

Exercise Thermoregulation Following 13 Days of Bed Rest

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**ABSTRACT**

This investigation examined two potential mechanisms, altered skin blood flow (SBF) and sweating rate (SR) responses, that may be responsible for an elevated core temperature during exercise after bed rest (BR) and space flight. Seven healthy men ( $29 \pm 5$  yr,  $179.6 \pm 7.1$  cm,  $77.2 \pm 17.0$  kg; mean  $\pm$  SD) underwent 13 days of  $6^\circ$  head-down BR. Pre- and post-BR, subjects completed supine submaximal cycle ergometry (20 min @ 40% and 20 min @ 65% of pre-BR supine  $\text{VO}_{2\text{pk}}$ ) in a thermoneutral room ( $23.4 \pm 0.5^\circ\text{C}$ ,  $56 \pm 8$  %RH) during which heat production ( $\text{VO}_2$ ; indirect calorimetry), intestinal temperature ( $T_{\text{in}}$ ; ingestible pill), SBF (laser Doppler velocimetry), local SR (dew point hygrometry), and total sweat loss (TSL;  $\Delta$ body weight) were measured. Pre- and post-BR plasma volume (PV) was measured using  $^{125}\text{I}$  dilution. After BR,  $T_{\text{in}}$  was elevated at rest ( $36.99 \pm 0.14$  vs.  $37.30 \pm 0.06^\circ\text{C}$ ;  $p \leq 0.05$ ) and at the end of exercise ( $37.57 \pm 0.13$  vs.  $37.90 \pm 0.09^\circ\text{C}$ ;  $P \leq 0.05$ ). However, the increase in  $T_{\text{in}}$  from rest to the end of exercise was not different after BR ( $0.59 \pm 0.07$  vs.  $0.60 \pm 0.07^\circ\text{C}$ ). There was no difference in  $\text{VO}_2$  pre- to post-BR during rest ( $0.28 \pm 0.04$  vs.  $0.24 \pm 0.03 \text{ l} \cdot \text{min}^{-1}$ ) or 40%  $\text{VO}_{2\text{pk}}$  ( $0.95 \pm 0.08$  vs.  $0.96 \pm 0.05 \text{ l} \cdot \text{min}^{-1}$ ), but  $\text{VO}_2$  was significantly less at the end of the 65%  $\text{VO}_{2\text{pk}}$  stage ( $1.53 \pm 0.09$  vs.  $1.42 \pm 0.11 \text{ l} \cdot \text{min}^{-1}$ ;  $p \leq 0.05$ ). The percent change in SBF from rest to end of exercise was less after BR ( $211 \pm 53$  vs.  $96 \pm 31\%$ ;  $p \leq 0.05$ ), the threshold for the onset of SBF was greater ( $37.17 \pm 0.18$  vs.  $37.51 \pm 0.17^\circ\text{C}$ ;  $p \leq 0.05$ ), and the slope of the response tended to be reduced ( $536 \pm 184$  vs.  $201 \pm 46 \text{ \%} \Delta / ^\circ\text{C}$ ;  $p = 0.08$ ). TSL was not different after BR ( $0.42 \pm 0.06$  vs.  $0.44 \pm 0.08$  kg), but the  $T_{\text{in}}$  threshold at the onset of sweating was delayed significantly ( $37.06 \pm 0.11$  vs.  $37.34 \pm 0.06^\circ\text{C}$ ;  $p \leq 0.05$ ). However, the slope of SR was not changed after BR ( $3.45 \pm 1.22$  vs.  $2.58 \pm 0.71 \text{ mg} \cdot \text{min}^{-1} \cdot \text{cm}^{-2}$ ). PV was decreased by 11% after BR ( $3,259 \pm 177$  vs.  $2,894 \pm 138$  ml;  $p \leq 0.05$ ). These results suggest that exercise SBF and SR responses after BR are altered, and heat production is unchanged or reduced, consistent with observations following space flight. The higher resting  $T_{\text{in}}$  with a proportional increase in  $T_{\text{in}}$  during exercise and delayed onset of SBF and SR suggest a centrally-mediated elevation in the thermoregulatory set point during microgravity exposure.

**Key Words:** core temperature, intestinal temperature, skin blood flow, sweating rate

## INTRODUCTION

Adaptation to bed rest and spaceflight includes decreased postflight aerobic capacity, lower muscular strength and endurance, alterations in cardiovascular function, and reduced plasma volume (Convertino, 1996). The ability to perform work during spaceflight, complete an unaided emergency egress upon landing, and participate in rehabilitation activities after spaceflight are issues of concern which may be compromised by these adaptations. Physical work capacity may be further reduced by impaired body temperature regulation during rest and exercise that in turn may lead to heat strain and injury. For example, the combined effects of plasma volume loss and loss of heat acclimation may result in excessive heat strain for Space Shuttle crewmembers wearing protective garments during launch and landing (Pandolf, 1995). During a nominal landing (STS-90, April 1998) prior to exit from the Space Shuttle, intestinal temperature ( $T_{in}$ ), a measure of core temperature ( $T_{core}$ ), was significantly elevated in four crewmembers wearing the Launch and Entry Suit (LES) despite the use of a liquid cooling garment (Rimmer, 1999). In the event of an emergency egress from the Shuttle, crewmembers would be disconnected from the thermoelectric cooling unit supplying the liquid cooling garment in order to exit the vehicle and be required to ambulate to a safe distance. This activity would be completed fully suited and may require an effort in excess of 70% of the crewmember's preflight peak oxygen consumption ( $VO_{2pk}$ ; Bishop, 1999). The combined thermal load of the protective garment and the elevated metabolic rate during egress would be expected to rapidly increase  $T_{core}$ .

We previously examined the thermoregulatory responses of two crewmembers after a 115-day spaceflight (Fortney, 1998).  $T_{in}$  was elevated moderately at rest and during exercise in these two crewmembers. Each crewmember had a delayed onset of and/or a decreased slope of sweating rate (SR) response and skin vasodilation. These changes in thermoregulation were observed even though crewmembers participated in an inflight exercise countermeasures program and data were collected five days after landing.

Previous investigators have found an impairment in thermoregulation after bed rest (BR), an analogue of spaceflight. A higher core temperature ( $T_{core}$ ) after BR has been observed during

submaximal exercise in both warm (Fortney, 1987) and temperate (Greenleaf & Reese, 1980; Ertl, 1999) conditions. The elevation in  $T_{\text{core}}$  was ascribed to a decreased ability to increase skin blood flow (SBF; Greenleaf, 1997) but also may be related to impaired sweating responses (Greenleaf & Reese, 1980). Crandall et al. (1994) passively heated subjects with a warm water-perfused suit before and after 15 days of BR. After BR, these subjects had a reduced forearm blood flow and vascular conductance both before and during whole body heating.

The purpose of this study was to determine whether heat loss responses were responsible for the impairment of thermoregulation during submaximal exercise after 13 days of BR, a duration similar to current Space Shuttle missions. Specifically, we hypothesized that after BR  $T_{\text{in}}$  would be elevated significantly due to an increase in the  $T_{\text{in}}$  threshold and a decrease in the slope of the SBF/ $T_{\text{in}}$  response and to an increase in the  $T_{\text{in}}$  threshold and a reduced slope of the SR/ $T_{\text{in}}$  response.

## METHODS

### *Subjects*

Seven healthy men ( $29 \pm 5$  yr,  $179.6 \pm 7.1$  cm,  $77.2 \pm 17.0$  kg; mean  $\pm$  SD) volunteered to participate in this investigation. All subjects completed a modified Air Force Class III Physical and were screened for cardiovascular disease using a Bruce protocol maximal treadmill test with 12-lead electrocardiogram. Subjects with significant ST-segment changes or ectopy were excluded as well as those with a history of hypertension or habitual tobacco, alcohol, and/or drug use. All subjects were given written and verbal explanation of testing and bed rest protocols and signed documentation indicating understanding and consent. All protocols were reviewed and approved by the NASA-Johnson Space Center and the University of Texas Medical Branch-Galveston Institutional Review Boards. The BR was conducted under medically-supervised conditions at the National Institutes of Health General Clinical Research Center at the University of Texas Medical Branch in Galveston, TX. Some aspects of this study have been previously reported (Bamman, 1997; Bamman, 1998).

*Overall Protocol*

To examine the effect of bed rest on exercise thermoregulation, we employed a repeated measures design in which subjects served as their own controls. We compared pre-BR responses to responses measured after 13 days of 6° head-down bed rest.

Prior to BR, subjects completed three testing sessions in the Exercise Physiology Laboratory (EXL) at NASA-Johnson Space Center. The first session was a test of supine  $\text{VO}_{2\text{pk}}$  using a cycle ergometer (Monark 818E) mounted on a specially-constructed frame. Subjects returned to the laboratory on two separate days to complete a supine submaximal exercise test which consisted of a continuous protocol of 25 min of supine rest, 20 min of cycling at 40%, and 20 min at 65%  $\text{VO}_{2\text{pk}}$ . Tests were separated by no less than 48 hours.  $T_{\text{in}}$ , skin temperatures ( $T_{\text{sk}}$ ), SBF, SR, and oxygen consumption ( $\text{VO}_2$ ) were measured during these tests. These exercise protocols and measurement techniques were used previously in our laboratory (Fortney, 1998; Lee, 2000).

Subjects were hospitalized for a total of 16 d: one day of ambulatory control, 14 d of 6° head-down BR, and one day of ambulatory recovery. On the morning of the first day of hospitalization, plasma volume (PV) and red cell mass (RCM) were measured. Thereafter, subjects remained active and upright and participated in muscle strength tests which were part of the companion study (Bamman, 1997; Bamman, 1998). After breakfast on the following morning, subjects were placed in 6° head-down tilt. Subjects remained in the head-down position, including meals and urination, but were allowed to defecate using a bedside commode. In addition, subjects were placed in a horizontal position for 30 min per day as a control for the companion study in which another group of subjects performed resistance exercise in the horizontal posture. No subjects in our study performed any exercise during BR except for the supine submaximal exercise test which was part of this protocol on the 13th day of BR. On BR day 14, PV and RCM were measured at the same time of day as pre-BR.

*Supine VO<sub>2</sub>pk Test*

Subjects reported to the laboratory within three weeks before the start of BR to complete a VO<sub>2</sub>pk test on a supine cycle ergometer. The VO<sub>2</sub>pk test consisted of cycling at a constant cadence of 60 rpm for one two-minute stage at 50 Watts followed by three 5-min stages of 100, 125, and 150 Watts. Thereafter the exercise intensity was increased each minute in 25-Watt increments until volitional fatigue. VO<sub>2</sub> was measured with a metabolic cart (Qplex I, Quinton Instruments, Inc., Seattle, WA) interfaced with a mass spectrometer (MGA-1100, Marquette Electronics, St. Louis, MO) and averaged over 30 sec intervals. The highest one-minute average was considered a measure of VO<sub>2</sub>pk. The exercise intensities for the subsequent submaximal exercise test were estimated (40% and 65% pre-BR VO<sub>2</sub>pk) from a simple linear regression of VO<sub>2</sub> and exercise intensity from the VO<sub>2</sub>pk test.

*Submaximal Exercise Test*

All subjects completed a submaximal exercise test for determination of thermoregulatory responses to exercise twice pre-BR and on day 13 of BR. Subjects refrained from exercise for 24 hours, alcohol ingestion for 24 hours, caffeine ingestion for 12 hours, and food consumption for 4 hours.

Each day of testing, subjects reported to the laboratory at the same time of day and were instrumented for the measurement of the thermoregulatory responses to exercise. Subjects rested for 20 minutes in the supine position on the cycle ergometer frame. Thereafter, data was collected during 5 min of supine rest and then during 20 min at 40% and 20 min at 65% pre-bed rest VO<sub>2</sub>pk. The same absolute exercise intensities (49±7 and 88±11 Watts; mean±SD) were performed during pre- and post-BR testing.

T<sub>in</sub> was measured at one min intervals with an ingestible core temperature pill (CorTemp Ingestible Temperature Sensor, Human Technologies, Inc., St. Petersburg, FL) swallowed approximately 6 hours prior to the test with a small amount of fluid. The temperature signal from the pill was transmitted to and stored on an external data logger (CorTemp Ambulatory Recorder,

Human Technologies, Inc., St. Petersburg, FL). We (Lee, 2000) and others (Kolka, 1993) have found that this measure of  $T_{\text{core}}$  is similar to esophageal temperature ( $T_{\text{es}}$ ) during moderate levels of exercise, including the specific exercise protocol used in this investigation.  $T_{\text{sk}}$  was measured on the upper arm ( $T_{\text{arm}}$ ), upper chest ( $T_{\text{chest}}$ ), thigh ( $T_{\text{thigh}}$ ), and calf ( $T_{\text{calf}}$ ) also at one min intervals using a separate data logger (Squirrel 1250, Science Electronics, Inc., Dayton, OH). Mean  $T_{\text{sk}}$  was calculated as  $T_{\text{sk}} = (0.3 \cdot T_{\text{chest}}) + (0.3 \cdot T_{\text{arm}}) + (0.2 \cdot T_{\text{thigh}}) + (0.2 \cdot T_{\text{calf}})$ , as described by Ramanathan (1964). Mean body temperature ( $T_{\text{body}}$ ) was calculated as  $T_{\text{body}} = (0.65 \cdot T_{\text{in}}) + (0.35 \cdot T_{\text{sk}})$ . Body heat content (BHC) was calculated at the beginning and end of the exercise protocol using the equation  $\text{BHC} = 0.83 \text{ kcal} \cdot \text{kg}^{-1} \cdot \text{C}^{-1} \cdot \text{BW} \cdot T_{\text{body}}$ , when 0.83 is the specific heat of body tissues and BW is body weight in kilograms, as described by Hortsman and Horvath (1972). Body heat storage (BHS) during exercise was calculated as the difference between BHC at the end of pre-exercise rest and BHC at the end of the 65%  $\text{VO}_2\text{pk}$  exercise stage.

SBF was measured continuously on the forearm using an integrating laser Doppler probe and measurement system (PeriFlux PF4001, Perimed, Inc., Stockholm, Sweden). Local  $T_{\text{sk}}$  at the site of skin blood flow measurement was held constant at 38°C using a heated probe holder collar (PeriTemp 4005, Perimed, Inc., Stockholm, Sweden). Analysis of SBF responses were made using the manufacturer provided software (Perisoft, Perimed, Inc., Stockholm, Sweden).

SR was measured using a multi-channel dew point hygrometry system (Bitronics, Inc., Guilford, CN) interfaced with a computer for calculations of SR at one min intervals. The dew point sensor was ventilated ( $500\text{-}800 \text{ ml} \cdot \text{min}^{-1}$ ) with ambient air. SR was measured with an accuracy of  $\pm 0.5 \text{ mg} \cdot \text{cm}^{-2} \cdot \text{min}^{-1}$ . Total body sweat loss (TSL) was calculated from dry body weight measured immediately before and after exercise on a standard calibrated scale (Detecto Scale, Inc., Rosalyn, NY).  $\text{VO}_2$  was measured in 30 sec intervals using a metabolic gas analyzer system (MedGraphics, Inc., St. Paul, MN) specifically designed for use on the Space Shuttle and Russian Mir Space Station. Heart rate (HR) was measured using a commercially available heart watch (Vantage XL, Polar Electro Oy, Finland) previously validated in our laboratory (Moore, 1997).

All measurement devices were calibrated prior to each testing session. Ingestible pills and  $T_{sk}$  thermistors were calibrated at four different temperatures against a certified mercury thermometer in a water bath at temperatures ranging from 30 to 42°C. A linear regression of the relationship between the measured temperatures and those from the certified thermometer was used post-test to adjust the pill and thermistor measurements. The laser Doppler probe was calibrated using the manufacturer provided motility standard and zero cell. Skin blood flow values were expressed as percent change from rest ( $\% \Delta SBF$ ) since absolute values within an individual can vary markedly over the surface of the forearm (Johnson, 1984). The gas analysis system was calibrated with standard gas concentrations (21% O<sub>2</sub>, balance N<sub>2</sub>; 10% O<sub>2</sub>, 10% CO<sub>2</sub>, balance N<sub>2</sub>), and the pneumotach was calibrated using a 3-L syringe. The cycle ergometer was calibrated to  $\pm 10$  Watts.

#### *Plasma Volume and Red Cell Mass*

PV and RCM were measured during the morning of the first day of hospitalization (ambulatory control) and at the same time on the last day of BR (day 14) using the <sup>125</sup>I-labeled human serum albumin (RISA) dilution method and a red cell labeling technique with <sup>51</sup>Cr, (Glass, 1973). Subjects remained supine for at least 30 min before and throughout PV and RCM measurements. Blood volume was calculated as the sum of PV and RCM. Peripheral hematocrit was measured using the microhematocrit method. Whole body hematocrit was calculated from the ratio of RCM to calculated blood volume. F-cell ratio was calculated as the ratio of whole body hematocrit to venous hematocrit corrected for trapped plasma (0.96).

#### *Data Analysis*

The first submaximal exercise test was considered a familiarization session. Data from the second pre-BR submaximal exercise test was compared with the data collected during the post-BR test. Measurements of  $T_{in}$ ,  $\% \Delta SBF$ , SR,  $VO_2$ , HR,  $T_{sk}$ ,  $T_{arm}$ ,  $T_{chest}$ ,  $T_{thigh}$ , and  $T_{calf}$  at specific time points in the testing protocol were expressed as the mean of two minutes of data collected at the end of rest and ending at min 5, 10, 15, and 20 of the 40%  $VO_{2pk}$  stage, and at min 5, 10, 15, and 20 of



the 65%  $\text{VO}_{2\text{pk}}$  stage. Pre- to post-BR comparisons of these variables were made using planned comparisons from pre- to post-BR at specific time points using the appropriate Bonferroni correction for the number of comparisons within each analysis. Pre- to post-BR change in these variables from rest to the end of exercise, body weight, BHS, TSL, PV, hematocrit, and RCM were compared using paired t-tests.

$T_{\text{in}}$  was plotted against  $\% \Delta \text{SBF}$  and SR for each subject pre- and post-BR. A linear regression describing the slope of each response was determined. The  $T_{\text{in}}$  thresholds for initiation of sweating and cutaneous vasodilation were calculated from the regression equation at a local sweating rate of 0.05 mg/cm<sup>2</sup>/min (Kolka, 1987) and a  $\% \Delta \text{SBF}$  of 25%. Pre- to post-BR thresholds for the onset of sweating and vasodilation and the slope of these responses were compared using paired t-tests.

Data are reported as mean  $\pm$ SE, unless otherwise stated. Statistical significance was determined *a priori* as  $p \leq 0.05$ .

## RESULTS

Pre-BR mean ( $\pm$ SD) supine  $\text{VO}_{2\text{pk}}$  of the subjects was  $2.52 \pm 0.54 \text{ l} \cdot \text{min}^{-1}$  ( $31.6 \pm 2.6 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ). Subjects attained a peak maximal HR of  $174 \pm 15 \text{ bpm}$  ( $91 \pm 7\%$  of age-predicted maximal HR [ $220 - \text{age}$ ]) and a peak respiratory exchange ratio of  $1.19 \pm 0.11$ . The peak exercise intensity was  $146 \pm 37 \text{ Watts}$ .

All subjects completed the entire submaximal exercise protocol both pre- and post-BR. Resting or exercise  $\text{VO}_2$  were similar pre- to post-BR at rest and during the 40%  $\text{VO}_{2\text{pk}}$  stage (Figure 1). However,  $\text{VO}_2$  was significantly less after BR at the end of the 65%  $\text{VO}_{2\text{pk}}$  stage. HR during the 40%  $\text{VO}_{2\text{pk}}$  stage was unchanged after BR, but was significantly greater after BR at rest and during the 65%  $\text{VO}_{2\text{pk}}$  exercise stage than pre-BR. SBP, DBP, or MAP (Table 1) were similar pre- to post-BR both at rest and during exercise. There was no difference in the ambient conditions of the testing room pre- ( $23.1 \pm 0.2^\circ\text{C}$ ,  $55.8 \pm 4.6 \%$ RH) to post-BR ( $23.6 \pm 0.3^\circ\text{C}$ ,  $55.4 \pm 2.8 \%$ RH).

**INSERT FIGURE 1 HERE**

Post-BR  $T_{in}$  (Figure 1) and  $T_{body}$  were significantly greater than pre-BR at rest and throughout exercise. Similarly, BHC was significantly greater after BR at rest ( $2,255 \pm 188$  vs.  $2,278 \pm 185$  kcal) and at the conclusion of exercise ( $2,290 \pm 195$  vs.  $2,320 \pm 193$  kcal) when compared to pre-BR. However, the change in  $T_{in}$  and  $T_{body}$  from rest to the end of exercise and BHS were not different pre- to post-BR ( $T_{in}$ :  $+0.59 \pm 0.07$  vs.  $+0.60 \pm 0.07$  °C;  $T_{body}$ :  $+0.67 \pm 0.11$  vs.  $+0.81 \pm 0.14$  °C; BHS:  $+35.0 \pm 9.2$  vs.  $+40.5 \pm 11.5$  kcal).

The  $\% \Delta SBF$  from rest during the 40%  $VO_{2pk}$  stage was not different from pre-BR to post-BR (Figure 2A). However, by minute 5 of the 65%  $VO_{2pk}$  stage and throughout the remainder of the exercise, post-BR  $\% \Delta SBF$  was significantly less than pre-BR. The threshold for the  $SBF/T_{in}$  relationship was delayed significantly after BR ( $37.17 \pm 0.18$  vs.  $37.51 \pm 0.17$  °C) and the slope of the response tended to be reduced ( $536 \pm 184$  vs.  $201 \pm 46$   $\% \Delta / ^\circ C$ ;  $p=0.08$ , Figure 2B).

**INSERT FIGURE 2 HERE**

There was no difference in TSL during submaximal exercise pre- to post-BR ( $0.42 \pm 0.06$  vs.  $0.44 \pm 0.08$  kg). Mean post-BR chest sweating rate was not significantly different from pre-BR at any time point (Figure 3A). The slope of SR response ( $4.03 \pm 1.69$  vs.  $2.33 \pm 0.90$  mg/min/cm<sup>2</sup>;  $p=0.48$ ) was not changed significantly after BR, but the  $T_{in}$  at the onset of sweating was increased significantly ( $37.06 \pm 0.11$  vs.  $37.34 \pm 0.06$  °C, Figure 3B).

**INSERT FIGURE 3 HERE**

Mean  $T_{sk}$  was not different at rest or during exercise from pre- to post-BR, but, regional differences existed (Figure 4).  $T_{arm}$  and  $T_{thigh}$  were unchanged from pre- to post-BR. However, at

rest and at min 5 of the 40%  $\text{VO}_{2\text{pk}}$  stage,  $T_{\text{chest}}$  was higher and  $T_{\text{calf}}$  was lower after BR compared to pre-BR. There were no pre- to post-BR differences at these sites from min 10 of the 40%  $\text{VO}_{2\text{pk}}$  stage through the remainder of the exercise protocol.

#### **INSERT FIGURE 4 HERE**

PV decreased significantly ( $-11.0 \pm 1.5\%$ ) as a result of BR whether expressed in absolute units (Pre:  $3,259 \pm 177$ , Post:  $2,894 \pm 138$  ml) or relative to body mass (Pre:  $43.3 \pm 0.9$ , Post:  $38.4 \pm 0.9$   $\text{ml} \cdot \text{kg}^{-1}$ ). However, there was no change in body weight from pre- to post-BR (Pre:  $77.2 \pm 6.4$ , Post:  $77.7 \pm 6.3$  kg). RCM also was significantly decreased from pre- to post-BR ( $-5.5 \pm 2.1\%$ ) when expressed as absolute values (Pre:  $1,982 \pm 115$ , Post:  $1,869 \pm 89$  ml) or relative to body mass ( $26.4 \pm 0.8$  vs.  $24.8 \pm 0.8$   $\text{ml} \cdot \text{kg}^{-1}$ ). Consequently, there was a significant decrease in blood volume (Pre:  $5,258 \pm 313$ ; Post:  $4,770 \pm 232$  ml). Peripheral (Pre:  $42.8 \pm 0.9$ , Post:  $44.5 \pm 1.2$ ) and whole body (Pre:  $37.9 \pm 0.8$ , Post:  $39.3 \pm 1.0$ ) hematocrit were significantly greater after BR compared to pre-BR. F-cell ratio was unchanged from pre- ( $0.92 \pm 0.1$ ) to post-BR ( $0.92 \pm 0.0$ ).

#### **DISCUSSION**

Our current findings confirm the results of previous studies that reported an impairment of thermoregulation after BR as an analogue of spaceflight. Our results suggest that this impairment is due to changes in both the vasodilatory and sweating responses. Delayed onset of SBF and SR responses relative to  $T_{\text{in}}$  after BR may suggest a resetting of the central control of thermoregulation. Although not statistically significant, the strong tendency for a reduced slope of the  $\text{SBF}/T_{\text{in}}$  relationship also may suggest a peripheral vascular adaptation. These changes did not prevent our subjects from completing this relatively mild exercise protocol after BR. However, the changes could have a negative impact during exercise in less temperate conditions, with more intense or upright exercise, following long duration BR or spaceflight (Fortney, 1998), and/or during work in impermeable garments such as the NASA LES or Extravehicular Activity (EVA) suits.

*Core Temperature*

Resting  $T_{in}$  was significantly elevated after BR in our subjects by an average of  $0.31 \pm 0.12$  °C. Under conditions similar to our study, Ertl et al. (1998) reported that rectal temperature ( $T_{rec}$ ) was significantly elevated during supine rest and after 24 hours of BR. Fortney (1987) also reported that  $T_{es}$  was significantly elevated after 12 days of BR during semi-recumbent rest in a warm environment (30°C, 50-60% RH). Crandall et al. (1994) observed a significant increase in supine resting oral temperature ( $T_{or}$ ) after 15 days of BR in subjects wearing a water-perfused suit prior to the introduction of warm water. In contrast, Greenleaf and Reese (1980) observed no change in supine resting  $T_{rec}$  in a cool environment in male subjects after 14 days of BR. An explanation for differences in these results is unclear, but an increased resting  $T_{core}$  after BR appears to be the predominant finding.

During exercise in our investigation,  $T_{in}$  was elevated after BR as compared to pre-BR ( $0.30 \pm 0.03$  °C), similar to other investigations (Ertl, 1998; Fortney, 1987; Greenleaf and Reese, 1980). However, the change in  $T_{in}$  from rest to the end of exercise in our study after BR was not different than pre-BR. Ertl et al. (1998) reported similar results during 70 min of moderate exercise (58% pre-BR  $VO_2max$ ) after only 24 hours of BR. In contrast, both Greenleaf and Reese (1980) and Fortney (1987) observed a greater increase in  $T_{core}$  from rest to the end of exercise after 14 days of BR. Subjects in the study by Greenleaf and Reese (1980) performed supine exercise at a lower exercise intensity than in our study, but exercised for a 70 min. Fortney (1987) employed a shorter exercise protocol (30 min) but at a higher exercise intensity (60% pre-BR  $VO_2max$ ), in a semi-recumbent position, and in a warm room (30°C). The differences between the results of these studies and ours may be related to the greater severity of the post-BR exercise challenge in the other investigators' studies.

Increased  $T_{core}$  during rest and exercise may be the result of increased heat production, changes in set point of  $T_{core}$  for heat loss responses, and/or a reduced transfer of heat from the body. Heat production at rest and during submaximal exercise has been reported to be unchanged

or decreased as a result of BR; there have been no reports of increased submaximal exercise  $\text{VO}_2$  (Fortney, 1996). In our subjects, there was no change in heat production either at rest, during the 40%, and the first half of the 65%  $\text{VO}_{2\text{pk}}$  exercise stage as exhibited by no change in  $\text{VO}_2$ ;  $\text{VO}_2$  was significantly less after BR at the end of the 65%  $\text{VO}_{2\text{pk}}$  stage. Greenleaf et al. (1996) observed no change in resting metabolic rate after 25 days of BR. Greenleaf and Reese (1980) observed no change in  $\text{VO}_2$  during exercise at 43% of pre-BR  $\text{VO}_{2\text{max}}$  after 14 days of BR, but Greenleaf et al. (1996) observed a decrease in exercise  $\text{VO}_2$  at 61% of pre-BR  $\text{VO}_{2\text{pk}}$  after 11 days of BR. Therefore, it is unlikely that increased heat production was responsible for the elevated  $T_{\text{core}}$  after BR.

#### *Core Temperature Set Point and Thresholds for the Onset of SBF and SR*

A change in  $T_{\text{core}}$  set point in this BR study may be related to loss of heat acclimation or changes in circadian rhythm. Heat acclimation is associated with decreased resting and exercise  $T_{\text{rec}}$  and no change in heat storage (Buono, 1998). Our subjects had elevated  $T_{\text{in}}$  at rest and during exercise, consistent with de-acclimation, and no change in heat storage from pre- to post-BR. Buono et al (1998) observed in data from earlier investigations that the thresholds for the onset of sweating and vasodilation appear to decrease to a similar magnitude after acclimation as the decrease in resting  $T_{\text{core}}$ . In our study,  $T_{\text{in}}$  was elevated at rest ( $+0.31 \pm 0.12^\circ\text{C}$ ) after BR to a similar magnitude as the increase in  $T_{\text{in}}$  at the onset of vasodilation ( $+0.33 \pm 0.09^\circ\text{C}$ ) and the onset of sweating ( $+0.28 \pm 0.11^\circ\text{C}$ ).

Change in  $T_{\text{core}}$  set point also may have been the result of a circadian shift induced by BR. In a 17-d BR, Monk et al. (1997) demonstrated that the sinusoidal shape of the circadian curve describing  $T_{\text{core}}$  was maintained during bed rest, but the amplitude of the curve was reduced. In agreement with this observation, Lkhagva (1980) observed that the nadir of the circadian curve was increased by  $0.22^\circ\text{C}$  in three men after 7 days of BR. Therefore, although our testing was conducted at the same time of day from pre- to post-BR (mid- to late morning), the post-BR  $T_{\text{in}}$  may have been elevated relative to pre-BR due to a change in the amplitude of the circadian curve.

This circadian change also may have influenced the thresholds for the onset of SBF and SR. The onset of SBF and SR with exercise (Stephenson, 1984) and passive heating (Aoki, 1997) have been shown to be correlated with circadian rhythm.

### *Skin Blood Flow*

Resting  $T_{in}$  in the present study also may have been elevated due to changes in SBF; SR at rest was very small and was not affected by BR. Resting SBF could not be assessed by the laser Doppler technique that we used in this investigation, but  $T_{sk}$  is often used as an index of regional SBF. Although resting mean  $T_{sk}$  was not altered after BR, resting  $T_{calf}$  was reduced and  $T_{chest}$  was elevated after BR. Similar observations were made during short-duration (90 min) head-down tilt (Novak, 1988), BR (Krupina, 1977; Tizul, 1974), and spaceflight (Novak, 1980). These changes may be reflective of an altered blood flow distribution, an increased central versus peripheral distribution of blood volume, which has been a consistent finding after BR (Fortney, 1996), and/or a greater relative vasoconstriction in the lower body after BR. Perhaps heat loss in our subjects at rest was reduced and  $T_{in}$  increased due to a shift in blood flow away from the limbs where the high surface area to volume ratio facilitates heat exchange and towards the trunk where the opposite is true. These regional  $T_{sk}$  differences disappeared in our subjects once exercise was commenced.

Our results suggest a significant impairment of SBF responses after BR. During exercise, the  $\% \Delta SBF$  from rest was reduced from pre- to post-BR in our subjects by the 5th minute of exercise at 65%  $VO_{2pk}$ . The onset of vasodilation was delayed, and the sensitivity (slope of the response relative to  $T_{in}$ ) tended to be reduced. Ertl et al. (1998) reported no change in SBF from pre- to post-BR during exercise despite an increased  $T_{rec}$ , suggesting a decreased sensitivity of the SBF response to increased  $T_{rec}$ . Crandall et al. (1994) reported a delayed onset of skin vasodilation and a decreased SBF sensitivity in men at rest after 15-day bed rest when  $T_{or}$  was raised passively with a water-perfused suit.

Altered SBF responses observed during exercise after BR may be due to several factors. A reduction in PV, even without a decreased RCM, has a powerful inhibitory effect on SBF during

exercise (Nadel, 1980). Lower PV may increase competition between the skin and muscle vascular system to supply their respective needs (Rowell). The reduced RCM as observed in this study may further reduce SBF as decreased oxygen carrying capacity of the blood may require that blood flow be diverted from the skin to the exercising muscles, although this has not been conclusively proven (Sawka & Coyle, 1999). Crandall et al. (1994) suggested that changes observed in thermoregulatory control of SBF after BR during passive heating may be related to a significant hypovolemia coupled with an increased plasma sodium and osmotic concentration, although PV loss during BR is typically isotonic (Fortney, 1996).

In addition, there may be a decreased ability to translocate blood from the splanchnic region to the skin. Savilov (1990) observed a decreased ability to reduce blood volume in the gut during lower body negative pressure after BR, and this decreased ability to decrease splanchnic blood flow also may occur during exercise stress. Previous investigators (Roberts, 1977) have suggested that fitness alters the slope of the SBF response and that fitness may effect the ability to increase SBF by shunting blood from the viscera (Ho, 1997). In our subjects, although not measured, aerobic fitness would have been expected to decline by 9-10% as a result of BR (Convertino, 1996), and the slope of the SBF response tended to be reduced.

It is unclear at this time whether the reduction in SBF following BR is related to increased vasoconstriction or decreased active vasodilation. At the onset of body heating, the release of vasoconstrictor tone causes an increase in SBF of approximately 60-100% above resting values (Rowell, 1974; Kellogg, 1989), similar to increases we observed in SBF during the 40%  $\text{VO}_{2\text{pk}}$  stage both pre- ( $85 \pm 51\%$ ) and post-BR ( $38 \pm 17\%$ ). As body heating continues, active vasodilation occurs resulting in a much greater increase in SBF (100-500%) above resting. In the present study a much greater impairment in SBF response was evident during the 65%  $\text{VO}_{2\text{pk}}$  stage, when active vasodilation was more likely to predominate; SBF was reduced from  $211 \pm 53\%$  at the end of pre-BR exercise to  $96 \pm 31\%$  at the end of post-BR exercise. These data do not conclusively prove the mechanism of the reduction in SBF during exercise after BR involves active vasodilation, but

previous investigators have suggested that active vasodilation is impaired by a reduction in PV (Kellogg, 1990) or a decrease in fitness (Thomas, 1999) as would occur after BR.

### *Sweating Rate*

In the present study, we observed no change in local SR during exercise, in the slope of the SR/ $T_{in}$  response, or in TSL, but a delayed onset of SR relative to  $T_{in}$ . Results with regard to SR from other BR investigations vary. Following 24 hours of BR, neither local SR nor change in body weight during exercise were different than following one hour of BR (Ertl, 1999). After 14-days of BR, TSL during exercise was unchanged despite a significantly greater increase in  $T_{rec}$  (Greenleaf & Reese, 1980). However, after 12 days of BR women in the study by Fortney (1987) had a significantly elevated TSL. Alterations in SR response as a result of BR are unclear at this time; Johnson et al. (1981) observed high variability in SR responses. Using our specific protocol, long duration BR (>14 d) may be required to observe significant changes in the slope of the SR/ $T_{in}$  response, as was seen after long duration spaceflight (Fortney, 1998).

Data from ambulatory subjects would suggest that reduced PV, as observed during BR, would be expected to alter SR responses. Hypovolemic subjects would be expected to have a decrease in the slope of the SR/ $T_{es}$  response, decreased TSL, and no change in the  $T_{es}$  threshold for the onset SR during exercise (Fortney, 1981). In contrast, we observed a delayed onset of the SR relative to  $T_{in}$  and no change in the slope of the response. Contradictions in the findings of these studies may be related an acute response to decreased PV due to diuretic usage in ambulatory subjects versus an adaptation to PV loss through inactivity and BR. However, it is more likely that the shift in the  $T_{in}$  threshold for SR observed in our BR subjects was related to a circadian effect.

### *Spaceflight, Countermeasures, and Rehabilitation*

If thermoregulation is impaired during spaceflight, this may impact inflight activities, including countermeasure exercises, as the microgravity and spacecraft environment may further challenge the thermoregulatory system. From the 823 days of available data during the NASA-Mir



program (Figure 5), the maximum temperature measured in the main module of the Mir Space Station was between 20 and 25°C on 217 days, was between 25 and 30°C on 528 days, and greater than 30°C on 78 days. The cabin humidity was primarily between 40% and 60% (618 days), but also was greater than 60% (121 days). The majority of days would be classified by the American College of Sports Medicine as moderate risk for heat injury, but many days would be considered high risk.

Leach et al. (1978) reported that evaporative water loss was reduced by an average of 11% in nine Skylab crewmembers during their inflight exercise as compared to preflight. The authors suggested that the sweating responses may have been reduced in the microgravity environment through the formation of a film of sweat on the surface of the skin, because of reduced sweat drippage, which impaired air flow across the skin and sweat evaporation. Further, the reduced gravity would have impaired natural convection, in which air rises or falls due to differences in density (Novak, 1991). In addition, low air flow in the cabin of space vehicles during spaceflight may limit heat loss capacity (Fortney, 1991).

Impaired thermoregulation also may affect crewmembers during re-entry and landing while wearing the NASA LES. Recent data collected during the landing of STS-90 in April of 1998 suggests that  $T_{in}$  in crewmembers is elevated even at rest during landing even though they were wearing a liquid cooling garment (Rimmer, 1999). This elevated  $T_{in}$  would be exacerbated should crewmembers be required to perform an emergency egress from the Space Shuttle; crewmembers would have to disconnect the liquid cooling garment from the thermoelectric cooling unit in the Shuttle. Dependent upon the level of inflation of the anti-gravity suit, the work required to walk in increases metabolic rate by nine to eleven fold above rest (Bishop, 1999). Upright posture may further exacerbate the situation (Johnson, 1981) during egress.

Changes in thermoregulatory control may be more extreme after long duration spaceflight than observed in the present investigation. In a previous study, we (1998) reported that the thermoregulatory mechanisms were severely impaired in two crewmembers when performing this same exercise protocol following 115 days of spaceflight onboard the Mir Space Station.

Postflight, neither crewmember completed the 65% preflight  $\text{VO}_{2\text{pk}}$  stage. During the postflight exercise test, there was a faster rise in  $T_{\text{in}}$ , and both crewmembers had reduced SBF and SR responses. Thermoregulation after spaceflight was altered in these long-duration crewmembers despite participating in the Russian exercise countermeasures program.

Similarly, Greenleaf and Reese (1980) reported that thermoregulatory responses were not maintained during a 14-d BR when subjects were performing either supine isometric or isotonic exercise protocols. However, the investigators were able to restore thermoregulatory responses in these subjects during the ambulatory recovery periods during which subjects performed daily upright cycle exercise for the final 10 days preceding the next BR period. Perhaps the countermeasures employed by Greenleaf and Reese (1980) during BR may have been more efficient if they had been of greater intensity or duration or included an orthostatic component to more thoroughly challenge the thermoregulatory system.

Dependent upon the length of time required to re-acclimate after spaceflight, impaired thermoregulation also may impact rehabilitation plans for long-duration crewmembers after spaceflight. Most U.S. astronauts live and train at NASA-Johnson Space Center in Houston, TX, where they may be exposed to high heat and humidity, especially during the spring and summer months. Therefore, care has been taken to limit crewmembers exposure to these conditions.

### *Limitations*

Several limitations were inherent in the design and the implementation of this investigation. First, the protocol for this study was designed to be applied to our previous long duration spaceflight investigation (Fortney, 1998). A protocol was selected that would allow the crewmembers to complete the exercise protocol without exceeding HR limits imposed by the flight crew surgeon, could be performed in ambient conditions as a climate chamber was not readily available at all potential landing sites, and would not result in excessive fatigue or risk to crewmembers. The present protocol was selected as a compromise to elicit sufficient stress to

produce the desired thermoregulatory responses yet require minimal time so as not to interfere with a limited testing schedule available in consideration of other postflight investigations.

Second, our SBF results were somewhat limited because we were able only to assess relative change in SBF from rest and did not measure an absolute resting SBF. Since resting SBF has been reported to be reduced after BR (Crandall, 1994), it is likely that the absolute impairment of SBF is more severe than the relative responses that we currently report.

Third, due to constraints imposed by other companion investigations, PV and RCM measurements were obtained within 24 h after the performance of the submaximal exercise protocol performed on BR day 13. High intensity exercise has been shown to increase PV for up to 48 h. Although the intensity of exercise in this study was low, but it is possible that the exercise performed in this study may have partially restored the BR-induced PV loss at the time of measurement.

### *Summary*

Thirteen days of BR resulted in higher  $T_{in}$  both at rest and during exercise without a significant increase in BHS. Higher  $T_{in}$  during rest and exercise appear to be related to reduced heat loss due to altered SBF and SR responses. These effects have the potential to impact the activities of astronauts during and after spaceflight, especially following long duration missions. In addition, patients in BR who may be undergoing heat or exercise therapies also may be adversely affected.

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**FIGURE LEGENDS***Figure 1*

$T_{in}$  was significantly greater at rest and throughout exercise after BR compared to pre-BR (Panel A). HR was significantly increased after BR at rest and during the 65%  $VO_{2pk}$  stage (Panel B), but  $VO_2$  was significantly less after BR at the end of the 65%  $VO_{2pk}$  exercise stage (Panel C).

\*Significantly different from pre-BR

*Figure 2*

$\% \Delta SBF$  (n=6) was reduced after BR compared to pre-BR at 5, 10, 15, and 20 min of exercise at 65% pre-BR  $VO_{2pk}$  (Panel A). Also, the onset of skin blood flow was significantly delayed and the slope of the response tended to decrease ( $p=0.08$ ) relative to  $T_{in}$  from pre- to post-BR (Panel B).

\*Significantly different from pre-BR

*Figure 3*

No change was observed in sweating rate across the exercise protocol from pre- to post-BR (Panel A). However, the onset of sweating was significantly delayed after BR (Panel B). \*Significantly different from pre-BR

*Figure 4*

$T_{chest}$  and  $T_{calf}$  were significantly different from pre- to post-BR during rest at and min 5 of the 40%  $VO_{2pk}$  stage. No differences were observed from pre- to post-BR in  $T_{arm}$  and  $T_{thigh}$ .

\*Significantly different from pre-BR

*Figure 5*

Maximum temperature and humidity (823 days of available data) measured in the main module of the Russian Mir Space Station from the NASA-Mir Program during which US astronauts participated in long duration space flights. Zones of risk of heat exhaustion or heat stroke while exercising vigorously in a hot environment from American College of Sports Medicine Position Stand on "Heat and Cold Illness During Distance Running"

TABLE 1

Blood pressure responses to submaximal exercise before and after BR at minutes 5 and 15 of each exercise stage (40 and 65% pre-BR  $\text{VO}_2\text{pk}$ )

		Rest	40%-5	40%-15	65%-5	65%-15
SBP	PRE	119±3	149±5	153±4	173±5	173±2
	POST	121±3	150±4	151±4	176±3	173±4
DBP	PRE	76±4	77±3	75±4	74±3	72±4
	POST	75±2	74±4	73±3	72±2	70±3
MAP	PRE	90±3	101±4	101±3	107±3	106±3
	POST	91±2	99±3	99±3	107±1	104±3

FIGURE 1

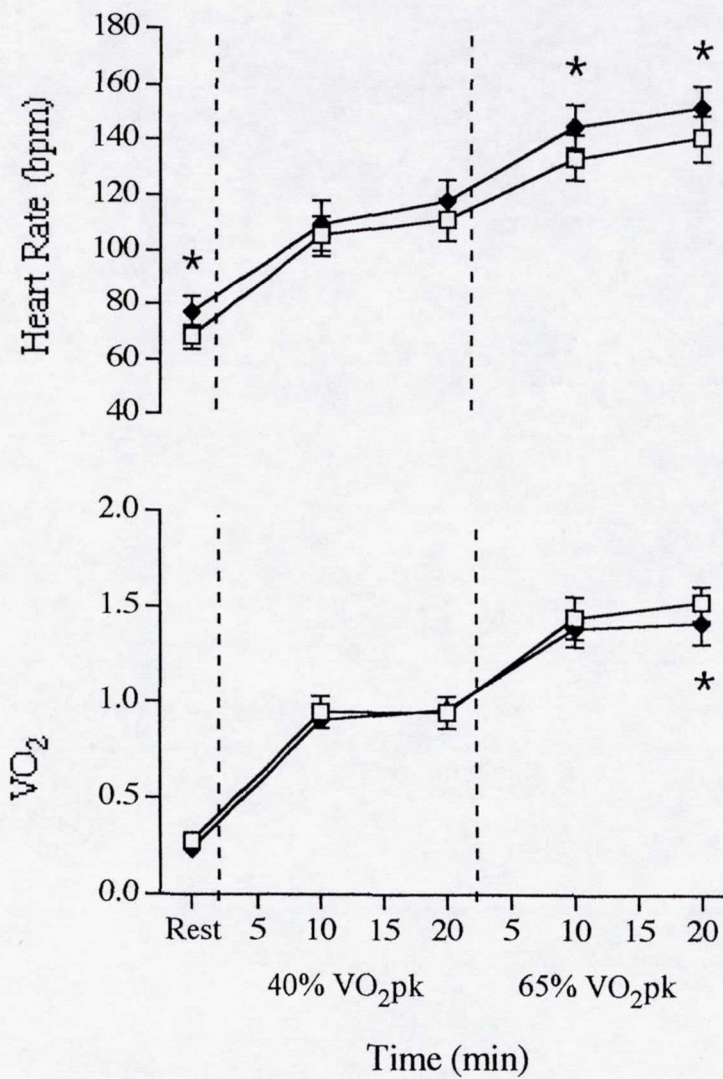
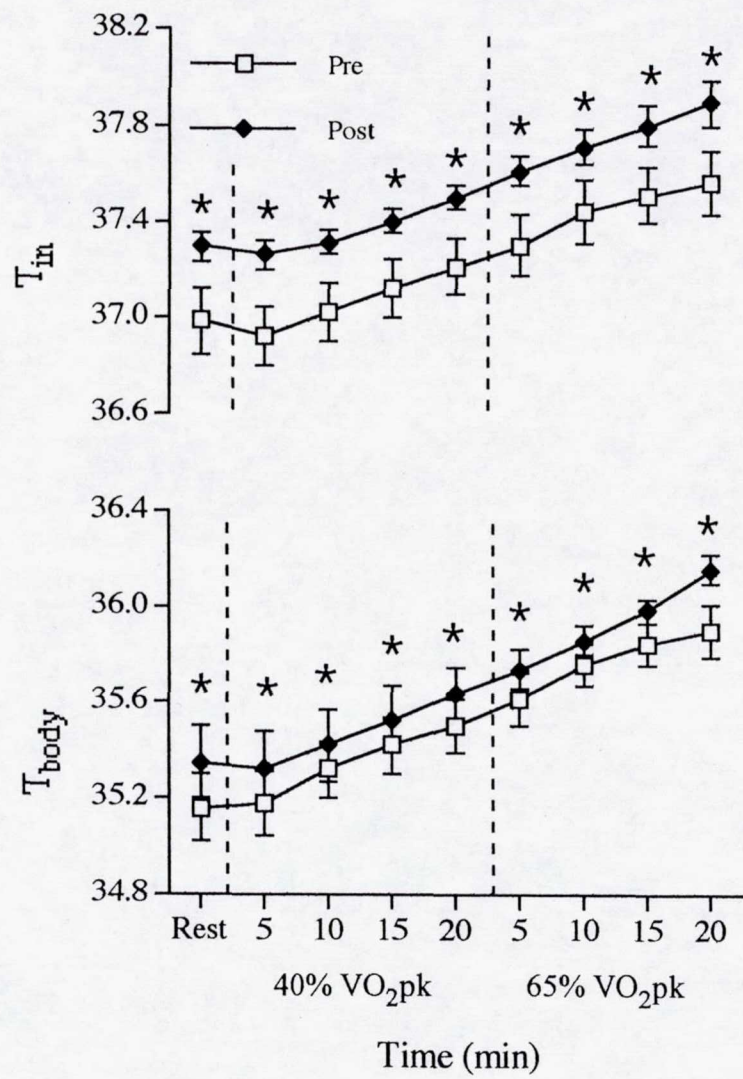


FIGURE 2

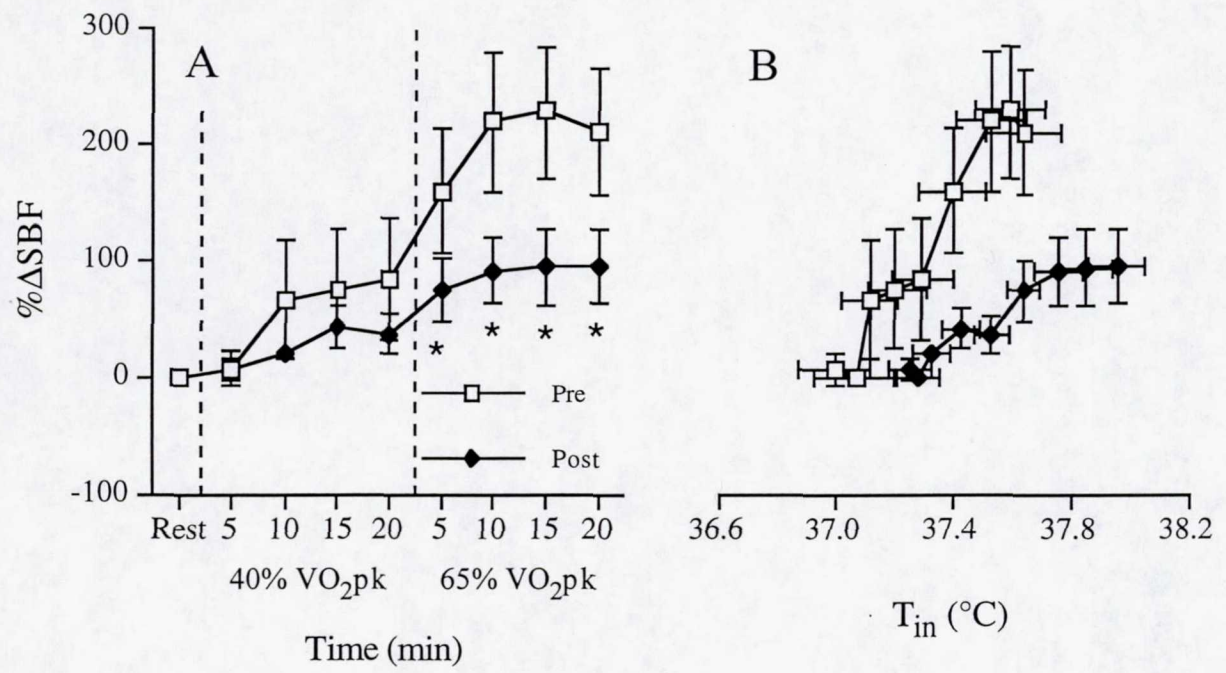


FIGURE 3

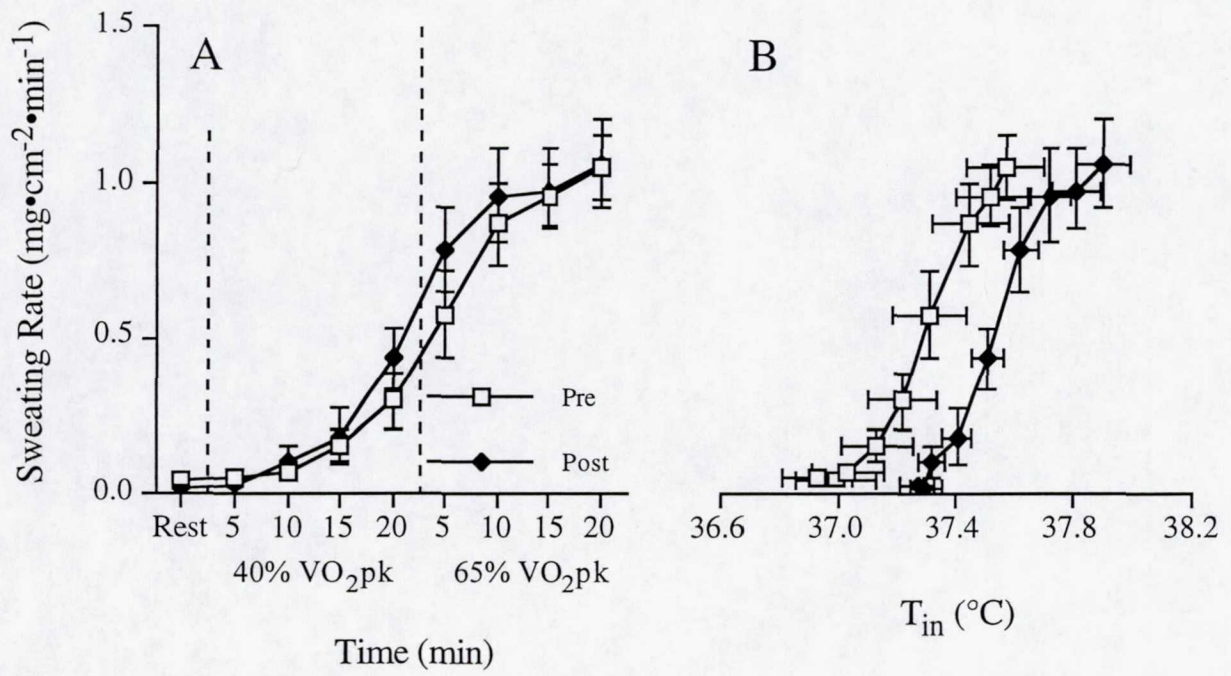




FIGURE 4

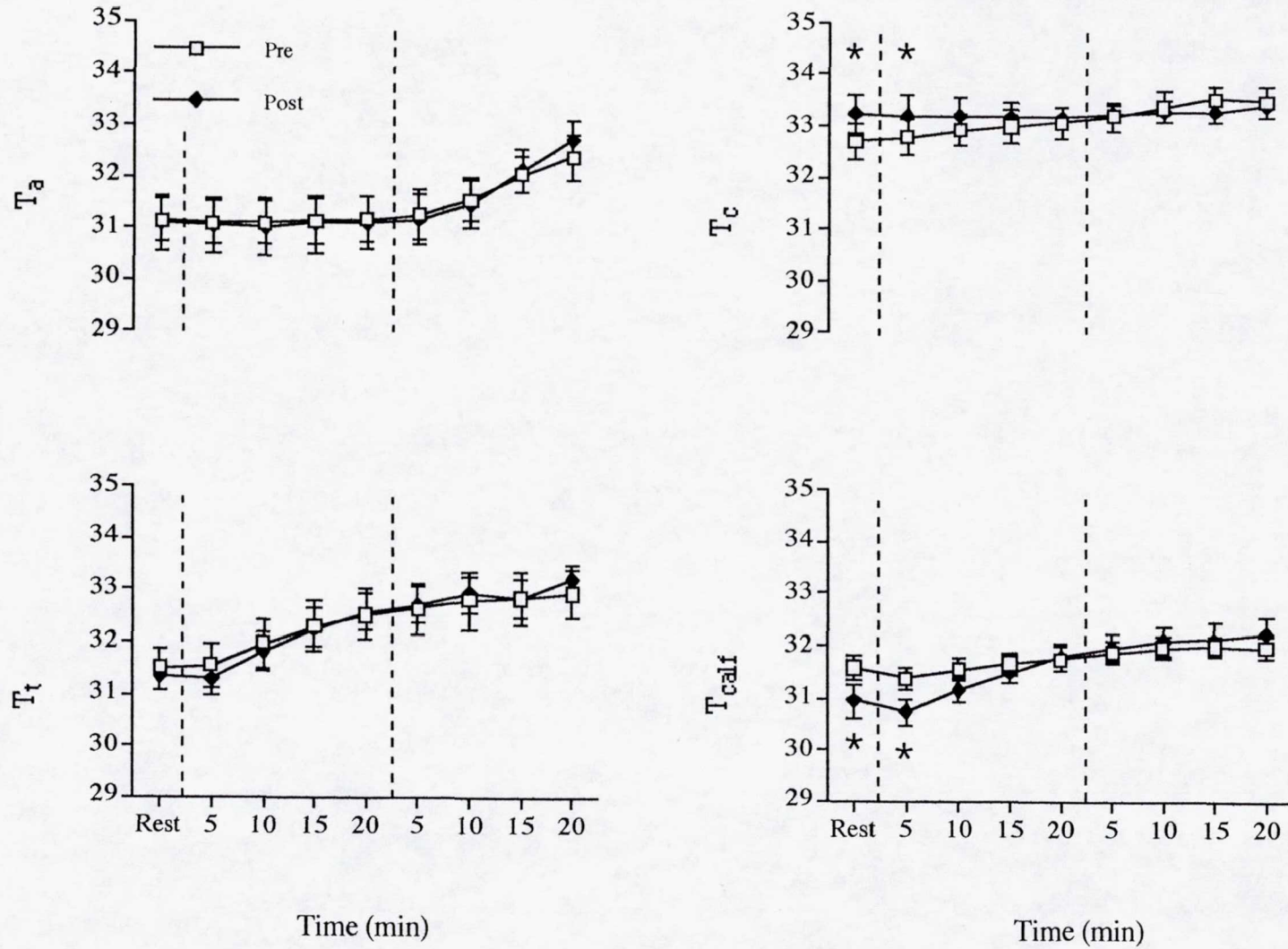


FIGURE 5

