**Title:** Control of Thermoregulatory Sweating During Exercise in the Heat

**Authors:** Michael N. Sawka, Richard R. Gonzalez, Andrew J. Young, Richard C. Dennis, C. Robert Valeri, and Kent B. Pandolf

**Abstract:**

The purposes of this study are to: (a) determine if erythrocyte infusion alters the control of thermoregulatory sweating; and (b) demonstrate how increases and decreases of both plasma tonicity and blood volume influence the thermoregulatory control parameters of threshold temperature and sweating sensitivity. Six non-heat acclimated and five heat acclimated males attempted Heat Stress Tests (HST's) both before and shortly after (48-96h) autologous erythrocyte infusion. The non-heat acclimated subjects were euhydrated for both HST's; whereas, the heat acclimated subjects were studied in a euhydrated and a hypohydrated (-5% body weight) condition both pre- and post-infusion (500 ml of solution containing 60% hct of autologous erythrocytes). The HST's consisted of treadmill exercise (335 W/m^2) in a hot (35°C, 45% relative humidity) environment, and esophageal temperature and local sweating rate were continuously measured during 25 minutes of exercise. These experiments resulted in a matrix of conditions where both plasma tonicity and blood volume were increased or decreased relative to control conditions (euhydration, pre-infusion).
The findings concerning thermoregulatory sweating during exercise in the heat are summarized: 1) acute polycythemia will decrease the threshold temperature and increase the sweating sensitivity; 2) both threshold temperature and sweating sensitivity are increased or decreased from control levels dependent upon the combined influence of plasma tonicity and blood volume; and 3) threshold temperature changes are primarily influenced by plasma tonicity, and sweating sensitivity changes are primarily influenced by blood volume.
CONTROL OF THERMOREGULATORY SWEATING DURING EXERCISE IN THE HEAT

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Abbreviated Title: Control of Thermoregulatory Sweating

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ABSTRACT

The purposes of this study are to: (a) determine if erythrocyte infusion alters the control of thermoregulatory sweating; and (b) demonstrate how increases and decreases of both plasma tonicity and blood volume influence the thermoregulatory control parameters of threshold temperature and sweating sensitivity. Six non-heat acclimated and five heat acclimated males attempted Heat Stress Tests (HST's) both before and shortly after (48-96h) autologous erythrocyte infusion. The non-heat acclimated subjects were euhydrated for both HST's; whereas, the heat acclimated subjects were studied in a euhydrated and a hypohydrated (-5% body weight) condition both pre- and post-infusion (500 ml of solution containing ~60% hct of autologous erythrocytes). The HST's consisted of treadmill exercise (335 W·m⁻²) in a hot (35°C, 45% relative humidity) environment, and esophageal temperature and local sweating rate were continuously measured during 25 minutes of exercise. These experiments resulted in a matrix of conditions where both plasma tonicity and blood volume were increased or decreased relative to control conditions (euhydration, pre-infusion). The findings concerning thermoregulatory sweating during exercise in the heat are summarized: 1) acute polycythemia will decrease the threshold temperature and increase the sweating sensitivity; 2) both threshold temperature and sweating sensitivity are increased or decreased from control levels dependent upon the combined influence of plasma tonicity and blood volume; and 3) threshold temperature changes are primarily influenced by plasma tonicity, and sweating sensitivity changes are primarily influenced by blood volume.

Index Terms: acute polycythemia, dehydration, erythrocyte infusion, hypervolemia, hypovolemia, hyperosmolality, sweating sensitivity, temperature regulation, thermoregulation, threshold temperature
INTRODUCTION

Acute polycythemia has been reported to reduce thermal strain and improve exercise performance in the heat for both non-heat acclimated (23) and heat acclimated (26) humans. These papers, however, did not address the question of whether acute polycythemia alters the thermoregulatory control system. In this paper, we determined if the thermoregulatory control parameters of threshold temperature and sweating sensitivity were modified by erythrocyte infusion. This paper also evaluates how these thermoregulatory control parameters are altered by the singular and combined effects of changes in plasma tonicity and changes in blood volume. Plasma tonicity and blood volume are believed to be the primary physiological variables that can modify the thermoregulatory effector responses (9,28). Fortuitously, the following experiments resulted in a matrix of conditions where both plasma tonicity and blood volume were increased and decreased relative to control conditions (euhydrated, pre-infusion). As a result, we were provided an opportunity to gain insight into the control of thermoregulatory sweating during exercise-heat stress.

The purposes of this study are to: (a) determine if erythrocyte infusion alters the control of thermoregulatory sweating; and (b) demonstrate how increases and decreases of both plasma tonicity and blood volume influence the thermoregulatory sweating control parameters of threshold temperature and sweating sensitivity.

METHODS

The described data reported in this paper were collected as part of a comprehensive research effort concerning erythrocyte infusion and exercise performance. Only the methodology directly related to the presented data are provided; additional methodological information can be obtained from previously published manuscripts (23,26).
Subjects. Eleven male subjects participated in these experiments; six subjects were non-heat acclimated, and five subjects were heat acclimated. The non-heat acclimated subjects had a mean (±SD) age of 30 ± 7 yr, body surface area of 2.0 ± 0.2 m², percent body fat of 15 ± 5 and maximal oxygen uptake of 54 ± 5 ml·kg⁻¹·min⁻¹. The heat acclimated subjects had a mean (±SD) age of 33 ± 2 yr, body surface area of 2.0 ± 0.2 m², percent body fat of 20 ± 5 and maximal oxygen uptake of 50 ± 7 ml·kg⁻¹·min⁻¹. All subjects gave their voluntary and informed consent to participate in these experiments, which have received approval by the appropriate Institutional Review Boards. Investigators adhered to AR 70-25 and United States Army Medical Research and Development Command Regulation 70-25 on Use of Volunteers in Research.

Protocol. For the non-heat acclimated subjects, the experiments were conducted in the early spring months. These subjects were members of a Special Forces team whose assignment was preparation for cold weather warfare. As a result, they were transported to cold environments for training during the months preceding these experiments. For the heat acclimated subjects, the experiments were conducted in the late fall-early winter months. Prior to the experimental days, the subjects were heat acclimated by performing treadmill exercise (0% grade at 1.34 m·s⁻¹) for 120 min on 9 days in a hot-dry (45°C ambient temperature, 20% relative humidity) environment (26).

Several months prior to experimental testing, two units of blood were removed from each subject by phlebotomy, and a minimum of 6 wk separated the removal of each blood unit. After each phlebotomy, the blood was separated into its erythrocyte and plasma components, and the erythrocytes were frozen with 40% (wt/vol) glycerol and stored at -80°C. Immediately prior to infusion, the frozen cell component was thawed and washed to reduce the glycerol concentration to <1%. For infusion, the subjects received ~500 ml of a sodium-chloride-glucose-
phosphate solution [comprised of (in g) 0.9 NaCl, 0.2 glucose, 0.0524 NaH2PO4
H2O and 0.1325 Na2HPO4 per 100 ml of solution] containing ~60% hematocrit
(autologous erythrocytes). Blood volume measurements were performed several
days before and 24 h after erythrocyte infusion.

The Heat Stress Tests (HST's) were conducted in a hot (35°C ambient
temperature, 45% relative humidity) environment. This environment was selected
to potentiate evaporative and limit convective and radiative heat exchange. Each
HST was 120 min (2 bouts of 15 min rest and 45 min exercise) in duration.
During exercise, the subjects walked (6% grade, 1.34 m·s⁻¹) on a treadmill. The
thermoregulatory data reported in this paper were collected during the initial 25
min of the first exercise bout. During rest and exercise, esophageal temperature,
skin temperature and local sweating rate were continuously determined.
Immediately after the collection of this thermoregulatory data, oxygen uptake was
measured. In addition, a venous blood sample was collected at rest and during
the ~20 min of exercise.

The non-heat acclimated subjects completed two HST's; one was attempted
~2 wk pre- and the other 48 h post-infusion (23). At least 10 days separated
the pre- and post-infusion HST's to minimize any partial acclimation from the
initial heat exposure. Both HST's were attempted while the subjects were
euhydrated; euhydration was determined by the achievement of a baseline body
weight, which was determined from morning weighings over the preceding month.
The heat acclimated subjects completed four HST's; two pre- (several days) and
two post- (48 h and 96 h) infusion (26). One HST was done while subjects were
euhydrated, and the other was done while subjects were hypohydrated by 5% of
body weight. Approximately 24-48 h before each hypohydration HST, the
subjects voluntarily restricted food and fluid intake. Also, in the afternoon the
day before the hypohydration HST's, the subjects performed light-intensity exercise
in a hot environment to dehydrate to their target body weight (5% below base line). After achieving the target body weight, the subjects were removed to a comfortable environment ($T_a$ 20°C) to spend the night, and were allowed fresh fruit and juice, but only in the amounts that maintained the desired body weight. All HST's were conducted at ~0930 to control for any diurnal patterns.

Measurements. Oxygen uptake was determined by open-circuit spirometry, with the respiratory gases collected in 150-liter Douglas bags. The volume of expired gases was measured with a Tissot gasometer, and the $O_2$ and $CO_2$ concentrations were measured with an electrochemical $O_2$ Analyzer (Applied Electrochemistry S-3A) and an infrared $CO_2$ analyzer (Beckman LB-2), respectively. Skin temperatures were obtained with a three-point thermocouple skin harness (chest, calf, and upper forearm), and mean weighted skin temperature ($T_{sk}$) was calculated. Esophageal temperature ($T_{es}$) was obtained from a thermistor in a catheter placed at the level of the heart, and local sweating rates ($m_{ds}$) from the upper arm were determined by a continuously ventilated dew-point sensor placed on the skin site (10). Since the passage of saliva will spuriously lower $T_{es}$ values (28), the subjects avoided swallowing by spitting into a cup. The threshold temperature for active thermoregulatory sweating, above that due to skin diffusion, was defined as the esophageal temperature at which the $m_{ds}$ value achieved 0.06 mg·min$^{-1}$·cm$^{-2}$ (22,24,25). The sweating sensitivity was defined as the slope of a regression line representing the individual $m_{ds}$ and $T_{es}$ values obtained at one minute intervals during the exercise transient (22,24,25).

Venous blood samples were collected from an indwelling Teflon catheter placed within a superficial forearm vein. Patency was maintained with heparinized saline; the catheter (2 ml of dead space) was flushed with 4 ml of blood before each 8 ml sample was obtained. Blood samples taken at rest were
obtained after the subjects had stood quietly for 20 min in the antechamber (20°C T_a, 40% rh), and exercise blood samples were taken during exercise while the subjects continued to walk. All blood samples were obtained with the catheterized arm hanging in a relaxed manner over the handrail of the treadmill. Triplicate measurements of all blood variables were made. An automated system was used to measure hemoglobin (Hemoglobinometer, Coulter Electronics), and plasma osmolality was measured by a vapor pressure osmometer (Model 5500, Wescor). Plasma volume and erythrocyte volume at rest (euhydrated) was measured by the iodine-labeled (^{125}I) albumin method, and the radioactively labeled chromium (^{51}Cr) method (32), respectively. The percent changes in plasma volume were calculated from the appropriate hemoglobin and hematocrit values (4). The absolute plasma volumes during exercise were calculated by adjusting the measured resting plasma volume by the appropriate percent change in plasma volume. Blood volume was calculated as the sum of plasma volume and erythrocyte volume.

**Statistical Analyses.** Means ±SD, simple and multiple regression, and analyses of variance for repeated and non-repeated measures were calculated. Statistical significance was tested at the P<0.05 level.

**RESULTS**

Table 1 provides data for the metabolic and thermoregulatory control responses during rest and exercise. Aerobic metabolic rate was not altered by erythrocyte infusion. In order to evaluate the effects of erythrocyte infusion on thermoregulatory control, two separate analyses of variance (ANOVA) were performed for both threshold temperature and sweating sensitivity. The first ANOVA examined the effects of erythrocyte infusion for euhydrated individuals who were either non-heat acclimated (n=6) or heat acclimated (n=5). The
second ANOVA examined the effects of erythrocyte infusion for heat acclimated individuals (n=3) who were either euhydrated or hypohydrated. Note that three data sets were employed for the second ANOVA, because two subjects were unable to swallow the esophageal catheter during the pre-infusion hypohydration experiments.

### TABLE 1 ABOUT HERE

Table 2 provides a statistical summary for the effects of erythrocyte infusion on the thermoregulatory control parameters of threshold temperature and sweating sensitivity. The first ANOVA indicated that erythrocyte infusion had not decreased \((p=0.08)\) threshold temperature but had increased \((p<0.01)\) sweating sensitivity by 71%. In addition, heat acclimation decreased \((p<0.05)\) threshold temperature and increased \((p<0.05)\) sweating sensitivity. The second ANOVA indicated that erythrocyte infusion decreased \((p<0.05)\) threshold temperature by 0.30°C and increased \((p<0.01)\) sweating sensitivity by 57%. In addition, hypohydration did not \((p=0.07)\) alter threshold temperature but decreased \((p<0.05)\) sweating sensitivity. Data examination, however, indicates that hydration did not statistically alter threshold temperature because the large pre-infusion increase (eu- to hypohydration) was offset by the large effects of erythrocyte infusion. Unfortunately, the small sample size resulted in an insignificant interaction term making this second ANOVA difficult to interpret. Figure 1 illustrates all of the individual data for the effects of erythrocyte infusion on threshold temperature and sweating sensitivity. Note that 11 of 14 threshold temperature values were decreased (below the line of identity), and all sweating sensitivity values were increased (above the line of identity) after erythrocyte infusion.
Table 3 provides the plasma osmolality and blood volume values for the subjects at rest and during exercise-heat stress. To determine these variables' influence on the control of thermoregulatory sweating, the individual changes in plasma osmolality and individual changes in blood volume relative to control conditions (euhydration, pre-infusion) were calculated. Regression analyses were performed to determine the relationships between the individual changes (compared to euhydration, pre-infusion) in these hematological variables to the individual threshold temperature shifts and individual sweating sensitivity changes (compared to euhydration, pre-infusion). The threshold temperature shifts had the strongest relationships with the changes in plasma osmolality (exercise values; r=0.85; P<0.01) and the changes in blood volume (pre-exercise values; r=-0.75; P<0.01); and the individual values are depicted in Figure 2. Note that each data point represents the comparison of two separate experiments. The threshold temperature shifts (compared to euhydration, pre-infusion) were best described by the equation:

\[ \Delta T_h = 0.03550 \Delta \text{Osmole}_{\text{ex}} - 0.01351 \Delta B_{V_r} - 0.03609 \]

\[ r=0.87; \ P<0.01 \]

where: \( \Delta T_h \) (°C) is the change in threshold temperature

\( \Delta \text{Osmole}_{\text{ex}} \) (mosmol*kg\(^{-1}\)) is the change in osmolality (exercise values)

\( \Delta B_{V_r} \) (%) is the change in blood volume (pre-exercise values)
The sweating sensitivity changes had the strongest relationships with the changes in blood volume (exercise values; \( r = 0.53; \, P<0.05 \)) and the changes in osmolality (pre-exercise values; \( r = -0.49; \, P<0.05 \)). The sweating sensitivity changes (compared to euhydration, pre-infusion) were best described by the equation:

\[
\Delta \text{ASS} = 0.01381 \, (\Delta \text{BV}_{\text{ex}}) + 0.00718 \, (\Delta \text{Osmol}_{\text{r}}) + 0.27038
\]

\( r = 0.55; \, P<0.05 \)

where:
- \( \Delta \text{ASS} \) (mg·cm\(^{-2}·\text{min}^{-1}·\text{K}^{-1} \)) is the change in sweating sensitivity
- \( \Delta \text{BV}_{\text{ex}} \) (%) is the change in blood volume (exercise values)
- \( \Delta \text{Osmol}_{\text{r}} \) (mosmol·kg\(^{-1} \)) is the change in osmolality (pre-exercise values)

**DISCUSSION**

Thermoregulatory sweating is believed to be regulated by a proportional control system (9,14,28). A proportional system is defined as the graded response of a controlled variable (e.g., sweating) to the displacement of the regulated variable (e.g., body temperature). Both peripheral and central thermal receptors provide afferent input into the hypothalamic thermoregulatory centers where this information is processed with a resultant effector signal to initiate and maintain sweating rate (9,14,28). For humans, \( T_{sk} \) provides an index of peripheral thermal information and \( T_{es} \) provides an index of central thermal information affecting sweating with relative weightings of 0.1 and 0.9, respectively (19). In our analyses, we used \( T_{es} \) as the index of thermal drive for sweating as the local and mean skin temperature values were not altered by any of the experimental conditions (23,26).

Erythrocyte infusion generally decreased the threshold temperature and always increased the sweating sensitivity during moderate intensity exercise in the
heat. The decrease in threshold temperature was modest for the euhydrated subjects but was striking for the hypohydrated subjects after erythrocyte infusion. Conversely, sweating sensitivity values were always markedly increased by erythrocyte infusion regardless of the subject's hydration status. Both a decreased threshold temperature and an increased sweating sensitivity indicate an improved thermoregulatory sweating response during exercise-heat stress.

The most significant finding is that the thermoregulatory sweating response can be improved beyond those levels observed for an individual with a normal plasma tonicity and blood volume. We are not familiar with other research demonstrating these results; however, one study (7) has reported that acute hypervolemia (9% expansion of blood volume) lowered core temperature values during exercise despite no change in the sweating response. Those experiments were conducted in a 30°C environment, so it is possible that the hypervolemia may have mediated an increased skin blood flow and dry heat loss to account for their lowered core temperature values (7). Other investigators (6,18,27) have found that acute hypervolemia does not provide a thermoregulatory advantage, compared to normovolemia, during exercise in the heat. Several investigators (3,11,13,17) have examined the effects of excessive fluid ingestion or hyperhydration on thermoregulatory responses during exercise in the heat. Moroff and Bass (17) found that hyperhydration resulted in an increased total body sweating rate and reduced core temperature during exercise in the heat. Other investigators, however, have reported that hyperhydration did not provide a thermoregulatory advantage (3,11) or that it reduced core temperature with no change in total body sweating (13) during exercise in the heat.

When comparing the present experiments with previous hypervolemia/hyperhydration investigations, several important factors need to be considered. First, the erythrocyte infusion elicited a hypervolemia that was fairly
long-term (at least 48 h - 96 h), unlike previous studies in which blood volume was acutely expanded immediately before the exercise-heat exposure (7,8,18,27). It is possible that hypervolemia is required for several hours to readjust the cardiovascular system (via the baroreceptor reflex) so that the thermoregulatory sweating can be enhanced. Second, in this study plasma tonicity (particularly the exercise values) and blood volume often changed in concert, so that a potentiating effect may have occurred that was greater than if each were altered independently of the other. Third, we evaluated thermoregulatory sweating in a more precise manner than some of the previous hyperhydration/hypervolemia studies which only examined total body sweating (11,13,17,27).

The threshold temperature for thermoregulatory sweating can be shifted above or below control levels (when normal plasma tonicity and blood volume are present) dependent upon both changes in plasma tonicity and blood volume (Figure 3); however, plasma tonicity changes accounted for more of the variance in threshold temperature shifts than did blood volume changes. A threshold temperature shift is often interpreted as indicative of a central nervous system mediated change in the thermoregulatory effector signal (28). The plasma tonicity changes, as measured in this study, may correlate to tonicity changes in the extracellular fluid bathing the hypothalamic neurons (16,21). Silva and Boulant (31) have demonstrated that in rat brain slices, there are preoptic-anterior hypothalamic neurons which are both thermosensitive and osmosensitive. Therefore, these data suggest a central interaction between thermoregulation and body water regulation. Numerous other animal studies have demonstrated that the intravascular (1,2,12,16) or intracranial (5) infusion of hypertonic solutions will elevate core temperature during rest and exercise in the heat. Several human studies have demonstrated that the ingestion of hypertonic fluid will elevate core temperature responses in the heat, despite the maintenance of euhydration
Consistent with this, in humans an inverse relationship ($r = -0.62$ to $-0.76$) between plasma osmolality, and total body sweating has been reported by several investigators (29,30). Likewise, Fortney et al. (8) have reported that hyperosmolality will increase the threshold temperatures for sweating and cutaneous vasodilation even without a blood volume reduction during exercise in the heat. The combined results of these studies indicate that plasma osmolality exerts a powerful influence on thermoregulatory sweating and body temperature responses to exercise and heat stress.

Sweating sensitivity can also be increased or decreased relative to control levels (when normal blood volume and plasma tonicity are present); with changes in blood volume having a slightly greater effect than plasma tonicity on the change in sweating sensitivity. Sweating sensitivity changes are generally interpreted to indicate a peripheral effect localized at the individual eccrine sweat gland (9,19,28); but others (7,25) have suggested that sweating sensitivity changes could reflect a central nervous system mediated alteration. For example, hypovolemia and hypervolemia will either unload or load the low pressure baroreceptors. Fortney et al. (7) have suggested that hypovolemia may alter the activity of atrial baroreceptors that could have afferent input to the hypothalamic thermoregulatory centers. Therefore, a peripheral input could result in a central nervous system mediated alteration in sweating sensitivity. Those investigators also reported that an isotonic hypovolemia (9% reduction in blood volume) reduced the sweating sensitivity by 42% from control levels. If sweating sensitivity changes do represent a peripheral effect, the increased plasma tonicity may also have exerted its influence via a high interstitial osmotic pressure inhibiting the fluid availability to the eccrine sweat gland (11,21).

Our findings concerning thermoregulatory sweating during exercise in the heat are summarized as follows: 1) acute polycythemia will decrease the
threshold temperature and increase the sweating sensitivity; 2) both threshold temperature and sweating sensitivity are increased or decreased from control levels (when normal plasma tonicity and blood volume are present) dependent upon the combined influence of plasma tonicity and blood volume; and 3) threshold temperature changes are primarily influenced by plasma tonicity and sweating sensitivity changes are primarily influenced by blood volume. Homeostatically, these observations are logical in that when an individual has an abundance of body water it will be employed to increase evaporative cooling and defend body temperature during exercise in the heat; conversely, if there is a shortage of body water, it will be conserved to maintain cardiovascular stability. During the hypohydrated state, the strategy may be that the reduced sweating which mediates a higher core temperature will elicit behavioral thermoregulatory actions to reduce the exercise intensity and remove the heat stress.
ACKNOWLEDGEMENTS

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The views, opinions and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army or Department of the Navy position, policy or decision, unless so designated by other official documentation. Approval for public release; distribution is unlimited.

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REFERENCES


FIGURE LEGENDS

Figure 1. Individual data for threshold temperature and sweating sensitivity responses to the pre- and post-infusion HSTs. The broken line is the line of sensitivity.

Figure 2. Individual data for the change (compared to euhydration, pre-infusion) threshold temperature’s relationship to the change in plasma osmolality (exercise values) and the change in blood volume (pre-exercise values).
<table>
<thead>
<tr>
<th>Subject Status</th>
<th>Aerobic Metabolic Rate</th>
<th>Sweating Threshold</th>
<th>Sweating Sensitivity</th>
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<tr>
<td></td>
<td>(W·m⁻²)</td>
<td>(°C)</td>
<td>(mg·cm⁻²·min⁻¹·K⁻¹)</td>
</tr>
<tr>
<td>Unacclimated Subjects</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Euhydrated</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre-infusion</td>
<td>358</td>
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<tr>
<td>(n=6)</td>
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<td>0.64</td>
</tr>
<tr>
<td>(n=6)</td>
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</tr>
<tr>
<td>Acclimated Subjects</td>
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<td></td>
</tr>
<tr>
<td>Euhydrated</td>
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<td></td>
</tr>
<tr>
<td>Pre-infusion</td>
<td>322</td>
<td>36.53</td>
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<tr>
<td>(n=5)</td>
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<td>(n=3)</td>
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Table 2. Summary of analyses of variance (probability levels) for the effects of erythrocyte infusion on theroregulatory control parameters.

<table>
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<tr>
<th>Variable</th>
<th>Main Effects</th>
<th>Factor Interaction</th>
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<td></td>
<td>Infusion x Acclimation</td>
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Table 3. Plasma osmolality and blood volume values during rest and exercise-heat stress.

<table>
<thead>
<tr>
<th>Subject Status</th>
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<th>Blood Volume (L)</th>
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<td></td>
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<td>Exercise</td>
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<th>Post-Infusion</th>
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Fig. 1.

**Threshold Temperature (°C)**

- **Pre-infusion**
  - Scatter plot with trend line, correlation coefficient $r = 0.75$

- **Post-infusion**
  - Scatter plot with trend line, correlation coefficient $r = 0.68$

**Sweating Sensitivity (mg cm$^{-2}$ min$^{-1}$ K$^{-1}$)**

- **Pre-infusion**
  - Scatter plot with trend line

- **Post-infusion**
  - Scatter plot with trend line
Fig. 2.