptations to exercise training, environmental stresses, and trauma/sickness	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
Sawka, M. N. Convertino, V. A. Eichner, E. R. Schnieder, S. M. Young, A. J.	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234**	8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT **SAR**	18. NUMBER OF PAGES **17**	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**			

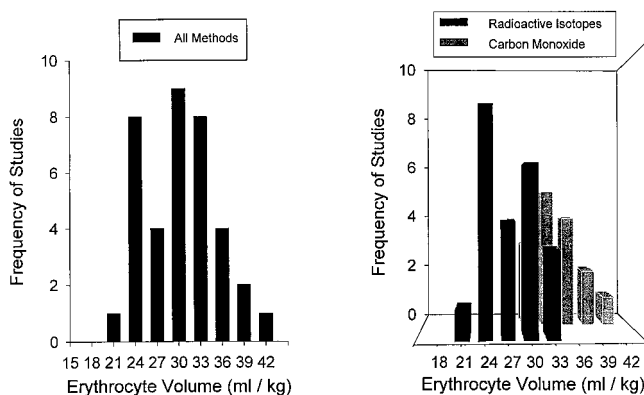**Standard Form 298 (Rev. 8-98)**
Prescribed by ANSI Std Z39-18

Figure 1—Frequency distribution of mean plasma volumes per kilogram body weight from 55 studies, overall distribution (*left*) and influence of methodology (*right*) (131). Reference 131. Sawka, M. N. and E. F. Coyle. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. In: *Exercise and Sport Sciences Reviews*, J. O. Hollozsy (Ed.). Baltimore, MD: Williams & Wilkins, 1999, pp. 167–218.

dilution methods represented subject populations with large vascular volumes or whether methodological problems, such as uncorrected loss of dye from plasma,existed.

Figure 2 presents the frequency distribution of mean erythrocyte volume values from studies reported in the literature (*left*) and the influence of methodology (*right*) (131). Note that radioactive isotope methods and carbon monoxide methods demonstrate two distinct distributions with the latter methods yielding substantially higher values. For erythrocyte volume measurement, radioactive isotope methodologies are the "gold standard" because they are less likely to leave the erythrocyte (78).

The erythrocyte volume method employed should be given great consideration when evaluating the effects of aerobic training and environmental stresses, all of which can increase the volume of distribution of various dilutant indicators beyond the vascular volume (145,146). If the extravascular volume of distribution increases with training or environmental stress, then the pre- to postchanges will overestimate the increase in vascular volume. For example,

Figure 2—Frequency distribution of mean erythrocyte volumes per kilogram body weight from 40 studies, overall distribution (*left*) and influence of methodology (*right*) (131). Reference 131. Sawka, M. N. and E. F. Coyle. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. In: *Exercise and Sport Sciences Reviews*, J. O. Hollozsy (Ed.). Baltimore, MD: Williams & Wilkins, 1999, pp. 167–218.
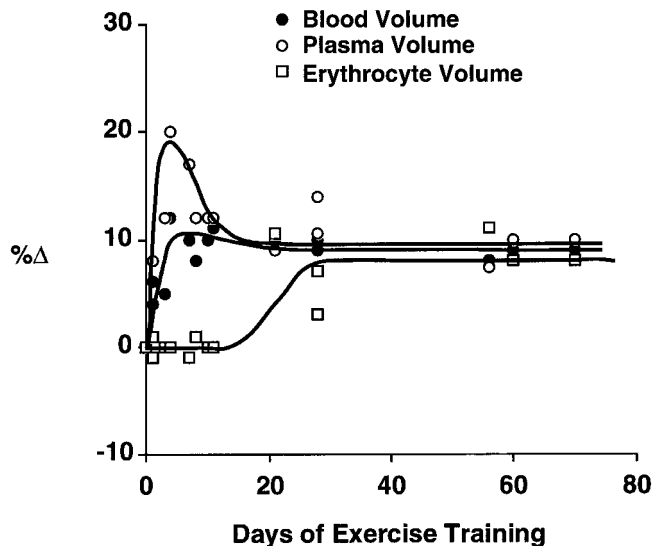
Figure 3—Estimated time course of relative (%) changes in blood volume (●; *middle line*), plasma volume (○; *upper line*) and erythrocyte volume (□; *bottom line*). Each point represents the average change reported in a group of subjects from one investigation. Data were extracted from 18 investigations in which all three vascular volumes were reported.

because of simplicity, scientists often estimate erythrocyte volume by the carbon monoxide rebreathing method. The volume of distribution for carbon monoxide is to all iron-porphyrin molecules, including those in skeletal muscle, heart muscle, and liver. As a result this indicator can over-estimate erythrocyte volume (92). The magnitude of this overestimation could be affected by aerobic training and hypoxia or any other condition that increases extravascular concentrations of molecules (such as myoglobin and muscle cytochrome oxidase) that bind with carbon monoxide (131).

PHYSICAL TRAINING AND AEROBIC PERFORMANCE

Effects of physical training. Early cross-sectional comparisons between endurance-trained and sedentary male and female subjects revealed that blood volume was higher in trained individuals compared with untrained individuals. This relationship was independent of body size and existed similarly in both males and females (85). Further comparisons demonstrated that larger blood volume in athletes was contributed by higher plasma volume and erythrocyte volume (13).

Twenty-three longitudinal investigations (30 subject groups) were identified that demonstrated a blood volume expansion with endurance exercise training (2,18,23,25,45, 51,55,57,58,63,71,83,98,102,116,122,123,126–128,148,156, 157). In one-half of those investigations, both plasma volume and erythrocyte volume were increased. To our knowledge, no investigation has provided a systematic examination of the time course of vascular volume alterations with exercise training. Figure 3 provides results from analyses where all three vascular volumes ($N = 18$ studies) were reported. These results might provide the average response of the three vascular volumes over time.

The plot of blood volume changes over time with exercise training demonstrating that the relative change (%Δ) in plasma volume can increase within 24 h following exercise and achieve ~10% above pretraining by 1 to 4 d. In the early stage (initial 2 wk of training), nearly all blood volume expansion can be accounted for by plasma volume expansion. After ~2–3 wk of exercise training, erythrocyte volume expansion is observed and increases, at an undetermined rate, until all vascular volumes achieve ~8–10% above the pretraining baseline. As a result of this new equilibrium between plasma and erythrocyte volumes, hematocrit (Hct) is re-established at its pretraining value.

The percent increase in blood volume appears similar when comparing elderly subjects (18), younger subjects (157), or female subjects to male subjects (2,45,71,102) following endurance exercise training programs. Thus, results support the notion that the typical response to endurance exercise training is an increase in blood volume independent of age and gender.

Some investigators have measured alterations in Hct to estimate changes in plasma and blood volume with exercise training (127,128,154). The time course depicted in Figure 3 suggests that this approach may be acceptable if applied during the initial 2 wk of training when there is no measurable change in erythrocyte volume. However, estimation of plasma volume expansion based on change in Hct after 2 wk of training can grossly underestimate training-induced hypervolemia, since the relative magnitude of erythrocyte expansion can eventually approach that of the plasma volume expansion.

As discussed, various labeling techniques are used to estimate the vascular volumes during exercise training studies. About 80% of investigations reviewed used carbon monoxide or dye dilution to measure the vascular volumes. Cross-sectional comparisons of average blood volumes in untrained and endurance-trained subjects with carbon monoxide labeling (76 ± 4 and 97 ± 3 mL·kg^{-1}, respectively) across investigations (13,31,85,153) are consistently and significantly greater than with those measured and compared across investigations (30,72,80,100,153,158) with Evans blue dye (67 ± 3 and 87 ± 2 mL·kg^{-1}, respectively). As discussed, the greater values with carbon monoxide might be an increased extravascular volume of distribution. The relative increase in blood volume, however, appears relatively consistent across investigations when using carbon monoxide or dye dilution (28% vs 30%, respectively). Caution should be employed when comparing absolute blood volumes between groups or investigations that used different labeling techniques to estimate blood volume.

Absence of blood volume expansion. The absence of blood volume expansion during endurance exercise training has been reported in 10 longitudinal investigations and presents confusion to the understanding of exercise training effects on vascular volumes. In three of these investigations (7,52,125) maximal aerobic power ($\dot{V}O_{2max}$) before and after training and the intensity of training were not reported. The investigators suggested that perhaps there was 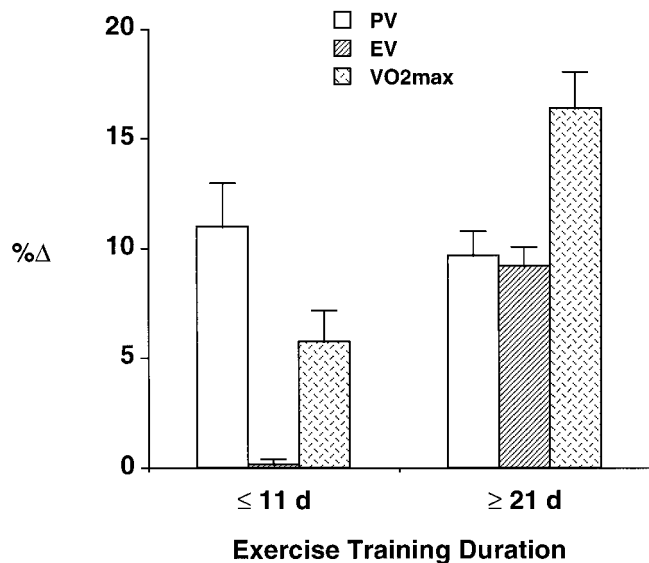not a training effect (i.e., increased $\dot{V}O_{2max}$) because of the initially high fitness state of the subjects or an inadequate training intensity. These possibilities seem reasonable explanations for the lack of hypervolemia since elevation of hormones associated with ECF and thus plasma expansion requires greater work intensities in trained subjects (27). Another study (96) on well-trained runners found that training did not alter $\dot{V}O_{2max}$ or blood.

In another study (156), a negligible 2% blood volume expansion in the exercise training group was significantly greater than a 6% reduction in blood volume in the control group, suggesting that blood volume was increased with exercise training. In a recent investigation (12), blood volume was increased in a group of subjects who underwent cycle ergometer exercise training but not in a group who trained on a treadmill at the same frequency, duration, and intensity, suggesting that exercise mode may influence blood volume adaptation to exercise training. This is an intriguing finding in light of the fact that 17 of 24 longitudinal studies that report blood volume expansion with exercise training have employed cycle ergometer exercise. Conversely, those investigators (12a) subsequently found that blood volume did not increase despite large (~20%) increases in $\dot{V}O_{2max}$ after low and high intensity training on a cycle ergometer.

The absence of blood volume expansion after 56 d of endurance exercise training has been cited (121) from investigations in which subjects trained in the supine posture (123) and water (171). Such results can be misleading since maintenance of blood volume in a relatively gravity neutral posture represents an 18% greater vascular volume when compared with a control group of subjects who remain in the supine posture without exercise (64). Therefore, the absence of blood volume expansion during exercise training may partially be explained by factors such as initial fitness level, training intensity, exercise mode and posture, and control group responses. With consideration of these factors, two investigation has been identified without any clear explanation of the absence of blood volume expansion with exercise training (12a,121). Since at least 23 of 32 investigations have demonstrated significant blood volume expansion with exercise training, it seems reasonable to contend that exercise training elicits a blood volume expansion.

Effects on aerobic performance. Blood volume adaptations represent only one of several physiological mechanisms that might underlie the increase in $\dot{V}O_{2max}$ associated with exercise training. However, controversy exists regarding the magnitude of contribution of blood volume on

TABLE 1. Correlations coefficients (r) for linear regressions between total blood volume and maximal oxygen uptake.

Investigation	Sample Size	r
Mack et al. (100)	11	0.92*
Convertino (22)	97	0.78*
Sawka et al. (146)	51	0.52*
Stevenson et al. (158)	30	0.79*
Davy & Seals (30)	14	0.73*
Jones et al. (80)	52	0.65*

* $P < 0.05$.

Figure 4—Relative changes (%Δ) in total blood volume (BV, *open bars*), erythrocyte volume (EV, *lined bars*), and maximal oxygen uptake ($\dot{V}O_{2max}$, *hashed bars*) following endurance exercise training of durations less than 11 d (= 11 d) and greater than 21 d (= 21 d). Bars with lines represent the mean ± SE of average data from investigations cited in references.

$\dot{V}O_{2max}$. Although the conclusion from one investigation indicated that $\dot{V}O_{2max}$ is generally not related to vascular volumes (145), Table 1 indicates that all six investigations that examined blood volume and $\dot{V}O_{2max}$ relationships have reported significant ($P < 0.05$) positive correlation coefficients (22,30,80,100,145,158). However, it is unclear whether hypervolemia is a prerequisite for aerobic power improvements since $\dot{V}O_{2max}$ increases after endurance exercise training have been reported without significant alterations in blood volume (12,121,156,171).

Possible interactions between blood volume and $\dot{V}O_{2max}$ may be explained by determining alterations in these physiological parameters with differences in duration of exercise training. Figure 4 demonstrates that responses of blood volume and $\dot{V}O_{2max}$ to exercise training can be divided into exercise training durations ≤ 11 d (25,55,57,63,83,102) and > 21 d (2,18,23,45,116,123,148,157). An average ($N = 7$ study group) plasma volume expansion of 11% with no change in erythrocyte volume was related to only a 6% $\dot{V}O_{2max}$ increase when exercise training was < 11 d in duration. But when exercise training was > 21 d, average ($N = 11$ study group) plasma volume expansion of 10% and erythrocyte volume expansion of 9% were related to a 16% $\dot{V}O_{2max}$ increase. This analysis suggests a greater $\dot{V}O_{2max}$ increase with exercise training duration of > 3 wk is associated with increased erythrocyte volume, i.e., oxygen carrying capacity and is further supported by a correlation of +0.73 between percent change in erythrocyte volume and percent change $\dot{V}O_{2max}$ across all 16 study groups. Erythrocyte volume expansion will consistently increase $\dot{V}O_{2max}$ (144), and a strong relationship between oxygen carrying capacity and $\dot{V}O_{2max}$ has been reported (31). Therefore, although numerous mechanisms underlie improved maximal systemic delivery and muscle utilization of oxygen,

there is compelling evidence that plasma and erythrocyte volume expansions during exercise training contribute to $\dot{V}O_{2max}$.

Dill et al. (31) demonstrated two curves that described a relationship between oxygen carrying capacity and $\dot{V}O_{2max}$, one at a lower range of $\dot{V}O_{2max}$ for active subjects and the other at a higher range of $\dot{V}O_{2max}$ for endurance-trained runners. Differences in hemoglobin (Hb)-$\dot{V}O_{2max}$ relationships between highly trained and active individuals support the notion that mechanisms that adapted to exercise training, other than oxygen carrying capacity, contributed to a higher $\dot{V}O_{2max}$. The hearts of endurance-trained athletes have been reported to be more compliant compared with nontrained individuals (95), a condition that could greatly enhance maximal cardiac filling and output. It is possible that a more compliant heart could cause increased cardiac filling and output independent of expanded blood volume following exercise training. If the increase in maximal cardiac output and $\dot{V}O_{2max}$ was associated with increased cardiac compliance independent of exercise training-induced hypervolemia, then acute expansion of plasma volume without erythrocytes should have no impact on $\dot{V}O_{2max}$. Contrary to this notion, acute plasma volume expansion following detraining in subjects above the blood volume in their trained state restored approximately 50% of their training state $\dot{V}O_{2max}$ (28). This observation reinforces that blood volume contributes to the increase in $\dot{V}O_{2max}$.

In summary, blood volume increases over time with exercise training. Plasma volume expansion can occur within 24 h and during the first 2 wk accounts for nearly all of the blood volume expansion. After approximately 2–3 wk of exercise training, erythrocyte volume expansion is observed and increases at an undetermined rate until both erythrocyte and plasma volume achieve a new steady state, often 8–10% above pretraining baseline. Blood volume adaptations represent one of several physiological mechanisms that underlie the increase in $\dot{V}O_{2max}$ associated with exercise training.

HEAT ACCLIMATION AND THERMOREGULATION

Heat acclimation. Heat acclimation is elicited through repeated heat exposures that are sufficiently stressful to elevate both core and skin temperatures and which elicit perfuse sweating (142). Erythrocyte volume does not appear to be altered by heat acclimation (7,26,44) or season (36). Plasma volume expansion is usually (8,113,151,152) but not always (7,32,73,171) present after repeated heat exposure and heat acclimation. Figure 5 provides seasonal changes in resting plasma volume (36). Note that resting plasma volume expanded by ∼5% in the hottest months and contracted by ∼3% in the coldest months. These investigators noted considerable variability and found that some people did not demonstrate a plasma volume expansion. Heat acclimation studies report that plasma volume expansion generally ranged from 0% to 30%, and the magnitude of increase is somewhat dependent on whether the person is at rest or performing exercise, their heat acclimation state, the day,
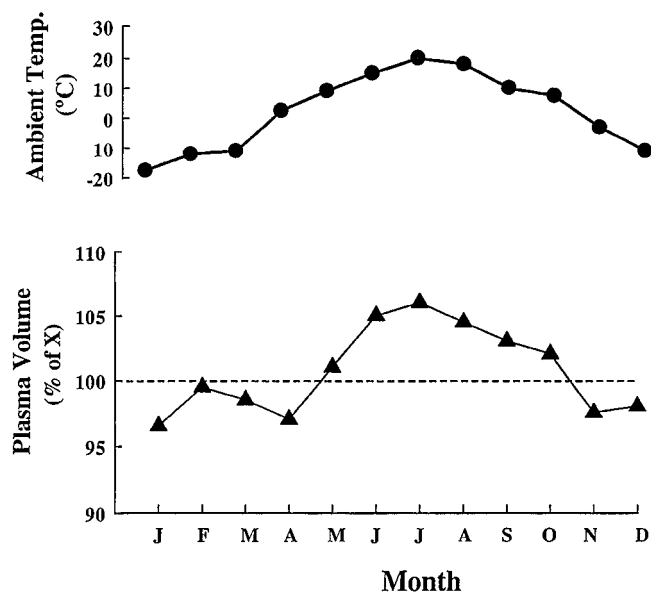
Figure 5—Seasonal changes in resting plasma volume (36) as redrawn from (131). References: 36. Doupe, J., M. H. Ferguson, and J. A. Hildes. Seasonal fluctuations in blood volume. *Can. J. Biochem. Physiol.* 35:203–213, 1957; 131. Sawka, M. N. and E. F. Coyle. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. In: *Exercise and Sport Sciences Reviews*, J. O. Hollozsy (Ed.). Baltimore, MD: Williams & Wilkins, 1999, pp. 167–218.

and their hydration level when measurements are made (131). Plasma volume expansion seems to be greatest when performing upright exercise on about the fifth day of heat acclimation and when fully hydrated.

Plasma volume expansion. To determine the role of plasma volume expansion on thermoregulation, scientists have acutely expanded these volumes before heat and/or exercise stress and then examined the subsequent effects on body temperature and exercise performance. These investigations employed subjects who were not heat acclimated and expanded plasma volume by an amount and method similar to that believed to occur from heat acclimation and aerobic training.

Some investigators (43,90,91,136) expanded plasma volume before performing aerobic exercise in the heat. Subjects were infused with either saline (control) or human albumin and saline solution (43,136) or hyperhydrated by drinking water/glycerol solutions (90,91) and subsequently exercised in the heat. Albumin infusion expanded plasma volume by ~13% above control levels. In comparison with control, plasma volume expansion elicited similar core temperature, skin temperature, sweating responses, and systolic blood pressure. Despite generally having lower heart rates (43,136), exercise tolerance time was not altered by plasma volume expansion relative to control (136). Water/glycerol hyperhydration can slightly (~5%) increase plasma volume (48,90) but elicits similar core temperature, skin temperature, and sweating responses in comparison with control (90,91).

Other investigators (54,56) expanded plasma volume before performing aerobic exercise in temperate conditions.

One study (56) examined the effects of training-induced plasma volume expansion on physiologic responses during aerobic exercise in temperate conditions. Subjects completed this experiment before and after 3 d of exercise training. Exercise training induced a 20% plasma volume expansion that did not alter core temperature responses despite lower heart rate and higher stroke volume and cardiac output. Another study (54) examined the effects of dextran-expanded plasma volume on physiologic responses during aerobic exercise in temperate conditions. Control conditions were compared with 14% and 21% plasma volume expansion before exercise. Core temperature was not different between treatments and heat storage appeared to be identical. Heart rate was lower and stroke volume and cardiac output were higher after plasma volume expansion, with no differences between the 14% and 21% expansion trials.

Erythrocyte volume expansion. Erythrocyte infusion has been employed to study the effects of erythrocyte volume expansion on thermoregulation during exercise in the heat. Several investigators (117,132) had unacclimated subjects perform aerobic exercise in the heat both before (control) and after being infused with ~300–400 mL of erythrocytes. Erythrocyte volume expansion reduced heat storage, core temperature, and skin blood flow, and improved sweating responses (117,134,135). In addition, blunted heart rate (117,132) and plasma cortisol (47) responses were observed.

Since heat acclimation provides a substantial thermoregulatory advantage (142), the importance of small thermoregulatory advantages conferred by erythrocyte volume expansion may be of questionable value. It could be argued that heat acclimation would provide a greater thermoregulatory advantage and might obviate any thermoregulatory advantages from erythrocyte volume expansion. One study (134) examined whether acute erythrocyte volume expansion would provide any thermoregulatory advantage to heat acclimated subjects exercising in the heat and whether hypohydration (decreased total body water) would illuminate an unrecognized disadvantage. Before and after (2–4 d) being infused with ~300 mL of erythrocytes, heat acclimated subjects performed aerobic exercise in the heat, once while euhydrated and, on a separate day, while hypohydrated by 5% of their body weight. Erythrocyte (~10%) and plasma volumes both expanded, resulting in a greater blood volume when euhydrated (8%) and hypohydrated (7%) compared with control trials. Erythrocyte volume expansion provided a substantial thermoregulatory advantage regardless of hydration status. It was concluded that erythrocyte volume expansion provides a greater thermoregulatory advantage for heat acclimated than unacclimated persons, and these advantages are greater when additional perturbations, such as hypohydration, are present.

Hypohydration. Hypohydration from sweat induced loss of body water will decrease plasma volume and increase plasma osmotic pressure in proportion to the decrease in total body water. Resting plasma volume decreases in a linear manner that is proportionate to the hypohydration

level in heat acclimated persons (139). Resting plasma osmolality increases in a linear manner from about 283 mosmol·kg^{-1} when euhydrated by more than 30 mosmol·kg^{-1} when hypohydrated by 15% of total body water (139). Plasma volume decreases because it provides the fluid for sweat, and osmolality increases because sweat is ordinarily hypotonic relative to plasma. Sodium and chloride are primarily responsible for the elevated plasma osmolality (89,150). The plasma hyperosmolality mobilizes fluid from the intracellular to the extracellular space to enable plasma volume defense in hypohydrated subjects (147). This concept is demonstrated by the observation that heat acclimated persons have a smaller plasma volume reduction for a given body water deficit than unacclimated persons (74,130). By virtue of having a more dilute sweat, heat acclimated persons have additional solutes remaining within the extracellular space to exert an osmotic pressure and redistribute fluid from the intracellular space (99).

Hypohydration increases core temperature responses during exercise in temperate (15,53,138) and hot (106,141,143) climates. As the magnitude of water deficit increases, there is a concomitant graded elevation of core temperature when one exercises in the heat (104,143). The magnitude of core temperature elevation ranges from 0.1° to 0.23°C for every percent body weight lost (1,104,143,160). The core temperature elevation from hypohydration is greater during exercise in hot than temperate climates (29). When hypohydrated, the elevated core temperature responses could result from either an increase of metabolic heat production or a decrease in heat loss.

Almost all studies of hypohydration do not find an increased metabolic rate during submaximal exercise (140) Therefore, reduced heat dissipation is responsible for hypohydration-mediated core temperature elevations during exercise. The relative contributions of evaporative and dry heat loss during exercise depends upon the specific environmental conditions, but both avenues of heat loss are adversely affected by hypohydration. Local sweating (43,105,134) and local skin blood flow (82,109) responses are both reduced for a given core temperature when hypohydrated. In addition, whole-body sweating rate is usually either reduced or unchanged during exercise at a given metabolic rate in the heat (133). However, even when hypohydration is associated with no change in whole-body sweating rate, core temperature is usually elevated so that whole-body sweating rate for a given core temperature is lower when hypohydrated (133).

Both the singular and combined effects of plasma hyperosmolality and hypovolemia have been suggested as mediating the reduced heat loss response during exercise-heat stress (130). Investigators report relationships for plasma hyperosmolality and plasma hypovolemia with adverse thermoregulatory responses during exercise in temperate and hot climates; however, stronger relationships are usually found with plasma hyperosmolality (29,130). Plasma hyperosmolality, with no change in blood volume, can increase core temperature by reducing heat loss during rest (34,94) or exercise (46,61,69,111,114,118) in the heat. In addition,

re-establishment of blood volume, while still being hyperosmotic, does not alter the core temperature elevation compared with responses when dehydrated during prolonged exercise in the heat (103).

Blood volume reductions with no change in osmolality can increase core temperature and impair heat loss during exercise in the heat (21,42,43,108). Studies (43,108) have demonstrated that isotonic hypohydration reduces skin blood flow for a given core temperature and therefore reduces the potential for dry heat exchange. Fortney et al. (43) have provided a rationale as to why an iso-osmotic hypohydration might reduce skin blood flow and sweating rate. They theorized that hypovolemia might reduce cardiac preload and alter the activity of atrial baroreceptors which have afferent input to the hypothalamus. Therefore, a reduced atrial filling pressure might modify neural information to the hypothalamic thermoregulatory centers which control skin blood flow and sweating.

In summary, plasma volume expansion can occur with repeated heat exposure. The magnitude of expansion varies greatly and is influenced by many factors, including the duration of heat exposure, activity level, and hydration. Acute plasma volume expansion provides no clear thermoregulatory benefits but reduces cardiovascular strain during exercise in the heat. Heat acclimation does not alter erythrocyte volume; however, erythrocyte volume expansion improves thermoregulation and performance during exercise in the heat. Hypohydration decreases plasma volume and osmolality which contributes to increased thermal and cardiovascular strain.

ALTITUDE ACCLIMATIZATION AND AEROBIC PERFORMANCE

When people living near sea level ascend higher, atmospheric oxygen pressure declines and reduced O$_2$ diffusion from the alveolus to blood causes a fall in arterial O$_2$ pressure (P$_a$O$_2$), O$_2$ saturation of Hb (S$_a$O$_2$), and arterial O$_2$ content (C$_a$O$_2$) (66). As a result, $\dot{V}O_{2max}$ declines with ascent (49), and during steady-state submaximal exercise, a higher cardiac output ($\dot{Q}$) is necessary at altitude than sea level to achieve O$_2$ delivery requirements for a given intensity (172). The reduction in $\dot{V}O_{2max}$ and increased cardiovascular strain associated with elevated $\dot{Q}$ during submaximal exercise are two key mechanisms degrading aerobic exercise in unacclimatized lowlanders on arrival at high altitude. Physiological changes enabling performance to recover in lowlanders remaining at high altitude include blood volume adjustments.

Blood volume adjustments during altitude acclimatization. Lifelong high-altitude residents have larger blood volumes than sea-level residents, primarily because of a large erythrocyte volume (129,165), an observation that has led to a widespread belief that altitude exposure induces a similar adaptation in acclimatizing lowlanders. Hb concentration clearly increases in lowlanders sojourning at altitude (172). However, the extent to which this represents

TABLE 2. Plasma volume changes (Δ PV) observed by different investigators in longitudinal studies of lowlanders acclimatizing at high altitude.

Elevation, m	Days	Study	Δ PV, %	Method		
				^{125}I ALB	Dye	EST
<3000 m	8	Greenleaf (59)	NC	X		
	21	Dill (31)	−7			X
<4000 m	4	Jung (81)	−14			X
	10	Alexander (3)	−13		X	
	12	Jain (79)	−17	X		
	14	Dill (33)	−20			X
	21	Myhre (107)	−13			X
<5000 m	6	Hutado (76)	+1		X	
	8	Surks (161)	−14		X	
	9	Sawka (146)	−9	X		
	15	Hannon (60)	−20		X	
	18	Wolfel (168)	−22			X
	65	Hannon (67)	−24		X	
<6000 m	18	Stokke (159)	NC	X		
	126	Pugh (120)	−29			X

Studies are grouped in 1000-m intervals according to increasing elevation, and, within each 1000 m group, are rank ordered by exposure duration. Investigators employed different methods of quantifying the percentage plasma volume change as indicated: labeled (^{125}I) albumin dilution (^{125}I ALB); indicator dye (e.g., Evans blue, brilliant red) dilution (DYE); indirect estimates of change based on coincident changes in hematocrit and hemoglobin and indices of erythrocyte volume (EST). NC, no change.

References: 59. Greenleaf, J. E., E. M. Bernauer, W. C. Adams, and L. Juhos. Fluid-electrolyte shifts and $\dot{V}O_{2max}$ in man at simulated altitude (2,287 m). *J. Appl. Physiol.* 44:652–658, 1978; 31. Dill, D. B., K. Braithwaite, W. C. Adams, and E. M. Bernauer. Blood volume of middle-distance runners: effects of 2,300-m altitude and comparison with nonathletes. *Med. Sci. Sports Exerc.* 6:1–7, 1974; 81. Jung, R. C., D. B. Dill, R. Horton, and S. M. Horvath. Effects of age on plasma aldosterone levels and hemoconcentration at altitude. *J. Appl. Physiol.* 31:593–597, 1971; 3. Alexander, J. K., L. H. Hartley, M. Modelski, and R. F. Grover. Reduction of stroke volume during exercise in man following ascent to 3100 m altitude. *J. Appl. Physiol.* 23:849–858, 1967; 79. Jain, S. C., J. Bardhan, Y. V. Swamy, B. Krishna, and H. S. Nayar. Body fluid components in humans during acute high-altitude exposure. *Aviat. Space Environ. Med.* 51:234–236, 1980; 33. Dill, D. B., S. M. Horvath, T. E. Dahms, R. E. Parker, and J. R. Lynch. Hemoconcentration at altitude. *J. Appl. Physiol.* 27:514–518, 1969; 107. Myhre, L. G., D. B. Dill, and D. K. Brown. Blood volume changes during three-week residence at high altitude. *Clin. Chem.* 16:7–14, 1970; 76. Hurtado, A., C. Merino, and J. Delima. Influence of anoxemia on the homopoietic activity. *Arch. Intern. Med.* 53:284–323, 1945; 161. Surks, M. I., K. S. K. Chinn, and L. O. Matoush. Alterations in body composition in man after acute exposure to high altitude. *J. Appl. Physiol.* 21:1741–1746, 1966; 146. Sawka, M. N., A. J. Young, P. B. Rock, et al. Altitude acclimatization and blood volume: effects of exogenous erythrocyte volume expansion. *J. Appl. Physiol.* 81:636–642, 1996; 60. Greenleaf, J. E., J. S. Bosco, and M. Matter. Orthostatic tolerance in dehydrated, heat-acclimated men following exercise in the heat. *Aerospace Med.* 45:491–497, 1974; 168. Wolfel, E. E., B. M. Groves, G. A. Brooks, et al. Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J. Appl. Physiol.* 70:1129–1136, 1991; 67. Hannon, J. P., J. L. Shields, and C. W. Harris. Effects of altitude acclimatization on blood composition of women. *J. Appl. Physiol.* 26:540–547, 1969; 159. Stokke, K. T., K. Rootwelt, R. Wergeland, and J. R. Vale. Changes in plasma and red cell volumes during exposure to high altitude. *Scand. J. Clin. Lab. Invest.* 46:113–117, 1986; 120. Pugh, L. G. C. E. Blood volume and haemoglobin concentration at altitudes above 18,000 ft. (5500 m). *J. Physiol.* 170:344–354, 1964.

erythrocyte volume expansion as opposed to hemoconcentration remains contentious.

Table 2 summarizes observations made using different methods of measuring plasma volume changes in lowlanders acclimatizing for varying time at different altitudes. Regardless of methodology, there is nearly complete agreement that lowlanders experience a hemoconcentration during altitude acclimatization. Also, two trends are apparent. First, the most pronounced plasma volume reductions have been in studies with the longest duration altitude sojourn. Second, plasma volume reductions tend to be larger at higher than lower elevations.

The relationship between hemoconcentration and altitude is more clearly illustrated in Figure 6 where mean plasma volume reductions observed in the fifteen separate studies (3,31,33,59,60,67,76,79,81,107,120,146,159,161,168) listed in Table 2 are plotted as a function of the elevation at which the subjects were sojourning. While all these studies involved sojourns of varying duration, collectively, the results suggest that the magnitude of hemoconcentration relates to the magnitude of hypoxic stress, i.e., elevation. In only one study (159) do findings not fit that pattern, and in that study the subjects ascended slowly over 18–20 d, whereas in the others ascent was rapid.

The mechanisms for plasma volume reduction during altitude acclimatization remain unresolved. Dehydration from drinking insufficient fluid to offset urinary, respiratory, and transcutaneous fluid losses, which all increase with hypoxia, may contribute (75). However, preventing dehydration does not prevent the plasma volume reduction in lowlanders at altitude (146). Recently, the magnitude of plasma volume reduction in acclimatizing lowlanders was shown to be closely related to the amount of circulating protein concomitantly lost from the plasma (146). This suggests an oncotically mediated hemoconcentration, but how the proteins are leaving the vascular space is unclear. The rapidity of hemoconcentration and declining plasma protein during the first week after arriving at altitude probably rules out increased degradation or decreased synthesis rates (85). An increased capillary permeability to proteins reportedly develops in lowlanders newly arrived at altitude (65,97), but others observe no capillary permeability changes in altitude sojourners (112).

Table 3 suggests less agreement regarding altitude acclimatization effects on erythrocyte volume. Studies of lowlanders acclimatizing for up to 3 wk at elevations below 4,000 m consistently fail to demonstrate altered erythrocyte volume, regardless of methodology (3,31,33,59,79,81,107). Studies of lowlanders acclimatizing at altitudes above 4000 m find discrepant effects with increases (6,76,159,168), decreases (161), and no changes (65,146) all being reported, and even acclimatization studies by the same laboratory report inconsistent findings (65,168). These discrepancies may have arisen because altitude exposure confounds some methods used to assess erythrocyte volume changes (146). The only acclimatization study that measured erythrocyte volume by a method not likely to be confounded by altitude exposure (146) observed no change.
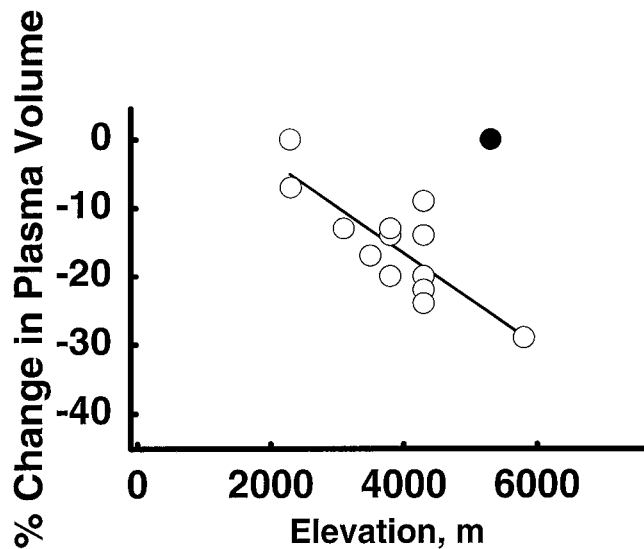
Figure 6—Plasma volume reductions in lowlanders acclimatizing at different altitudes. Data obtained from fifteen separate studies by different investigators (3,31,59,60,67,68,79,81,107,120,146,159,161,168). References: 3. Alexander, J. K., L. H. Hartley, M. Modelski, and R. F. Grover. Reduction of stroke volume during exercise in man following ascent to 3100 m altitude. *J. Appl. Physiol.* 23:849–858, 1967; 31. Dill, D. B., K. Braithwaite, W. C. Adams, and E. M. Bernauer. Blood volume of middle-distance runners: effects of 2,300-m altitude and comparison with nonathletes. *Med. Sci. Sports Exerc.* 6:1–7, 1974; 59. Greenleaf, J. E., E. M. Bernauer, W. C. Adams, and L. Juhos. Fluid-electrolyte shifts and $\dot{V}O_{2max}$ in man at simualted altitude (2,287 m). *J. Appl. Physiol.* 44:652–658, 1978; 60. Greenleaf, J. E., J. S. Bosco, and M. Matter. Orthostatic tolerance in dehydrated, heat-acclimated men following exercise in the heat. *Aerospace Med.* 45:491–497, 1974; 67. Hannon, J. P., J. L. Shields, and C. W. Harris. Effects of altitude acclimatization on blood composition of women. *J. Appl. Physiol.* 26:540–547, 1969; 68. Hansen, J. M., N. Vidiendal, B. Feldt-Rasmussen, et al. Albuminuria and overall capillary permeability of albumin in acute hypoxia. *J. Appl. Physiol.* 76:1922–1927, 1994;

Given that the erythropoietic response observed in some altitude acclimatization studies may, to some degree, reflect methodological artifact, the magnitude and time course of the erythrocyte volume expansion reported should be viewed cautiously. For example, aerobic exercise training causes erythrocyte volume to expand, but only at rates 6 to 20 times less (125,171) than that reported for altitude acclimatization (76,120,159,168). Dose-response studies of erythropoietin administration to healthy humans indicate that the maximal erythropoietin-stimulated rate of erythrocyte volume expansion was 50 mL·wk^{-1} (11), which, again, is much less than reported in any of the altitude acclimatization studies (76,120,159,168). It seems unlikely that altitude acclimatization stimulates a faster expansion of erythrocyte volume than the maximal expansion rate produced by erythropoietin administration because the increase in circulating erythropoietin in sojourning lowlanders is short-lived, peaking after about a day at altitude and then returning to normal sea level values within a few days (146).

Pugh et al. (120) reported what appears to be the largest erythrocyte volume expansion observed in an altitude acclimatization study. In this case, however, the reported expansion of erythrocyte volume was not unreasonable. The subjects of that investigation sojourned higher (over 5000 m)

for much longer (over 4 months) than subjects of the other studies, and the erythrocyte volume expansion rate observed in that study is actually very close to the estimated maximal expansion rate (11). Therefore, an expansion of erythrocyte volume probably does develop during long sojourns at altitude, especially at very high elevation.

Physical activity might also modulate the erythrocyte volume expansion during altitude acclimatization. The subjects for the investigations listed in Table 2 were physically fit and active to varying degrees, but they were not elite athletes engaged in aerobic training. Recently, Levine and Stray-Gundersen (96) reported that elite distance runners living for 4 wk at moderately high altitude (2500 m) and training hard there or at a somewhat lower elevation (1250 m) exhibited a modest expansion of erythrocyte volume averaging about 35 mL·wk^{-1}, while subjects training similarly at sea level exhibited no change. Subsequent research (19) demonstrated that about 50% of a group of competitive distance runners studied were "nonresponders" who failed to exhibit the increase in erythropoietin and erythrocyte volume expansion demonstrated by "responders" under the same altitude and training conditions. The mechanisms underlying the large variability in responsiveness could not be discerned, although the investigators speculated that genetically inherited factors might modulate hypoxic hypoxic ventilatory drive, Hb P_{50}, or erythropoietin responsiveness to hypoxia. If genetic factors do influence erythropoietin responses to altitude and training, then the incidence of responders among competitive distance runners may actually be much higher than that in the general population.

Thus, blood volume adjustments during altitude acclimatization have two phases. In the early phase, plasma volume decreases, beginning within hours after arrival at high altitude, while erythrocyte volume remains stable. As a result, Hb concentration increases and blood volume decreases. This early phase of blood volume adjustment persists for at least 3–4 wk. If altitude exposure continues for several months, then erythrocyte volume expands. Development of the second phase may be accelerated in some lowlanders who sustain an intense aerobic training program while at high altitude.

Blood volume adjustments and aerobic performance at altitude. As lowlanders acclimatize to altitude, aerobic exercise performance quickly begins to improve (49). A variety of cardiovascular, respiratory, metabolic, hematologic, and neuroendocrine changes (66,169,172) developing with acclimatization contribute to this improvement, but, among those, blood volume adjustments have been considered central. It is commonly thought that the elevation of Hb concentration (from plasma loss) is the most important factor contributing to the performance improvement by facilitating O_2 transport and delivery to metabolically active tissues.

Hemoconcentration does increase the blood's O_2 carrying capacity, but that only accounts for part of the increase in arterial oxygen content (C_aO_2) with altitude acclimatization. Altitude acclimatization also causes increased pulmonary ventilation, raised alveolar ventilation, and consequently

TABLE 3. Erythrocyte volume changes (Δ EV) observed by different investigators in longitudinal studies of lowlanders acclimatizing at high altitude.

Elevation, m	Days	Study	Δ EV, %	Method 51Cr	Method CO	Method EST
<3000 m	8	Greenleaf (59)	NC			X
	21	Dill (31)	NC		X	
<4000 m	4	Jung (81)	NC		X	
	10	Alexander (3)	NC			X
	12	Jain (79)	NC			X
	14	Dill (33)	NC		X	
	21	Myhre (107)	NC		X	
<5000 m	6	Hutado (76)	+22 (+719 mL·wk⁻¹)			X
	8	Surks (161)	−22			X
	9	Sawka (146)	NC	X		
	18	Wolfel (168)	+20 (+185 mL·wk⁻¹)		X	
	20	Grover (65)	NC		X	
<6000 m	18	Stokke (159)	+28 (+250 mL·wk⁻¹)			X
	126	Pugh (120)	+47 (+62 mL·wk⁻¹)			X

Studies are grouped in 1000-m intervals according to increasing elevation and, within each 1000-m group, are rank ordered by exposure duration. Investigators employed different methods of quantifying the percentage erythrocyte volume change as indicated: labeled (^{51}Cr) erythrocyte dilution (^{51}Cr), carbon monoxide uptake (CO), indirect estimates of erythrocyte volume change based on coincident changes in hematocrit and measurements or estimates of plasma volume (EST). For studies reporting significant erythrocyte volume expansion, the rate of erythropoiesis is provided parenthetically (ml erythrocytes/week). NC, no change.

References: 59. Greenleaf, J. E., E. M. Bernauer, W. C. Adams, and L. Juhos. Fluid-electrolyte shifts and $\dot{V}O_{2max}$ in man at simulated altitude (2,287 m). *J. Appl. Physiol.* 44:652−658, 1978; 31. Dill, D. B., K. Braithwaite, W. C. Adams, and E. M. Bernauer. Blood volume of middle-distance runners: effects of 2,300-m altitude and comparison with nonathletes. *Med. Sci. Sports Exerc.* 6:1−7, 1974; 81. Jung, R. C., D. B. Dill, R. Horton, and S. M. Horvath. Effects of age on plasma aldosteronelevels and hemoconcentration at altitude. *J. Appl. Physiol.* 31:593−597, 1971; 3. Alexander, J. K., L. H. Hartley, M. Modelski, and R. F. Grover. Reduction of stroke volume during exercise in man following ascent to 3100 m altitude. *J. Appl. Physiol.* 23:849−858, 1967; 79. Jain, S. C., J. Bardhan, Y. V. Swamy, B. Krishna, and H. S. Nayar. Body fluid components in humans during acute high-altitude exposure. *Aviat. Space Environ. Med.* 51:234−236, 1980; 33. Dill, D. B., S. M. Horvath, T. E. Dahms, R. E. Parker, and J. R. Lynch. Hemoconcentration at altitude. *J. Appl. Physiol.* 27:514−518, 1969; 107. Myhre, L. G., D. B. Dill, and D. K. Brown. Blood volume changes during three-week residence at high altitude. *Clin. Chem.* 16:7−14, 1970; 76. Hurtado, A., C. Merino, and J. Delima. Influence of anoxemia on the homopoietic activity. *Arch. Intern. Med.* 53:284−323, 1945; 161. Surks, M. I., K. S. K. Chinn, and L. O. Matoush. Alterations in body composition in man after acute exposure to high altitude. *J. Appl. Physiol.* 21:1741−1746, 1966; 146. Sawka, M. N., A. J. Young, P. B. Rock, et al. Altitude acclimatization and blood volume: effects of exogenous erythrocyte volume expansion. *J. Appl. Physiol.* 81:636−642, 1996; 168. Wolfel, E. E., B. M. Groves, G. A. Brooks, et al. Oxygen transport during steady-state submaximal exercise in chronic hypoxia. *J. Appl. Physiol.* 70:1129−1136, 1991; 65. Grover, R. F., M. A. Selland, R. G. McCullough, et al. Beta-adrenergic blockade does not prevent polycythemia or decrease in plasma volume in men at 4300 m altitude. *Eur. J. Appl. Physiol.* 77:264−270, 1997; 159. Stokke, K. T., K. Rootwelt, R. Wergeland, and J. R. Vale. Changes in plasma and red cell volumes during exposure to high altitude. *Scand. J. Clin. Lab. Invest.* 46:113−117, 1986; 120. Pugh, L. G. C. E. Blood volume and haemoglobin concentration at altitudes above 18,000 ft. (5500 m). *J. Physiol.* 170:344−354, 1964.
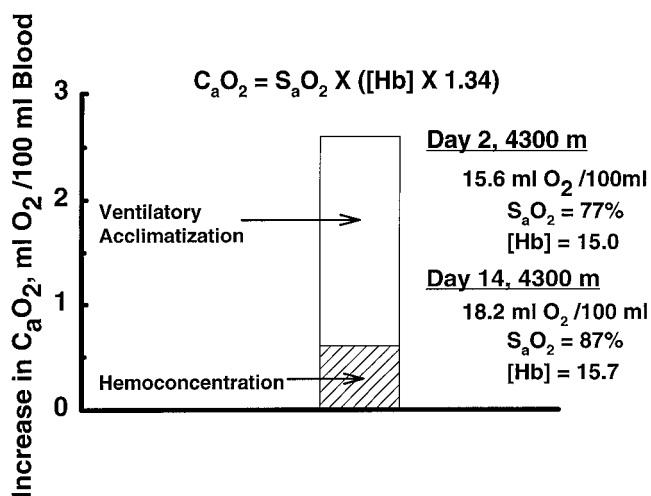

Figure 7—The increase in C_aO_2 during altitude acclimatization because of the increase in Hb compared with that accounted for by increased pulmonary ventilation (ventilatory acclimatization). Drawn from data reported by Hannon and Vogel (67).Reference 67. Hannon, J. P., J. L. Shields, and C. W. Harris. Effects of altitude acclimatization on blood composition of women. *J. Appl. Physiol.* 26:540−547, 1969.

alveolar oxygen partial pressure (P_aO_2), saturation (S_aO_2) and C_aO_2. As illustrated in Figure 7, hemoconcentration and hyperventilation both contribute to the increased C_aO_2. How much each factor contributes to the increase in C_aO_2 will vary according to the elevation, exposure duration, and individual variation, all of which modulate the hemoconcentration and ventilatory adjustments during acclimation.

The point is that the increase in Hb is not the sole factor and in some cases may not be the most significant acclimatization factor acting to increase C_aO_2.

A common misconception regarding the improvement in aerobic exercise performance with altitude acclimatization is that it results from the amelioration of peripheral oxygen delivery limitations that develop on arrival at high altitude. Even though increasing Hb concentration contributes to the increase in C_aO_2 that develops with altitude acclimatization, an enhanced O_2 transport and subsequent alleviation of muscle hypoxia does not appear to be the primary factor acting to improve exercise performance with acclimatization. If this were the case, then the increased Hb concentration and C_aO_2 should produce an increase in both $\dot{V}O_{2max}$ and steady-state $\dot{V}O_2$ during submaximal exercise. However, despite increasing Hb and C_aO_2 with acclimatization, the decrement in $\dot{V}O_{2max}$ does not abate because a decline in maximal cardiac output during acclimatization prevents an increased total systemic oxygen transport during maximal exercise (172). Similarly, artificially increasing Hb concentration by blood "doping" before ascent does not prevent the decline in $\dot{V}O_{2max}$ at high altitude, probably because the doping has no effect on P_aO_2 (170). Steady-state oxygen uptake during a given intensity of submaximal exercise at high altitude remains the same after acclimatization as on arrival, despite the increased Hb and C_aO_2 that develop, because a concomitant decrease in $\dot{Q}$ during submaximal exercise precludes any increase in oxygen delivery to active muscle (10,172). Thus, improvements in aerobic exercise
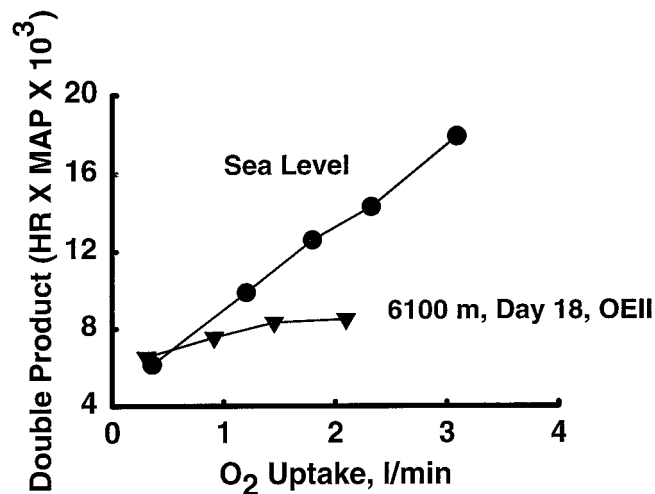
Figure 8—The double product (heart rate times MAP), which can be used as an index of cardiac work, during exercise before and after altitude acclimatization. Drawn from Operation Everest II data reported by Reeves et al. (124) and Sutton et al. (162).

performance with acclimatization do not seem attributable to increased blood oxygen transport and delivery.

Since blood volume adjustments resulting from altitude acclimatization do not contribute to improvements in aerobic exercise performance by increasing blood O_2 carrying capacity and alleviating peripheral hypoxia, what possible role might these adjustments play? One possibility is that the ergogenic effects of the blood volume adjustments occurring with altitude acclimatization are attributable to hemodynamic effects of the adjustments. The $\dot{Q}$ sustained during steady-state submaximal aerobic exercise at high altitude decreases with acclimatization as compared with that on arrival; the increased Hb and C_aO_2 permit oxygen uptake to be achieved with a lower $\dot{Q}$ (172). As shown in Figure 8, cardiac work during exercise, quantified as the product of heart rate and mean arterial pressure (MAP), is decreased by altitude acclimatization, and it may be that the lower $\dot{Q}$ during steady-state submaximal exercise accounts for the reduced cardiac work, thereby improving exercise tolerance.

In summary, the key blood volume adjustment occurring during the first few weeks at high altitude is a loss of plasma volume which increases Hb concentration and decreases blood volume. The rapid improvement in aerobic exercise tolerance during these first few weeks at high altitude is probably attributable as much to the hemodynamic effects of the blood volume adjustments and reduced cardiac work during exercise as to any effects of increased O_2 carrying capacity resulting from higher Hb concentration. With altitude sojourns lasting several months, possibly earlier in persons engaged in heavy physical training, an expansion of erythrocyte volume develops, and this adjustment probably accounts for any ergogenic effects persisting upon return to lower elevations.

SPACEFLIGHT/MICROGRAVITY

Spaceflight offers a unique opportunity to challenge our basic concepts about blood volume and body fluid regula-

tion. Some of the earliest observations during spaceflight were that, with insertion into microgravity, fluid is displaced from the lower to upper body resulting in bird-like legs and puffy faces (20). With this cephalad displacement of fluid, water and electrolytes are excreted resulting in a new, lower level of body fluid regulation. While these fluid shifts and the ensuing hypovolemia during spaceflight are well documented, the mechanisms responsible for these changes are unexpected. Reductions in plasma volume and erythrocyte volume following even short duration space flights are presumed to contribute to the orthostatic intolerance and decreased exercise capacity observed in astronauts after return to earth.

Recent observations of the central volume shifts and plasma volume changes during spaceflight. With the removal of gravity and the headward fluid shifts associated with spaceflight, one would expect an increase in central blood volume and central venous pressure (CVP). Therefore, it was surprising when the first CVP estimations from catheters placed in the arm suggested that CVP decreases rather than increases during spaceflight (84). These early findings were received with skepticism because of possible complications from the peripheral venous sampling sites. However, recent direct CVP measurements with both fluid filled (14) and nonfluid filled (41) catheters placed in the superior vena cava near the right atria in four astronauts confirm a sudden sustained drop in CVP when they enter microgravity.

White et al. (166) suggested that a mechanical effect can explain this drop in CVP upon insertion in microgravity: the removal of solid tissue pressures from around the heart. In a 1-g environment, compressive forces are exerted on the heart because of the weight of the chest wall and of the surrounding tissues and organs which exert a downward force on the chest cavity. Sudden removal of these compressive forces may result in a relaxation of the chest with a concomitant increase in chest cavity volume, leading to a decrease in intrapleural pressure. In addition, there is evidence that cardiac compliance can increase independent of alterations in intrapleural pressure (86), perhaps as a result of less compression forces exerted on the heart by redistribution from the base to the apex of the lung. The net effect of this would be equivalent to a sudden increase in cardiac transmural filling pressure which would enhance venous return. These responses might explain why despite the reduced CVP, the echocardiographic measurements from these astronauts revealed increases in cardiac volumes and cardiac output with no change in cardiac contractility (14).

Along with the reduction in CVP during spaceflight, Leach et al. (93) found unexpected changes in fluid-regulating hormones. With an increase in central blood volume, one would expect a decrease in antidiuretic hormone (ADH) and an increase in atrial natriuetic peptide (ANP). Instead, during the first few hours of spaceflight, ADH increased while ANP decreased. These hormonal changes are consistent with the reduction rather than increase in CVP.

These CVP and hormonal results raise another question, however; why does plasma volume decrease during the first

hours of flight? During the first and second U.S. Space Life Science Missions (SLS-1 and SLS-2) there was a pronounced plasma volume decrease (17%) within the first 22 h of flight which remained about 10% below preflight levels for the remainder of the flight (93). One explanation could be changes in the action of volume receptors (baroreceptors, osmoreceptors) and the effector systems (kidneys, hypothalamic thirst center) which results in a new set point for body fluid balance. Natochin et al. (110) proposed a resetting of the renal response to ADH, aldosterone, urodilatin, or ANP after spaceflight and bed rest. These authors observed a dissociation between blood ADH levels and plasma osmolality inflight, osmolality was decreased or normal, while ADH concentration remained elevated above preflight values. After 370 d of bed rest there was a smaller increase in urine osmolality after ADH administration. Similarly, a lower setpoint for CVP has been hypothesized based on the observation that urine outputs during saline loading in ambulatory subjects were not altered by exposure to head-down tilt bead rest and that bed rest caused a shift to the left of the stimulus response relationship between CVP and forearm vascular resistance (24). A decreased renal sensitivity to ADH or aldosterone, and/or reduced CVP operational point may result in greater free water clearance thus inducing a new, lower level of body fluid balance during spaceflight.

Effect of microgravity on total body water. Another surprising finding from the SLS-1 and SLS-2 data (93) was the insignificant change in total body water after 8 d ($N = 6$) and 12 ($N = 3$) of spaceflight. Since the ECF volume was significantly reduced in these subjects, it was concluded that preservation of the total body water must have occurred by an expansion of the intracellular fluid (ICF).

Scientists have wondered whether cell volumes are sensitive to changes in gravity. A similar question has been addressed to explain the decrease in ICF during water immersion. Krasney (88) has suggested that this cellular response may be do to pressure sensitive receptors in the cell membrane. Water pressure during immersion may be transmitted through the body to cause a graded tissue hydrostatic compression. Pressure sensors within cell membranes might then activate membrane pumps that are normally associated with the regulation of cell volume. Normally cells would perceive an increase in membrane pressure as an indicator that cell volume is too large and they would actively move water, K^+, and amino acids out of the cell. The increase in membrane pressure during immersion results in reduced intracellular water. During spaceflight an opposite situation may occur. Removal of the tissue hydrostatic pressure in microgravity may cause a decrease in tissue compression which inhibits activity of the cell membrane pumps resulting in a gradual increase in intracellular water.

Erythrocyte volume decreases precipitously during spaceflight. Another surprising finding from the SLS-1 and SLS-2 missions was that the rate of decrease in erythrocyte volume was about twice that predicted (4). Previously it was believed that erythrocyte volume declines during spaceflight because of inhibition of erythrocyte production (163). Although erythropoietin concentration was significantly reduced early in the SLS-2 mission (flight days 2–4), it had returned to preflight levels by the 8th-12th days of flight. Even assuming a complete cessation of new erythrocyte production, this could only account for about 30% of the observed reduction in erythrocyte volume. Alfrey et al. (4) further observed that the Hct did not increase during the SLS-2 mission. Considering the initial loss of plasma volume in these subjects, a hemoconcentration would be expected. Also, there was a significant reduction in the average mean corpuscular volume, suggesting a decrease in the mean size of the circulating erythrocytes.

Alfrey et al. (4) have suggested that the mechanism responsible for these observations is an acute effect of microgravity to selectively destroy new erythrocytes. New reticulocytes are larger than the average, older erythrocytes. Therefore, selective destruction of new erythrocytes would decrease the average mean corpuscular volume. This hypothesis suggests a new undefined mechanism by which erythrocyte volume might be adjusted rapidly in response to a new environmental situation. They proposed that, in the absence of a threshold level of some specific plasma marker (cytokine, growth factor, erythropoietin), receptors on reticuloendothelial cells and/or cytoadhesive molecules on newly produced erythrocytes may cause them to adhere to one another and be catabolized. This process would continue until the optimum erythrocyte volume is achieved for that environment. This would be an entirely new mechanism of erythrocyte volume regulation which may have significant impact for the clinical treatment of patients with anemia.

In summary, recent findings from spaceflight have caused reconsideration of some of the oldest tenets of body fluid and blood volume regulation. Plasma volume and erythrocyte volume are reduced even after short-term space flight. Plasma volume decreases possibly as a result of a new lower set-point for total body water or CVP via actions on volume receptors (baroreceptors and osmoreceptors) and effector organs (kidneys, hypothalamic thirst centers). Erythrocyte volume decreases probably from increased destruction via an undefined mechanism and possibly reduced production of new erythrocytes.

RECOVERY FROM TRAUMA AND SICKNESS

Missing blood syndrome. During the Vietnam conflict, military physicians Valeri and Altschule recognized, studied, and later published on *The Missing Blood Syndrome* (164) on soldiers evacuated stateside because of major wounds. These men had a "serious chronic illness" that lasted many weeks or months, in the sense of slow-healing, often infected wounds, mainly of the limbs. They were weeks removed from the war-zone and were up and about as much as possible, so obviously were not in shock. Yet, when they underwent general anesthesia for corrective surgery, they developed troubling hypotension. This led to the idea

that they might have a low blood volume, a "hidden hypovolemia of trauma." Radioactive isotope labeled erythrocyte studies confirmed abnormally low erythrocyte volumes compared with normative standards, deficits up to 40%. Plasma volumes were also calculated as abnormally low (by the same standards), which kept Hct at about 35%, thus masking a "hypovolemic anemia."

Laboratory results included normal reticulocyte counts, bone marrows that appeared normal, urine erythropoietin levels low for the degree of anemia, erythrocyte production (by ferrokinetics) also low for the anemia, and serum iron levels normal to low. Iron therapy was not effective. The investigators theorized that their patients had not the classical "acute central vasoconstriction" (renal, gut) of hemorrhagic shock but instead a "chronic peripheral vasoconstriction" in the extremities that slowed wound healing. They found that preoperative erythrocyte transfusion prevented the hypotension and that repeated transfusion seemed to "refill the limbs" and speed wound healing.

The pathophysiology underlying this syndrome was unclear. Valeri and Altschule (164) argued that it was not an "adaptive" anemia (i.e., to reduced oxygen needs because of limb atrophy, weight loss, and inactivity) because erythrocyte levels of 2,3-diphosphoglycerate (2,3-DPG) were increased. However, others investigators report that in the anemia of cancer or rheumatoid arthritis, for example, erythrocyte 2,3-DPG is increased (35). Erythrocyte 2,3-DPG is also increased in the "anemia" of early pregnancy (the erythrocyte volume falls in early pregnancy, returns steadily to nonpregnant levels by week 30, and further increases in late pregnancy), and that anemia is adaptive (9). So an elevated erythrocyte 2,3-DPG level did not necessarily mean the anemia is not adaptive.

In addition, Valeri and Altschule (164) were puzzled by the failure of plasma volume to increase as much as they expected in compensation for the contracted erythrocyte volume. Plasma volumes, however, were not measured but were estimated from erythrocyte volume and total body Hct, and results were compared with normative values from a body surface area nomogram. Such nomograms come from healthy men not wounded soldiers. Probably the relative inactivity (and perhaps a contraction of vascular beds in atrophic limbs) contributed to low plasma volumes in these wounded men.

Valeri and Altschule concluded that the reduced erythrocyte volume mainly resulted from the suppression of erythropoiesis, perhaps from plasma-borne inhibitors. Recent research suggests that they were correct in this conclusion. Mononuclear cells infiltrating the chronic, infected limb wounds will release a myriad of cytokines, such as interleukins (especially IL-1 and IL-2), interferons, and tumor necrosis factor (TNF). Such multifunctional cytokines do indeed suppress erythropoiesis and so lead to the "anemia of chronic disease."

The major wounds most likely led to extensive cytokine production because even exhausting or eccentric exercise—with its minor muscle damage—elevates plasma levels of cytokines. For example, 1 h of vigorous eccentric cycling elevates plasma IL-1 (16), whereas marathon running elevates plasma TNF, IL-6, and the hepatic protein that IL-6 induces, C-reactive protein (40). Also, 45 min of downhill treadmill running elevates the secretion of IL-1 and TNF from blood-borne mononuclear cells (17).

Recent research also demonstrates that cytokines play a key role in the anemia of chronic disease, which results from: 1) impaired renal release of erythropoietin, 2) impaired marrow action of erythropoietin, and 3) a "lock-up" of iron in macrophages. For example, different studies find that: 1) the *in-vitro* growth of human erythroid colonies is inhibited by interferon, by IL-1 (perhaps via interferon), and by TNF; 2) TNF, IL-1, and IL-2 increase intracellular ferritin production (which may "lock-up" iron in macrophages); and 3) IL-2, IL-6, and TNF cause anemia when given to patients (87). Conversely, when rheumatoid arthritis patients receive a monoclonal antibody that neutralizes TNF, their anemia improves (38). Finally, research shows that erythropoietin *in vitro* can reverse the inhibition of erythropoiesis by interferon (87).

All considered, it seems likely that the "missing blood syndrome" is a form of the anemia of chronic disease and stems mainly from immune activation and cytokine release. The low plasma volume accompanying it may result largely from a decreased vascular bed (limb atrophy) and from inactivity. It can be argued that this anemia may be adaptive; for example, "thinner blood" may help prevent venous thrombosis. If, as Valeri and Altschule argue from anecdotal reports (164), the repeated transfusions they gave these soldiers really did speed wound healing, perhaps treating with recombinant human erythropoietin (rhEpo) would do the same. On the other hand, by increasing Hct and blood viscosity—and so the risk of thrombosis—rhEpo could be a two-edged sword.

Use of rhEpo in medicine today. The foremost use of rhEpo is for the anemia of chronic renal failure. Published in 1989 was the benchmark American trial in 333 patients with end-stage renal disease, stable on hemodialysis (39). On rhEpo, Hct rose from 22 to 35% within 12 wk in 95% of patients. Few side effects were observed. Blood pressure rose slightly in 35% of patients. Seizures occurred in five percent, but this was probably not higher than would have been expected without rhEpo. Similarly, no increase in shunt thrombosis was seen. Quality of life (self-report, no control group) increased on rhEpo.

After this report, rhEpo quickly gained wide use in end-stage renal disease; now about 300,000 patients worldwide receive it. The news is that anemia persists despite rhEpo therapy in about 50% of patients on hemodiaysis in the United States (77). Research finds that, as gauged by urea clearance, inadequate dialysis contributes to rhEpo resistance, and intensifying dialysis for 6 wk boosts Hct by about 15% with no change in rhEpo dose. The biological implication is that "uremic inhibitors" of rhEpo exist. The social implication is that some dialysis centers shortchange patients to save money (77).

Pilot research suggests that in patients with rheumatoid arthritis, rhEpo can reverse the anemia but not change pain

or quality of life (119). Because most patients are not transfusion dependent and are relatively sedentary, rhEpo is not used widely in rheumatoid arthritis. Similarly, pilot research finds that rhEpo—perhaps by countering IL-1—can boost Hb modestly in inflammatory bowel disease, but rhEo is not yet used widely for such patients (149).

Besides renal disease, rhEpo therapy is used most commonly in AIDS or cancer. Among AIDS patients with low baseline erythropoietin levels, rhEpo therapy for 12 wk can boost Hct by about five points, cut transfusion needs, and improve quality of life (70). Similar benefits can be seen in patients with cancer, but only about 50% respond to rhEpo (155), so the focus is on defining who with cancer is most apt to benefit. Finally, rhEpo is used preoperatively in selected anemic patients who bank blood for autologous transfusion, and perioperatively to speed convalescence in selected patients, notably those whose religion precludes transfusion.

Abuse of rhEpo by athletes. Recently the American College of Sports Medicine issued a Position Stand decrying the abuse of rhEpo. It concluded that "blood doping. . . to improve athletic performance is unethical, unfair, and exposes the athlete to unwarranted and potentially serious health risks" (137). Indeed, it is widely believed that the spate of sudden deaths in 1987–1990 among competitive cyclists in Europe was a result in part to rhEpo abuse (37). The use of rhEpo by athletes still continues as recent media reports indicate abuse of rhEpo by some competitive cyclists, marathoners, cross-country skiers, and triathletes.

The medical problem is that rapidly expanding the erythrocyte volume via rhEpo increases blood viscosity and—especially in the setting of endurance races—might predispose the athlete to unwanted blood clots and the complications therefrom. The problem for sport is that, despite pilot studies on detection via electrophoresis or transferrin-receptor to ferritin ratio (50,167), no practicable method yet exists to detect rhEpo abuse. Some ski and cycling federations are screening prerace Hct and barring any athlete above a cutoff, for example, Hct > 50% for a

man, 47% for a woman (115). This screening might make that race safer but likely will not catch rhEpo abusers who will learn to lie down, drink half-normal saline, and demand to be retested.

In summary, trauma is associated with reduced blood volume. Erythrocyte volume is reduced because of hemorrhage and immune activation with cytokine release which suppresses erythropoiesis. Plasma volume is reduced because of decreased vascular bed (limb atrophy) and inactivity. The re-establishment of erythrocyte volume might improve wound healing and improve the patient's quality of life. Medical treatment for the anemia of chronic renal failure, AIDS, some cancer, and rheumatoid arthritis can include administration of rhEpo to induce erythrocyte volume expansion. Some athletes, however, illegally use rhEpo (and erythrocyte transfusions) as an ergogenic aid and this may be associated with several fatalities.

SUMMARY

Blood volume changes occur with human adaptations to physical exercise, environmental stresses, and trauma/illness. Erythrocyte volume and plasma volume will change independently of each other and make separate contributions to each adaptation. Our understanding is limited by information regarding the magnitude of change, time course, stimuli, and mechanisms for these vascular volume changes. A fundamental problem in interpreting the literature is the need for valid and reliable measurement methodologies that are not confounded by the perturbations and repeated measurements.

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