

## PRIOR EXERCISE ALTERS RESPONSES TO HEMORRHAGE

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**ABSTRACT**—Traumatic injuries often occur to individuals while exercising. The author sought to determine whether exercise before injury resulting in hemorrhage would alter cardiovascular, metabolic, and neuroendocrine responses. Fifteen chronically instrumented splenectomized immature female swine were trained to run on a treadmill at 70% of maximum heart rate for 60 min. In six swine, responses to exercise were evaluated and found to return to baseline after 60 min of recovery. Swine were then randomly assigned to exercise ( $n = 7$ ) or rest ( $n = 8$ ) followed by hemorrhage of 25 mL/kg for 60 min then observed for an additional 60 min. The decrease in mean arterial pressure (MAP) was less after exercise,  $26 \pm 9$  mmHg compared with  $49 \pm 2$  mmHg with rest, with the difference sustained during the posthemorrhage period. Cardiac output decreased similarly in both groups. Posthemorrhage lactate and glucose concentrations were lower in exercise. The increase in plasma epinephrine was reduced in exercise, with significantly lower levels in epinephrine and norepinephrine noted posthemorrhage. Vasopressin levels and plasma renin activity were not different. In response to hemorrhage after exercise, blood pressure is better maintained although catecholamine levels were reduced, suggesting increased adrenoceptor sensitivity. In addition, indices of increased glucose utilization and correction of lactate acidosis support a metabolic shift after exercise. Prior exercise alters responses to hemorrhage that mask the extent of hypovolemia and should be considered in the initial evaluation of a patient with hemorrhage caused by traumatic injuries.

**KEYWORDS**—Cardiac output, blood pressure, vasopressin, catecholamines, plasma renin activity

### INTRODUCTION

Traumatic injuries are often incurred in the presence of confounding factors, such as dehydration, ingestion of alcohol, or disease (1–4). These confounding factors modify compensatory responses to hemorrhage and complicate the delivery of health care, thus impacting morbidity and mortality. Individuals who participate in physical exercise are not immune to traumatic injuries. These injuries, if extensive, can involve a significant loss of blood—for example, a runner or a bicyclist hit by a car or a soldier in battle who is seeking cover by running from place to place and is subsequently injured (5, 6). An understanding of the responses of patients who have been exercising before injury causing hemorrhagic hypotension could aid in their care.

Exercise acutely reduces blood volume, increases plasma lactate concentrations, and alters the hormonal/immunologic milieu, all of which may adversely affect compensatory response to hemorrhage. Convertino and colleagues (7–14) have demonstrated the positive effects of exercise in ameliorating or attenuating blood pressure reductions in response to lower-body negative pressure, a surrogate to hemorrhage. The beneficial effects of exercise are present for more than 24 h. Various mechanisms are suggested to contribute to the protective effects of exercise. Gillen et al. (15) and Mack et al. (16) reported

that after exercise, greater increases in peripheral vascular resistance occur in response to reductions in central blood volume. For a given decrease in central venous pressure, there was a greater reduction in forearm blood flow. Convertino (7) reported that this response is caused by increased  $\alpha$ -1 adrenoceptor responsiveness after exercise, eliciting a greater increase in vascular resistance and blood pressure for a given increase in sympathetic tone. In addition, Convertino and Adams (8) demonstrated an increase in heart rate (HR) caused by a given decrease in carotid pressure for 24 h after exercise. Gillen et al. (15) and Mack et al. (16) suggested that some of these differences may be influenced by the expansion of blood volume after exercise. Although the benefits of exercise have been identified with acute decreases in central blood volume induced by lower-body negative pressure or passive standing or head-up tilt, responses in the presence of hemorrhage have not been investigated. Furthermore, in many of these studies, exercise was performed well before the hypotensive challenge to the cardiovascular system. Alterations immediately after exercise have not been extensively investigated.

We have attempted to mimic in a swine model what may occur to a physically active individual participating in moderate exercise and subsequently injured incurring blood loss resulting in hypotension. We hypothesized that exercise would enhance compensatory mechanisms in response to hemorrhage by maintaining blood pressure and cardiac output (CO) at higher levels for a given volume of blood loss.

### MATERIALS AND METHODS

#### *Animal use*

These experiments used 15 immature Yorkshire-cross swine obtained from a commercial breeder. The swine were housed in a common indoor area for 1 to 3 weeks before enrollment in the experiment. Housing the swine indoors allowed time for them to acclimate to the institutional environment and diet. The swine were fed Purina Pig Chow (Ralston Purina Co, St Louis, Mo) and

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provided water *ad libitum*. All procedures were approved by the Institutional Animal Care and Use Committee (Letterman Army Institute of Research) and conducted in compliance with the Guidelines for the Care and Use of Laboratory Animals.

### Exercise program

All the swine were trained to exercise on a motor-driven treadmill. They were placed in an open box on the treadmill and acclimated to the exercise procedures. On the initial day of acclimation, they were brought to the exercise room in a transport cage and exposed to the noise of the running treadmill for an hour. The next day, the swine were placed in the treadmill box for an hour and then into a sling for an additional hour with the treadmill running. On subsequent days, they were progressively run on the treadmill until they could run continuously for 1 h at a speed that was estimated to elicit a workload of 70% of maximum. On alternate days, the swine were trained to be partially restrained in a sling for an hour after exercise. They were run for an hour 5 days per week for 2 weeks before enrollment in the experiment. They then underwent surgery to place catheters. After a recovery period of 3 to 5 days, the swine reinitiated the exercise training protocol. The experimental procedures were conducted 7 to 10 days after surgery.

### Surgical procedures

Instrumentation of the swine followed a well-established procedure (3, 4, 17). Briefly, after an overnight fast, they were given an i.m. injection of atropine sulfate (0.8 mg/kg), ketamine HCl (2.2 mg/kg), and xylazine (2.2 mg/kg). Halothane anesthesia was introduced by mask and maintained by endotracheal tube. A celiotomy was performed, the spleen was removed, and a catheter was placed in the abdominal aorta. A splenectomy was performed to stabilize the red blood cell mass of the vasculature because swine have a contractile spleen sequestering up to 20% of the red blood cells. The other end of the catheter was brought out under the skin on the back. Through a neck incision, catheters were implanted in the carotid artery and pulmonary vein. Placement was confirmed by pressure wave forms. The catheters were tunneled under the skin and exited on the back. All catheters were placed in a pouch sutured to the skin. The veterinary staff observed the swine throughout the recovery period and then returned them to individual holding cages. Pain relief was provided as the veterinary staff deemed necessary. After a 3- to 5-day recovery period, the swine began exercising again until they attained their presurgery performance level.

### Experimental procedures

The day before an experiment, the swine did not exercise. On the morning of an experiment, after an overnight fast, they were brought to the laboratory and placed in the treadmill box. After connection of catheters and recording devices, baseline measurements were taken, and a blood sample was collected. The swine then ran or rested for an hour. On completion of this period, they were placed in a sling for the next 2 h, and measurements were taken.

Two experiments were performed. The purpose of the first experiment was to determine the swine's response to exercise and recovery. Six swine were randomly selected and monitored during a daily training procedure to determine their responses to exercise. Exercise workload was to be maintained at an HR of 210 beats/min, which was estimated to be 70% of the maximum HR reserve (18–20). Cardiovascular measurements were obtained during the exercise period and during a subsequent 2 h. Blood samples (15 mL) were taken before exercise; immediately after exercise; and 60, 75, 90, and 120 min later. These swine then underwent the second experiment 4 days later.

The purpose of the second experiment was to assess the effect of exercise on responses to hemorrhage. The swine were brought to the laboratory after a day of rest. They were placed in the treadmill box, and baseline measurements were obtained. They were then randomly assigned to exercise ( $n = 7$ ) or resting groups ( $n = 8$ ). Those swine assigned to exercise ran at speeds adjusted

to maintain an HR of 210 beats/min. Resting animals were placed in the treadmill box but did not run. At 30 min and at the end of the hour, samples were taken, and the animals were placed in a sling where they were still able to bear weight on their legs if they wished. The swine were then hemorrhaged a total of 25 mL/kg for 60 min (37% of the calculated blood volume). The volume removed was drawn for five periods at 5 mL/kg for 9, 11, 11, 13, and 16 min, respectively. At the end of each period, a 25-mL blood sample (included in the hemorrhage volume) was taken. Hemodynamic measurements were also obtained. After completion of the hemorrhage, measurements were again taken at 15, 30, and 60 min of recovery.

### Hemodynamic measurements

Heart rate was measured during exercise from an electrocardiogram obtained from skin leads. During other periods, HR was determined from pulse pressure tracing. Cardiac output was measured by the thermal dilution technique using a Swan-Ganz catheter. Arterial pressures were measured from the carotid artery catheter. Mean arterial pressure (MAP), stroke volume (SV), and total peripheral resistance (TPR) were calculated from standard equations. Mean venous pressure (MVP) was measured from the side port of the Swan-Ganz catheter.

### Assay procedures

Plasma sodium and potassium concentrations were measured with an Instrumentations Laboratory flame photometer. Plasma osmolality was determined by freezing point depression (Advanced Instruments osmometer). Plasma protein concentrations were measured with an American Optical refractometer. Hematocrit was determined by using the microcapillary tube method. Lactate acid concentration was measured enzymatically with a commercial kit (Sigma Chemical Co, St Louis, Mo). Hormone concentrations were measured with techniques validated for the swine in our laboratory (4, 17). Plasma renin activity (PRA), aldosterone, cortisol, and adrenocorticotropic hormone (ACTH) were measured with commercial radioimmunoassay kits. Lysine vasopressin (LVP) was measured by radioimmunoassay. Plasma catecholamine concentrations were determined by electrochemical detection after extraction and high-performance liquid chromatography.

### Statistical analysis

The data were evaluated by analysis of variance (ANOVA) adjusted for repeated measurements. Experiments were divided into three periods: the first 60 min to determine the effects of exercise, the next 60 min to assess responses to hemorrhage, and the final 60 min to evaluate recovery from hemorrhage. Treatment, time, and group time interactions were assessed. When an F ratio was significant, the Newman-Keuls test was used to identify specific differences. Data were transformed to log values when appropriate to adjust for increases in variance. Differences were considered significant at  $P < 0.05$ . Reported values are mean  $\pm$  standard error of the mean (SEM).

## RESULTS

### Response to exercise

The swine ( $n = 6$ ) weighed  $19.6 \pm 1.4$  kg. Exercise resulted in significant increases in HR, SV, and CO that were sustained throughout the exercise period (Table 1). Blood pressure remained constant throughout the experiment; thus, TPR was significantly decreased during exercise and returned to prevalues upon completion of the exercise bout. Within minutes

TABLE 1. Hemodynamic measurements during exercise and recovery

| Parameter       | Pre-exercise   | 30 min exercise  | 60 min exercise  | 9 min            | 60 min         | 120 min        |
|-----------------|----------------|------------------|------------------|------------------|----------------|----------------|
| CO, L/min       | $3.7 \pm 0.41$ | $6.8^* \pm 0.38$ | $7.4^* \pm 0.89$ | $4.2 \pm 0.50$   | $3.7 \pm 0.45$ | $3.7 \pm 0.41$ |
| HR, beat/min    | $114 \pm 6.6$  | $177^* \pm 9.0$  | $201^* \pm 5.3$  | $144^* \pm 10.8$ | $123 \pm 9.0$  | $130 \pm 11.5$ |
| SV, mL/beat     | $32 \pm 0.3$   | $39 \pm 0.3$     | $37 \pm 0.4$     | $30 \pm 0.4$     | $30 \pm 0.2$   | $28 \pm 0.1$   |
| MAP, mmHg       | $107 \pm 3.4$  | $109 \pm 3.4$    | $110 \pm 3.8$    | $110 \pm 3.6$    | $112 \pm 3.7$  | $115 \pm 3.1$  |
| TPR, mmHg*min/L | $31 \pm 3.2$   | $16^* \pm 0.9$   | $16^* \pm 2.4$   | $28 \pm 2.8$     | $32 \pm 2.9$   | $34 \pm 4.0$   |
| MVP, mmHg       | $22 \pm 3.3$   | —                | $25 \pm 3.3$     | $22 \pm 1.6$     | $19 \pm 3.8$   | $19 \pm 2.8$   |

Values are means  $\pm$  SE.

\*These values are significantly different from pre-exercise,  $P < 0.05$ .

of exercise completion, pre-exercise values were attained and sustained during the next 2 h.

Plasma concentrations of lactate were increased during exercise and recovered within 60 min (Table 2). Plasma potassium was reduced after exercise, whereas plasma sodium, glucose, and osmolality were not altered significantly. Plasma protein and hematocrit were unchanged.

Plasma ACTH concentrations were increased during exercise and remained elevated (Table 3). This increase was accompanied by elevations in the plasma concentrations of aldosterone and a trend for a rise in cortisol. Plasma levels of norepinephrine were acutely elevated with exercise, but resting levels were attained within an hour.

### Response to hemorrhage

The swine were randomly assigned to treatment groups, rest ([R]  $n = 8$ ) or exercise ([E]  $n = 7$ ), with no significant difference in body mass (R,  $18.8 \pm 0.8$  kg; E,  $18.8 \pm 1.3$  kg) or hemorrhage volume (R,  $525 \pm 21$  mL; E,  $526 \pm 36$  mL) between groups. Before exercise, no significant difference was noted between groups in any measured parameters, and all were within normal values for swine at this age (21).

The MAP was not changed during exercise but was significantly reduced in response to hemorrhage. At the end of the hemorrhage, the reduction in MAP of control animals was  $49 \pm 3$  mmHg in contrast to a  $26 \pm 9$  mmHg decrease in the exercise group ( $P < 0.05$ ; Fig. 1A). This difference persisted during the recovery period. Cardiac output, although significantly increased during exercise, was not different between treatments during hemorrhage or recovery (Fig. 1B). Hemorrhage resulted in a significant decrease in CO. Heart rate and SV, although increased during exercise, showed no difference between groups or over time during hemorrhage or recovery (Table 4). Total peripheral resistance was reduced during exercise but was significantly increased during hemorrhage and returned to initial levels during recovery (Table 4). There was no significant effect of treatment on TPR. Hemorrhage resulted in a progressive reduction in MVP with no effect of treatment (Table 4). During the recovery period, the MVP of control animals continued to decrease, being significantly reduced at 75 and 90 min compared with the exercise group.

Plasma protein levels and hematocrit were not significantly altered during exercise (Table 5). In response to hemorrhage,

TABLE 3. Plasma hormone concentrations before, during, and after exercise

| Hormone               | Pre-exercise   | Exercise          | 60 min         | 120 min        |
|-----------------------|----------------|-------------------|----------------|----------------|
| ACTH, pg/mL           | $43 \pm 6.9$   | $161^* \pm 56.2$  | $96 \pm 38.2$  | $83 \pm 21.1$  |
| Cortisol, $\mu$ g/dL  | $2.7 \pm 0.75$ | $5.9 \pm 1.89$    | $5.3 \pm 2.29$ | $6.5 \pm 2.22$ |
| Aldosterone, ng/dL    | $2.0 \pm 0.68$ | $12.5^* \pm 3.14$ | $4.2 \pm 1.59$ | $7.0 \pm 1.63$ |
| PRA, ngAl/mL per h    | $2.2 \pm 0.75$ | $1.6 \pm 0.29$    | $1.9 \pm 0.40$ | $3.0 \pm 0.49$ |
| Norepinephrine, pg/mL | $199 \pm 42.0$ | $561^* \pm 127.8$ | $291 \pm 66.4$ | $288 \pm 82.9$ |
| Epinephrine, pg/mL    | $147 \pm 17.8$ | $201 \pm 21.1$    | $183 \pm 23.7$ | $195 \pm 46.9$ |

Values are means  $\pm$  SE.

\*These values are significantly different from pre-exercise,  $P < 0.05$ .

there was an earlier reduction in hematocrit in the exercise group. Protein concentrations were initially not different but were reduced to a greater extent in the control group. No differences in hematocrit or protein were noted during recovery between groups. Plasma sodium concentrations and osmolality were not altered by exercise or hemorrhage or during recovery. Plasma potassium was increased with exercise and fell in both groups during hemorrhage and recovery. During exercise, there were no differences between groups in plasma glucose levels (Fig. 2A). However, during hemorrhage, both groups exhibited significant increases in glucose levels that persisted into the recovery period. Plasma lactate concentrations were increased during exercise (Fig. 2B). This difference persisted into the onset of hemorrhage. There was no difference in lactate concentration between groups after 11 min of hemorrhage; however, the rate

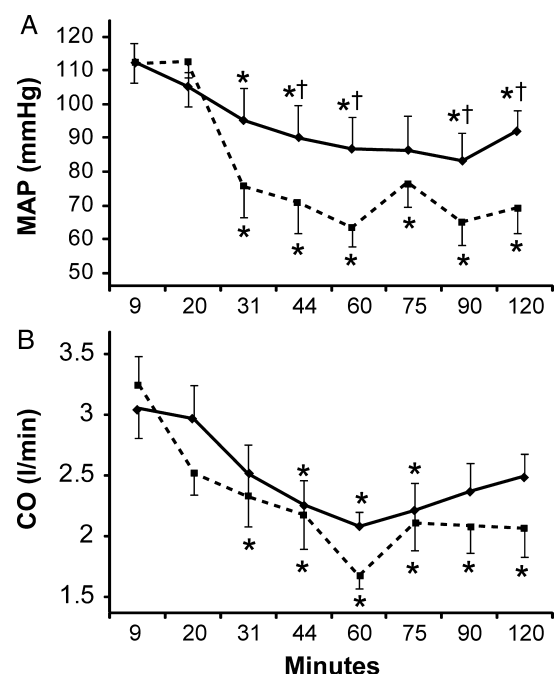


FIG. 1. Mean arterial pressure (MAP) and cardiac output (CO) during hemorrhage (0–60 min) and recovery for swine at rest (dashed line) or after exercise (solid line). \*Significantly different from pre-exercise,  $P < 0.05$ ; †significantly different from R,  $P < 0.05$ .

TABLE 2. Plasma concentrations during and after exercise

| Parameter           | Pre-exercise   | Exercise         | 60 min           | 120 min          |
|---------------------|----------------|------------------|------------------|------------------|
| Lactate, mg/dL      | $4.8 \pm 0.61$ | $8.7^* \pm 2.19$ | $4.5 \pm 0.82$   | $5.2 \pm 1.15$   |
| Sodium, mmol        | $137 \pm 0.7$  | $137 \pm 0.9$    | $137 \pm 0.8$    | $137 \pm 0.8$    |
| Potassium, mmol     | $5.1 \pm 0.16$ | $5.3 \pm 0.15$   | $4.4^* \pm 0.22$ | $4.1^* \pm 0.23$ |
| Osmolality, mOsm/kg | $276 \pm 1.7$  | $274 \pm 1.3$    | $275 \pm 1.5$    | $274 \pm 0.8$    |
| Glucose, mg/dL      | $71 \pm 2.8$   | $75 \pm 2.9$     | $72 \pm 3.3$     | $74 \pm 3.2$     |
| Protein, g/dL       | $5.7 \pm 0.19$ | $5.7 \pm 0.14$   | $5.6 \pm 0.15$   | $5.6 \pm 0.16$   |
| Hematocrit, %       | $27 \pm 2.4$   | $27 \pm 2.2$     | $25 \pm 3.5$     | $24 \pm 3.0$     |

Values are means  $\pm$  SE.

\*These values are significantly different from pre-exercise,  $P < 0.05$ .

TABLE 4. Hemodynamic measurements of swine before, after, and during exercise, hemorrhage, and recovery assigned to rest (n = 8) and exercise (n = 7)

| Parameter       | Status | Before    | After                   | 9 min      | 20 min     | 31 min      | 44 min      | 60 min      | 75 min                | 90 min                | 120 min                 |
|-----------------|--------|-----------|-------------------------|------------|------------|-------------|-------------|-------------|-----------------------|-----------------------|-------------------------|
| HR, beats/min   | R      | 116 ± 9.7 | 138 ± 12.9              | 154 ± 12.3 | 147 ± 14.9 | 156* ± 15.9 | 143 ± 12.2  | 136 ± 12.8  | 134 ± 10.7            | 147 ± 16.4            | 154* ± 14.3             |
|                 | E      | 116 ± 9.7 | 204* <sup>†</sup> ± 8.7 | 140* ± 8.0 | 143* ± 8.9 | 151* ± 16.2 | 144* ± 11.8 | 135* ± 12.5 | 145* ± 10.6           | 159* ± 17.9           | 120 <sup>†</sup> ± 21.9 |
| SV, mL/beat     | R      | 27 ± 0.3  | 25 ± 0.4                | 22 ± 0.3   | 17* ± 0.2  | 14* ± 0.2   | 14* ± 0.2   | 12* ± 0.1   | 16* ± 0.3             | 14* ± 0.2             | 14* ± 0.2               |
|                 | E      | 27 ± 0.2  | 37* <sup>†</sup> ± 0.4  | 22 ± 0.1   | 21 ± 0.1   | 17* ± 0.1   | 16* ± 0.1   | 16* ± 0.1   | 15* ± 0.2             | 15* ± 0.1             | 18* <sup>†</sup> ± 0.1  |
| TPR, mmHg*min/L | R      | 39 ± 3.5  | 36 ± 3.5                | 35 ± 3.6   | 48 ± 5.3   | 33 ± 4.6    | 36 ± 6.0    | 38 ± 4.8    | 38 ± 4.1              | 33 ± 4.4              | 38 ± 5.5                |
|                 | E      | 38 ± 6.2  | 15* <sup>†</sup> ± 1.3  | 37 ± 1.7   | 36 ± 3.0   | 38 ± 2.8    | 40 ± 2.9    | 41 ± 3.0    | 40 ± 4.4              | 36 ± 3.6              | 33 ± 5.3                |
| MVP, mmHg       | R      | 21 ± 3.6  | 20 ± 4.1                | 21 ± 3.3   | 20 ± 2.4   | 16 ± 2.6    | 14 ± 2.4    | 14 ± 4.0    | 13 ± 2.4              | 13 ± 2.0              | 15 ± 2.3                |
|                 | E      | 16 ± 2.9  | 20 ± 5.5                | 19 ± 2.9   | 19 ± 3.3   | 20 ± 4.0    | 15 ± 3.9    | 16 ± 2.6    | 16 <sup>†</sup> ± 3.6 | 17 <sup>†</sup> ± 3.0 | 14 ± 2.8                |

Values are means ± SE.

\*Significantly different from pre-exercise,  $P < 0.05$ .

<sup>†</sup>Significantly different from R,  $P < 0.05$ .

of return to basal levels was greatly enhanced in the exercise group during recovery. During the 1 h of recovery, the rest group sustained elevated lactate levels; whereas in the exercise group, values were decreased to levels not significantly different from those at the end of exercise before the onset of hemorrhage.

During the initial 60-min period, there were significant increases in ACTH, cortisol, aldosterone, and PRA in both groups to similar levels irrespective of exercise (Table 6). During hemorrhage, both groups had significant increases in ACTH and a subsequent reduction during the recovery period. Plasma cortisol was increased during hemorrhage, with a significant group effect noted. At the end of hemorrhage, the cortisol response was reduced in the exercise group. This difference persisted during recovery as a significant group difference. Plasma renin activity was increased during hemorrhage and persisted during recovery, with no significant group effect. Lysine vasopressin was not altered by exercise but was significantly increased during hemorrhage and decreased during recovery (Table 6). There were no differences between groups in the responses of PRA or LVP. Plasma norepinephrine concentrations were increased during exercise, whereas epinephrine levels were not altered (Fig. 3,

A and B). Plasma norepinephrine and epinephrine levels increased during hemorrhage. There was a significant reduction in catecholamine levels during recovery in the exercise group from the values attained at the end of hemorrhage. For the resting swine, the elevation of norepinephrine was sustained during recovery.

## DISCUSSION

The swine exercised immediately before hemorrhage maintained a higher blood pressure during hemorrhage. Blood pressure is used as a major index on the extent of blood loss and the adequacy of subsequent resuscitation. Thus, the higher blood pressure values in patients who had been actively exercising immediately before injury may give a false sense about the extent of hypovolemia and restitution of blood volume.

The volume of blood removed in both groups was not significantly different. Furthermore, the dilution of plasma protein and hematocrit during hemorrhage were similar. Thus, the transcapillary movement of interstitial fluid into vascular space was not influenced by prior exercise. Heavy exercise has been shown to acutely reduce plasma volume, with a subsequent increase during the next 24 h. Gillen et al. (15) and

TABLE 5. Plasma concentrations after exercise, during hemorrhage, and recovery for swine assigned to rest (n = 8) and exercise (n = 7)

| Plasma              | Status | Pre-exercise | Postexercise | 9 min       | 20 min      | 31 min      | 44 min      | 60 min                   | 75 min      | 90 min      | 120 min     |
|---------------------|--------|--------------|--------------|-------------|-------------|-------------|-------------|--------------------------|-------------|-------------|-------------|
| Sodium, mmol        | R      | 137 ± 1.4    | 139 ± 1.4    | 139 ± 1.4   | 138 ± 1.4   | 138 ± 1.6   | 137 ± 1.2   | 138 ± 1.2                | 137 ± 1.5   | 138 ± 1.4   | 138 ± 1.7   |
|                     | E      | 138 ± 1.3    | 139 ± 1.5    | 139 ± 1.6   | 139 ± 1.9   | 140 ± 1.7   | 141 ± 2.2   | 141 ± 3.0                | 141 ± 2.3   | 141 ± 1.4   | 138 ± 2.2   |
| Potassium, mmol     | R      | 4.8 ± 0.09   | 4.6 ± 0.12   | 4.6 ± 0.15  | 4.4 ± 0.16  | 4.0* ± 0.12 | 4.2* ± 0.14 | 4.1* ± 0.17              | 3.7* ± 0.11 | 3.5* ± 0.11 | 3.6* ± 0.11 |
|                     | E      | 5.1 ± 0.12   | 5.5* ± 0.08  | 4.6* ± 0.11 | 4.3* ± 0.10 | 4.1* ± 0.09 | 4.2* ± 0.15 | 4.0* ± 0.18              | 3.6* ± 0.14 | 3.6* ± 0.10 | 3.5* ± 0.12 |
| Osmolality, mOsm/kg | R      | 275 ± 1.9    | 275 ± 1.2    | 275 ± 1.1   | 276 ± 1.3   | 277 ± 1.2   | 276 ± 1.5   | 278 ± 1.6                | 280* ± 1.9  | 280* ± 1.7  | 280* ± 1.9  |
|                     | E      | 275 ± 1.9    | 273 ± 2.0    | 273 ± 1.4   | 275 ± 2.0   | 275 ± 2.6   | 275 ± 2.6   | 278 ± 2.9                | 278 ± 3.1   | 277 ± 2.1   | 276 ± 2.2   |
| Protein, g/dL       | R      | 5.9 ± 0.14   | 5.9 ± 0.15   | 5.8 ± 0.15  | 5.7 ± 0.15  | 5.5 ± 0.13  | 5.2* ± 0.14 | 5.0* ± 0.14              | 5.0* ± 0.15 | 4.9* ± 0.14 | 5.0* ± 0.13 |
|                     | E      | 6.0 ± 0.12   | 5.9 ± 0.09   | 5.8 ± 0.09  | 5.8 ± 0.08  | 5.5* ± 0.04 | 5.4* ± 0.06 | 5.3* <sup>†</sup> ± 0.09 | 5.2* ± 0.06 | 5.1* ± 0.08 | 5.1* ± 0.10 |
| Hematocrit, %       | R      | 29 ± 1.5     | 28 ± 1.3     | 28 ± 1.2    | 27 ± 1.1    | 26 ± 0.9    | 24* ± 0.9   | 22* ± 1.0                | 22* ± 1.0   | 21* ± 0.8   | 21* ± 0.8   |
|                     | E      | 29 ± 1.1     | 27 ± 0.8     | 27 ± 1.1    | 26 ± 1.3    | 25* ± 1.1   | 24* ± 1.3   | 23* ± 1.3                | 21* ± 1.0   | 22* ± 1.2   | 21* ± 1.1   |

Values are means ± SE.

\*Significantly different from pre-exercise,  $P < 0.05$ .

<sup>†</sup>Significantly different from R,  $P < 0.05$ .

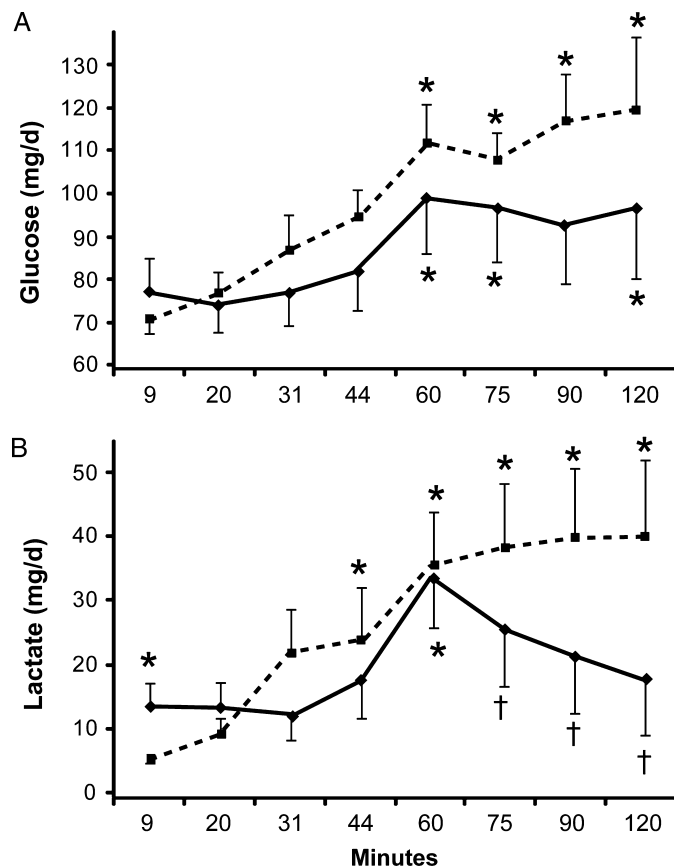


FIG. 2. Plasma lactate and glucose concentrations during hemorrhage (0–60 min) and recovery for swine at rest (dashed line) or after exercise (solid line). \*Significantly different from pre-exercise,  $P < 0.05$ ; †significantly different from R,  $P < 0.05$ .

Mack et al. (16) suggested that the attenuation of cardiovascular responses to reductions in central blood volume was in part caused by expansion of blood volume after exercise as well as by changes in the rate of transcapillary fluid flux. Alterations of indices of plasma volume in response to exercise were not observed in the present study. Thus, modification of the blood pressure response to hemorrhage does not seem to be related to changes in blood volume or mobilization of interstitial fluid.

The improvement in MAP was not associated with a significant difference in CO. Thus, TPR would seem to increase; however, significant changes were not observed. Convertino (7) demonstrated an increase in adrenergic responsiveness after exercise-attenuated responses to hypovolemia induced by lower-body negative pressure. In the present study, there was no significant difference in norepinephrine concentrations between groups during hemorrhage, indicative of no difference in sympathetic tone. Because there were no differences in PRA or vasopressin, for a given level of sympathetic tone after exercise, the exercise group had a greater MAP, supporting an increase in adrenoreceptor sensitivity.

Although not significant between groups, there was a trend for the response to hemorrhage of all of the pressor hormones to be decreased in the exercise group. These hormones, LVP, angiotensin II (as indicated by PRA), and the catecholamines have a tight synergistic relationship acting in concert to sustain blood pressure during hemorrhage and exercise (17, 19, 20, 22). The trend for lower levels of these hormones during hemorrhage after exercise may be the product of the sustained MAP rather than a change in responsiveness to changes in pressure.

Hemorrhage is associated with tissue hypoperfusion leading to anaerobic metabolism and an increase in plasma lactate. Exercise also results in a similar response because of the increased metabolic demands at the tissue level. At the end of exercise, a significant increase in plasma lactate concentrations persisted. In the presence of hemorrhage, similar values were observed at the end of hemorrhage irrespective of the groups. However, during recovery from hemorrhage lactate, values were significantly reduced in the exercise group. This difference suggests a shift in substrate metabolism favoring lactate utilization after exercise and allowing a greater repayment of the oxygen debt. Previous work suggests that glucose utilization is increased after exercise. The response to a second bout of exercise results in increased use of circulating glucose and greater aerobic energy contribution to meet the increase in metabolic demand (23). These changes occur in the absence of a difference in total adenosine triphosphate requirements (24). In the present study, the reduction in plasma lactate and the lower plasma glucose concentrations in

TABLE 6. Plasma hormone concentrations during exercise, hemorrhage, and recovery for animals assigned to rest ( $n = 8$ ) and exercise ( $n = 7$ )

| Hormone            | Status | Pre-exercise | Postexercise | 9 min         | 20 min       | 31 min        | 44 min        | 60 min        | 75 min       | 90 min       | 120 min      |
|--------------------|--------|--------------|--------------|---------------|--------------|---------------|---------------|---------------|--------------|--------------|--------------|
| ACTH, pg/mL        | R      | 43 ± 11.9    | 129 ± 44.2   | 207 ± 110.9   | 315 ± 127.4  | 285 ± 100.9   | 550* ± 179.1  | 532* ± 166.5  | 386* ± 142.3 | 281* ± 90.6  | 263 ± 77.5   |
|                    | E      | 55 ± 15.6    | 122 ± 28.0   | 113 ± 13.7    | 73 ± 11.1    | 253* ± 82.5   | 314* ± 88.7   | 466* ± 65.4   | 391* ± 119.8 | 250 ± 60.5   | 181 ± 42.7   |
| Cortisol, µg/dL    | R      | 3.8 ± 0.65   | 6.7 ± 1.51   | 7.8 ± 1.9     | 10.3* ± 1.88 | 13.8* ± 1.82  | 17.3* ± 1.81  | 17.5* ± 1.93  | 18.2* ± 2.37 | 15.3* ± 2.57 | 17.3* ± 3.78 |
|                    | E      | 3.1 ± 0.94   | 5.8 ± 1.37   | 5.7 ± 1.51    | 5.6 ± 0.91   | 8.6*† ± 1.49  | 10.1*† ± 1.66 | 10.9*† ± 1.34 | 11.9* ± 1.64 | 12.5* ± 1.9  | 12.3* ± 2.32 |
| Aldosterone, ng/dL | R      | 2.2 ± 0.42   | 5.2 ± 2.07   | 5.3 ± 1.73    | 15.9* ± 4.82 | 20.9* ± 4.96  | 26.4* ± 6.61  | 26.4* ± 3.22  | 23.3* ± 2.63 | 20.4* ± 2.95 | 19.4* ± 2.64 |
|                    | E      | 3.7 ± 0.67   | 9.7*† ± 3.09 | 10.5*† ± 3.56 | 8.3*† ± 2.72 | 12.1*† ± 3.41 | 16.9* ± 3.06  | 23.6* ± 3.25  | 20.4* ± 3.24 | 18.6* ± 3.75 | 17.8* ± 5.00 |
| PRA, ngAI/mL per h | R      | 0.71 ± 0.21  | 1.04 ± 0.25  | 2.71 ± 0.68   | 6.24* ± 1.61 | 5.69* ± 1.40  | 6.94* ± 2.14  | 6.85* ± 2.30  | 7.24* ± 2.08 | 5.39* ± 1.31 | 5.67* ± 1.91 |
|                    | E      | 0.93 ± 0.31  | 1.57 ± 0.48  | 2.10 ± 0.39   | 3.95* ± 1.12 | 5.07* ± 1.88  | 6.43* ± 1.84  | 7.35* ± 1.49  | 8.30* ± 2.53 | 7.20* ± 1.66 | 7.37* ± 1.80 |
| LVP, pg/mL         | R      | 5 ± 1.7      | 6 ± 2.0      | 8 ± 3.5       | 19 ± 11.0    | 76* ± 27.8    | 237* ± 70.2   | 257* ± 75.3   | 198* ± 66.5  | 151* ± 56.6  | 128* ± 42.9  |
|                    | E      | 4 ± 1.2      | 7* ± 1.6     | 10 ± 1.5      | 17 ± 6.0     | 60* ± 40.2    | 81* ± 30.4    | 133* ± 34.1   | 96* ± 37.5   | 71* ± 28.6   | 42 ± 6.3     |

Values are means ± SE.

\*These values are significantly different from pre-exercise,  $P < 0.05$ .

†Significantly different from R,  $P < 0.05$ .

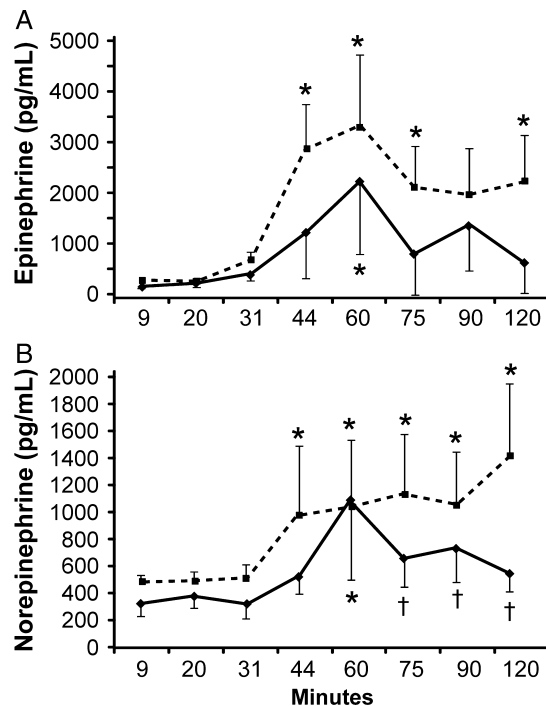


FIG. 3. Plasma epinephrine and norepinephrine concentrations during hemorrhage (0–60 min) and recovery for swine at rest (dashed line) or after exercise (solid line). \*Significantly different from pre-exercise,  $P < 0.05$ ; †significantly different from R,  $P < 0.05$ .

the exercise group during recovery would be indicative of a metabolic shift to an increase in aerobic energy contribution and thus an improved outcome (25).

The influence of exercise on responsiveness to hypotension in humans has been demonstrated to be acute and to persist for more than 24 h (8, 13, 14). In those studies, maximal exercise was performed. In the present study, we focused on a sustained submaximal exercise because it seems to reflect the conditions in which traumatic injuries are incurred. The level of exercise performed in the present study was fully recovered for most parameters within 60 min. However, plasma levels of ACTH, cortisol, and aldosterone remained increased. These hormones are indicative of a generalized stress response that could adversely affect responses to hemorrhage (26–28). Stressful stimuli have been shown to attenuate the reduction in blood pressure in response to hemorrhage similar to that observed after exercise in the present study. Furthermore, responsiveness of these hormones during hemorrhage may facilitate transcapillary refill and modulate the response of hormones responsible for the maintenance of blood pressure. In the hemorrhage experiments at the end of the exercise period, there was no significant difference between groups in cortisol or aldosterone; however, ACTH was increased by exercise. In response to hemorrhage, the levels of ACTH were not different; however, the cortisol concentrations were significantly decreased, suggesting a hyporesponsiveness. The hyporesponsiveness of cortisol to hemorrhage after exercise may affect immunologic function and susceptibility to infection (29).

There are limitations of the present study that must be acknowledged. Although the controlled hemorrhage model used mimics the fall in pressure of a moderate injury, it does not reflect the pressure change associated with damage of a major

vessel with uncontrolled bleeding. The model also does not have an injury component. The initial response to injury may overwhelm the more subtle response modifications caused by prior exercise. With these limitations in mind, the present study again points out the plethora of factors that can modify responses to hemorrhage (1–4).

In summary, submaximal exercise causes acute changes in cardiovascular measurements and hormone concentrations, which are rectified within 60 min. Responses to hemorrhagic hypotension are altered during the 60-min period after exercise. Blood pressure is better maintained and plasma lactate is corrected earlier, suggesting improved outcome. However, these responses may mask the extent of the hypovolemia, delaying resuscitation and care. Thus, prior exercise activity of the patient should be considered in evaluating patients with traumatic injuries resulting in hemorrhagic hypotension.

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