RENAL RESPONSE TO 7 DAYS OF LOWER BODY POSITIVE PRESSURE IN THE SQUIRREL MONKEY

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ABSTRACT

The purpose of this study was to further characterize the renal response to central volume expansion using the ground-based model of lower body positive pressure (LBPP). As a ground-based model for weightlessness, the response of the chair-trained squirrel monkey (Saimiri Sciureus) to LBPP was evaluated in a length of study similar to a typical Space Shuttle mission (7 days). Results were compared to time control experiments that included chair-sitting without exposure to LBPP. Adult male squirrel monkeys (600-1000g) were chronically implanted with arterial and venous catheters to facilitate maintenance infusion of saline, monitoring of vascular pressures, and blood sampling; urine was collected via a condom-like tube. Animals were placed in a specially-designed metabolism chair for two days prior to increasing air pressure in the lower chamber of the chair thus exposing the animal to 20 mmHg pressure from the waist down. Individual monkeys were subjected to both a LBPP and time-control protocol. Urine volume and sodium excretion were significantly increased the first day of LBPP with most of this response occurring in the first 6 to 12 hours. From the second to the seventh day of LBPP, urinary excretion rates for sodium and water were not different from chair-sitting controls. A significant negative sodium and water balance was observed on the first day of LBPP and was not observed in time-controls. Removal of the stimulus resulted in a modest conservation of sodium and water. The renal responses were not associated with any changes in plasma aldosterone levels. We conclude that chronic exposure to LBPP results in an acute diuretic and natriuretic response independent of changes in plasma aldosterone concentrations and produces a chronic reduction in fluid volume lasting the duration of the stimulus.

Key words: volume expansion; diuresis; natriuresis; weightlessness; spaceflight

INTRODUCTION

Physiological responses to central volume expansion produced by exposure to the hypogravic environment of space have not been well characterized although it is clear that weightlessness induces a shift of fluid from the lower extremities toward the upper body (1, 9, 10, 15, 17). The relative lack of specific information is in part due to operational considerations which have limited spaceflight data collection to the pre-, mid-, or post-flight periods, thus missing the critical early hours during which acute adaptation occurs. Interpretation of available in-flight data from human subjects has been further complicated by voluntary fluid restriction pre-flight, variable in-flight activity, and the occurrence of space motion sickness. Nonetheless, evidence of early in-flight reductions in body weight (11) and of post-flight body fluid volume contraction, fluid and electrolyte conservation and orthostatic intolerance (1, 9, 10, 15, 17) have led to the hypothesis that a reflex renal diuresis and natriuresis occurs early in spaceflight in response to the cephalad fluid shift and the perception of an overfilled circulation. There is evidence to suggest that cardiovascular adjustments to central volume expansion induced during spaceflight are incomplete and a sustained hypervolemia may persist throughout the term of exposure to 0g although further investigation is needed to confirm this possibility (1, 9, 10, 13, 15, 17).

To address these issues in an earthbound setting, human and animal models using head-out water immersion (3, 4, 7, 8, 18, 19, 22), bedrest (7), and head-down tilt (5, 20, 24) have been developed to simulate the central volume expansion of weightlessness. Studies employing these models have yielded extensive although conflicting data on the nature and mediators of the renal response. Unfortunately, the two models most commonly studied, water immersion

and head-down tilt, are not ideally suited to chronic experimentation and have been unable to adequately address the question of whether or not the body achieves a new steady-state equilibrium prior to removal of the stimulus.

Our laboratory has developed a primate model suitable for study of both the short- and long-term physiological mechanisms underlying the fluid-electrolyte response to 0g exposure. A continuous lower body positive pressure (LBPP) is used to induce a cephalad fluid shift in squirrel monkeys. In a previous study using this model, LBPP produced a diuresis and natriuresis that was sustained for the duration of the four day experiment (12). The purpose of the present study is to extend the initial investigation into the renal response to central volume expansion produced by LBPP in primates. We evaluated the excretory response of the chair-trained squirrel monkey to LBPP in a length of study chosen to be similar to a typical Space Shuttle Mission, i.e. 7 days. Furthermore, results were compared to time control experiments that included chair-sitting but without exposure to LBPP.

METHODS

All experiments were performed in conscious, chronically catheterized, adult male squirrel monkeys (Saimiri Sciureus) (body wt 600-1000g). Venous and arterial catheters constructed of renothane (0.025" id; 0.040" od) attached to tygon tubing (0.025" id; 0.040" od) were implanted during a sterile operative procedure. Antibiodic (50 mg/kg oxacilin), atropine (0.02 mg/kg), and diazepam (1 mg/kg) were given prior to induction of anesthesia with sodium pentobarbital (10 mg/kg). The renothane portion of the venous catheter was inserted into the thoracic vena cava via the external iliac vein so that the tip of the catheter was above the diaphram and below the right atrium. Arterial catheters were

inserted into the abdomenal aorta through the internal iliac artery with the tip being just distal to the renal arteries. Placement of catheters was confirmed by post-surgical x-ray of contrast-filled catheters. The PVC portions of the catheters were passed through the back muscle, tunneled subcutaneously, and exposed to the exterior through separate sites in the upper back of the animal. The distal ends of the catheters were plugged with sterile stainless obturators and the coiled catheters stored in an inside pocket of an open nylon mesh jacket worn continuously. The catheters contained a 1:1 50% dextrose:heparinized saline (100 units/ml) solution to maintain patency and retard bacterial growth. A blood sample was cultured biweekly to monitor for catheter sterility. Animals were treated with intramuscular injections of gentamicin (4 mg/kg) for 5 days and oxacilin (10 mg/kg) for 10 days post-surgery.

Seven animals underwent both a 7-day experimental study (with LBPP) and a 7-day time control study (without LBPP) in random order and at least 3 weeks apart. Animals were trained to sit for up to 10 days in a specially designed metabolism chair (Fig. 1). When each study began, previously trained animals were placed in a metabolism chair within a light-regulated isolation chamber. The seating perch was cushioned with a waterbag and an adjustable footrest was positioned to allow the animal to squat in a comfortable, natural position. A latex urine collection tube was fit over the penis and scrotum. The distal end of the tube was enlarged to act as a reservoir and was attached to a solenoid valve at the base of the chair. Urine was released via a conduit into a fraction collector below the isolation chamber. Urine collection tubes contained mineral oil to prevent evaporation and 0.02 mg of sodium azide to inhibit bacterial growth. The solenoid valve and fraction collector were both driven by timed computer signals (DEC MINC 11/23). Arterial and venous catheters were connected

to sterile extension tubing (PVC 0.025"id; 0.040" od) which were then connected to sterile pressure transducers (HP # 1090). Lines were maintained patent by constant infusion of heparinized saline (10 units/ml; 2.7 ul/min/line). The lower chamber below the animal's waist was sealed tight with a custom-fitted periabdomenal foam cuff. The animal was allowed to equilibrate in isolation for 24-30 hours prior to beginning the data collection protocol.

Animals were provided with food (Teklad TD75282 SKF diet with 10% cottonseed oil and vitamin D) and tap water ad libidum with daily intake of both being determined gravimetrically. A 12:12 L:D cycle was maintained by providing illumination at 600 lux from 08:00 to 20:00 each day. The animals were not disturbed while in the isolation chambers except during food and water measurement and a daily health status check.

Data collection was started at 14:00 on the day following the equilibration period (Day 0). Urine was collected every 1 or 2 hours and central venous and arterial pressures measured every 15 minutes. Arterial blood samples (1 ml) were obtained at approximately 13:00 each day and at 15 min after the onset of LBPP. Each blood sample was drawn into a chilled tuberculin syringe containing 50 ul of EDTA (30 mg/ml). Blood was immediately transferred to a prechilled, sterile tube, capped and centrifuged at 2500g for 5 min at 4°C. Plasma was withdrawn and immediately stored at -30°C. Red blood cells were resuspended in 0.6 ml of sterile saline, gently mixed and reinfused into the animal.

When animals were undergoing the experimental protocol, a 20 mmHg positive pressure was introduced into the lower chamber of the metabolism chair in a step-wise fashion over a 10-15 min period at 14:00 of the first experimental day (Day 1, after the equilibration day and Day 0). Lower body positive pressure was maintained for a 7-day period. At 14:00 on the last day, LBPP was withdrawn

in a step-wise fashion over 10-15 min. Data collection was continued during a final recovery period of 24 hours (Day 8). The time control protocol was identical except that no LBPP was applied.

Positive air pressure was regulated by inflow and outflow of pressurized room air. Pressure was monitored continuously by a gas transducer (Vallidyne Model No. 8262036) outside the chamber and adjusted manually if necessary. The average chamber pressure for the 7-days of LBPP was 19 $\pm$ 0.3 mmHg. Passage of outflow through a tall water reservoir served to buffer small variations in pressure. Air temperature was maintained at 29°C by passage of air through a thermostatically controlled water bath.

Vascular and lower chamber pressure signals were processed by Hewlett-Packard conditioners (8805D) with chamber pressure and central venous pressure also being preamplified. Chamber temperature as well as delivery of triggering signals for the solenoid valve, fraction collector and strip-chart recorder were controlled by computer (DEC MINC 11/23). Simultaneous study of up to 4 animals was enabled by a custom multiplexing system (Auburn Instruments) which interfaced with the computer via a Hewlet-Packard Monitoring System (7754A).

Osmolality of both plasma and urine was measured by freezing-point depression (Precision Systems No. 5004). Plasma and urine concentrations of sodium and potassium were measured with a flame photometer (Instrumentation Laboratories model 143). Plasma aldosterone concentrations were measured by a microvolume radioimmunoassay procedure based on the technique of Sancho and Haber (23).

Statistical analysis consisted of paired comparison of LBPP and time control data at each time period using Student's t-test. In addition, a similar

comparison was made except that all values were expressed as a change from Day 0 (control day in both the LBPP and time control protocols). Because of variation in catheter resistance and/or tip position between studies, changes in arterial and venous pressures due to onset and offset of LBPP were evaluated by paired comparison of data obtained on day 0 vs. day 1 and day 7 vs. day 8 (Student's t-test). Values are reported as mean $\pm$ SE and were considered significantly different when $P < 0.05$.

RESULTS

Average daily urinary responses for both the LBPP and time control experiments are presented in Fig. 2. Chronic exposure of squirrel monkeys to LBPP was associated with an early increase in urine volume and sodium excretion along with a decrease in urine osmolality. These effects were limited to the first 1-2 days of stimulus after which these variables were not different from time control values for the remaining period of LBPP. In the 24 hrs following removal of pressure, a modest trend toward fluid conservation occurred; this trend was also observed on the same day in time control experiments.

Sodium excretion increased significantly in the 24 hrs following initial exposure to LBPP (Fig. 2). In this period, monkeys excreted 3.6 $\pm$ 0.6 mEq/d of sodium as compared to 1.6 $\pm$ 0.4 mEq/d in the control series. On days 2 and 3 of LBPP, sodium excretion decreased by about one-half the value on Day 1 and dropped even further to a new steady-state level on days 4-7. However, sodium excretion was significantly greater than in time controls only on day 1. Comparison of LBPP and time control data based on the changes in sodium excretion from the prestimulus control day (day 0) to each subsequent day revealed that the increase in sodium excretion during LBPP remained significantly elevated

through day 3 ($P < 0.05$). This finding, however, appears to be due to the lower level of sodium excretion on day 0 during the LBPP protocol rather than a persistent natriuresis due to LBPP. On the day following withdrawl of pressure (day 8), sodium excretion in the LBPP series was decreased compared to the value during the last day of LBPP (0.6 ± 0.2 vs. 1.4 ± 0.2 mEq/d); this change was significant based on a paired comparison ($P<0.025$). The decrease in sodium excretion observed from days 7 to 8 in the time control series was not significant (1.8 ± 0.5 vs. 1.4 ± 0.6 mEq/d).

During the first day of LBPP, urine volume was 50.2 ± 8.7 ml, a significant increase over both day 0 (29.8 ± 4.4 ml) and the time control value for this day (29.6 ± 2.8 ml) (Fig. 2). Although urine volume remained noticably higher on days 2 and 3 of LBPP, these differences were significantly different from time control values only when expressed as changes from the prestimulus control day (day 0) ($P<0.02$). For the remaining days of the study (days 3-8), a similar pattern of urine output was observed in the LBPP and time control protocols. Although urine volume in the 24 hr period following removal of pressure (day 8) decreased by 28% (10.4 ml) in the LBPP study, a similar and perhaps serendipitous change also occurred in the control group for this day (20%, 7.3 ml). As was the case for sodium excretion, the decrease in urine volume from days 7 to 8 was significant only in the LBPP series ($P<0.05$).

Initiation of LBPP induced a marked fall in 24 hr urine osmolality that was significantly below the value measured in the time control series for day 1 (972 ± 104 vs. 1575 ± 129 mosm/kg H_2O; $P < 0.01$) (Fig. 2). Osmolality remained significantly depressed on the second day of LBPP (1450 ± 119 vs. 1079 ± 110 mosm/kg H_2O; $P < 0.03$). In accordance with urine volume data, the time control series displayed a trend towards a more dilute urine after day 2 negating the

apparent continuation of diuresis observed in the LBPP series. Values were not different between LBPP and time control protocols from Days 3 through 8. However, a significant increase in urine osmolality was observed upon withdrawl of pressure in the LBPP group (day 7 vs. day 8; 1188 $\pm$ 60 vs. 1272 $\pm$ 56 mosm/kg H_2O; $P < 0.05$). There were no significant differences between LBPP and time control series in terms of free water clearance or osmolar clearance for any day of the study. This was also true when data were analyzed as the change from day 0 to any subsequent day.

The urinary excretion data in Fig. 3 represent values obtained every 2 h for the control day (Day 0) and the first two days of LBPP (Days 1 and 2). Sodium excretion was significantly increased in response to LBPP at several points during the first 24 h but was similar to time control on Day 2. Likewise, urine volume was increased only during the first half of the first day of LBPP. In contrast, the decrease in urine osmolality in the LBPP series was persistent for most of the first 48 hrs of pressure. The time of the maximal urinary response to LBPP was quite variable from animal to animal but always occurred within the first 24 h. The average peak diuretic and natriuretic responses occurred within 1-2 hours of each other in all experiments. The maximum decrease in urine osmolality temporally coincided with maximum sodium and water output in only 4 of 7 animals.

Daily sodium balance calculated as dietary intake minus urinary output is presented in Fig. 4. The constancy of body temperature and absence of diarrhea in all experiments allowed for the calculation of balance data without accounting for insensible losses. When animals were subjected to the LBPP protocol, a negative sodium balance was observed on the first day of LBPP that was less than the same day of the time control protocol ($P < 0.02$). This observation was due

to a combination of increased urinary sodium excretion and decreased intake. On the first day of LBPP, animals consumed less food than control although this difference was of borderline significance (15.2 $\pm$ 1.2 g vs. 25.3 $\pm$ 4.2 g; $0.10 < P < 0.05$). There were no differences in sodium balance between LBPP and time control series for any other day, although animals in the LBPP series tended to retain more sodium on days 5-7 ($0.01 < P < 0.05$).

Mean daily water balance calculated as water intake minus urinary volume is also shown in Fig. 4. As observed for sodium, water balance was significantly less on day 1 in the LBPP series as compared to time controls. Water intake in the two protocols was not different on any individual day of the two studies so that the negative water balance observed on day 1 of the LBPP series was solely due to increased urinary output.

Urinary potassium excretion was largely unaffected by LBPP as values on each day were not different between the time control and LBPP series (Fig. 5). When calculated as the change from the prestimulus control day (day 0) to each subsequent day, again there were no differences between protocols. Although daily averages were not different, removal of pressure in the LBPP series resulted in a decrease in 24 hr potassium excretion not observed in time controls (day 7 vs. day 8; 4.5 $\pm$ 0.4 vs. 2.9 $\pm$ 0.4 mEq/d; $P < 0.05$).

Plasma aldosterone values measured each day at 13:00 and also at 17:00 on day 1 are presented in Fig. 6. Data obtained in six animals revealed that there were no significant differences for any time period between the LBPP and time control series. However, a slight trend towards decreased aldosterone levels was observed in animals undergoing LBPP; when data were calculated as a change from day 0, plasma aldosterone concentrations were decreased on days 4 and 6 compared with the changes observed in time controls ($P < 0.05$). Hematocrit,

plasma sodium and potassium concentrations and osmolality did not change in response to LBPP and were not different between the two series of experiments on any day (data not shown).

An elevation of central venous pressure (CVP) was observed in 6 of the 7 animals following the application of LBPP. The average maximal increase was 1.8 $\pm$ 0.5 mmHg ($P < 0.02$ versus prestimulus) and occurred within 20 min of initiation of LBPP. CVP returned to prestimulus values within 4 hours. Due to zero shifting in the transducer system, CVP was only measured periodically throughout the daytime so that the transducer could be manually zeroed immediately prior to taking a reading. Mean daily CVP values were unchanged by LBPP. Similarly, when CVP in each group was expressed as a difference between the prestimulus day and each subsequent day, there were no differences between the two series of experiments over the course of the study. When LBPP was withdrawn, a decrease in CVP occurred within 30 minutes in every animal; the maximum poststimulus decline in CVP averaged 1.96 $\pm$ 0.5 mmHg ($P < 0.001$).

Mean arterial pressure (AP) was measured in 5 monkeys undergoing the LBPP protocol. During the initial control day AP averaged 108 $\pm$ 5 mmHg. In all of these animals a very brief increase in AP occured 5 to 25 min after onset of LBPP; the average maximum change in AP was 10.2 $\pm$ 3.9 mmHg. Daily averages of arterial pressure were not different on days 0 through 7. However, in four animals in which data were available, a significant decrease of 16.3 $\pm$ 5.3 mmHg ($P < 0.01$) was observed the day after removal of LBPP (day 8) compared to the last day of LBPP (day 7). This decrease was evident within two hrs after LBPP was withdrawn and was sustained throughout the entire day after withdrawl of the stimulus.

DISCUSSION

We report for the first time basic renal excretory responses to a prolonged (7 day) stimulus for central volume expansion in the nonhuman primate. Furthermore, to evaluate the influence of chair-sitting, we compared these responses to time control data in which the same animals were studied under identical conditions with the exception that LBPP was not applied. Prolonged exposure of the squirrel monkey to LBPP resulted in a two-phase response: an acute phase characterized by a natriuresis and diuresis that was confined to the first 24-48 hours of the stimulus, and an adaptive phase lasting for the remainder of the stimulus during which urinary excretion patterns under LBPP were not different from those observed in the same animals under control conditions. The renal responses were not associated with changes in plasma aldosterone levels. In addition, a modest renal conservation of fluid and electrolytes was detected following removal of the stimulus.

Our results agree with the 5-15% reduction in plasma volume observed in spaceflight and the water-immersion and head-down tilt models (8, 9, 16, 18). Assuming isotonic fluid was lost from the extracellular compartment as is suggested by the absence of a change in plasma osmolality and sodium concentration, the increase in sodium excretion on the first day of LBPP of 2 mEq would be associated with a total fluid loss on the order of 14 ml. The observed increase in urine volume of 21 ml would suggest a slightly larger volume lost. These estimations represent roughly 13-19% of the total plasma volume or 5-7% of the total extracellular fluid volume. It also seems likely that interstitial fluid mobilized into the vascular compartment prevented any increase in hematocrit which would normally accompany an acute reduction in plasma volume. Such a shift of fluid would be expected given the hydrostatic gradients resulting

from the decrease in peripheral venous pressure and increase in external tissue pressure accompanying LBPP.

The lack of a change in plasma aldosterone levels during LBPP is in contrast to earlier findings using this model. Kass and Moore-Ede previously reported a significant decline in plasma aldosterone and potassium concentration at 4 and 24 hrs after initiation of the stimulus but did not examine time controls (12). Our new findings reveal there were clearly no differences in aldosterone levels or plasma potassium concentrations when comparing LBPP and time control protocols. Although data from human models and spaceflight do not support a role for the renin-angiotensin-aldosterone system in mediating the renal response to central volume expansion associated with weightlessness, a definitive role for this system cannot be eliminated at present due to the lack of data from the critical early hours of weightlessness. In humans, several laboratories have reported the lack of any early changes in either plasma renin activity or aldosterone concentration in response to head-down tilt (9, 20, 24). In water-immersion studies, significant decreases in these parameters have been reported but are not temporally related to the urinary response (3, 7, 8, 21).

Factors such as changes in glomerular filtration rate (GFR), renal nerve activity, atrial natriuretic factor (ANF) and antidiuretic hormone (ADH) levels may be involved in the acute renal response to LBPP. Evidence for an increase in GFR in response to central volume expansion is mixed, but given that GFR did not change in response to the maximal stimulus of heat-out water immersion or 6° head-down tilt, it is unlikely that changes in GFR occurred under the more modest stimulus of LBPP (3, 18, 24). Although there is no clear evidence to suggest that the renal nerves may be involved in this phenomenon, further study is necessary. A role for ANF in mediating the natriuretic and diuretic response

to LBPP may be a more attractive hypothesis since this hormone is known to be released in response to head-down tilt and water immersion (5, 19). The role of ADH in the renal response to central volume expansion is not clear. Gilmore and co-workers have reported that volume expansion does not affect ADH levels in the non-human primate (6). However, changes in plasma ADH are observed in the various models for weightlessness although a true causal relation to the natriuretic and diuretic response has not been developed (3, 4, 6, 21). It is teleologically attractive to postulate that the number of renal effectors involved in the response to central volume expansion depends on the strength of the stimulus. Accordingly, the 20 mmHg LBPP model most likely causes the mildest central volume expansion and thus may "unmask" modulators not immediately apparent with the stonger and more complex stimului of water immersion or head-down tilt.

Our study was designed to examine more prolonged periods of central volume expansion (7 days) in an attempt to more closely mimic conditions of a typical Space Shuttle mission. The latter phase of study is more difficult to interpret than the initial acute phase since we observed that after the third day of LBPP, excretory and hemodynamic variables achieved a relative steady-state and was similar to time controls. A previous investigation by this laboratory using the same model indicated that the natriuretic and diuretic responses were sustained throughout the 4 day period of LBPP, albeit at a reduced level from the first day of the stimulus (12). We extend those initial findings by determining the influence of prolonged chair-sitting on renal and cardiovascular function in the same animals that had undergone the LBPP protocol. From these data it is clear that a gradual increase in urine volume and decrease in osmolality occur over the duration of the 7 day observation period; the mechanism producing this

response to prolonged chair-sitting is not understood at present. In any event, the apparent maintenance of the natriuresis and diuresis when viewing the LBPP urinary response can be accounted for in the control series. Following the inital loss of plasma volume, urinary excretion of solute and water return toward the control excretion values. Therefore, our data suggest that the animals come into balance again but at an apparently reduced extracellular fluid volume. This idea is supported by the constancy of sodium and water balance and its equivalence to that measured in time controls throughout this adaptive period (days 2-7).

There are clear differences in the time course of adaptation for the excretory variables. While sodium excretion tends to return to baseline rapidly (within a few hours), urine volume and osmolality drift more slowly downward over the first 24-48 hrs of LBPP. As with the acute response, further studies will be required to determine the effectors that control the reduction in renal sodium and water excretion and the return of urinary concentrating ability during the adaptive phase. Clearly a rise in plasma aldosterone does not occur and thus the return to normal sodium balance must be mediated by other mechanisms.

If exposure to 0g and the models for weightlessness produce a reflex renal response to decrease the effective circulating vascular volume, then reexposure to 1g or removal of the stimulus in an appropriate model should set in motion a series of responses to the opposite challenge--an inadequately filled vascular space. Data from the human models and spaceflight suggest that hypovolemia does occur and that the renal conservation of fluids and electrolytes is probably driven by increasing levels of aldosterone and ADH (9, 13, 16, 17). Data from the present study are not conclusive perhaps due to the possible serendipitous changes in excretory patterns in the time controls on the day equivalent to that

following removal of LBPP. The clear trend towards fluid conservation in the LBPP series on the recovery day was significant when compared to values for the last day of pressure but not when the two series were directly compared. In contrast to what may have been expected, plasma aldosterone concentrations in the LBPP series did not increase significantly on this day. Obviously, further study of a more prolonged period of recovery will allow a more definitive conclusion about the mechanisms involved in the recovery period.

The hemodynamic response to LBPP onset was characterized by a variable and relatively short-lived elevation in CVP. Given the large compliance of the central venous reservoir, a relatively large cephalad shift of fluid is indicated by the average peak increase in CVP of 1.8 mmHg. Mean arterial pressure also briefly increased but may be a startle reaction to the onset of air flow through the lower chamber. The transient nature of the CVP elevation would suggest that a vasodilatory mechanism such as a withdrawl of sympathetic tone and/or an increased release of ANF may offset the increase in central vascular volume. The nature of the effector limb linking the cardiovascular and renal systems is not readily apparent from these studies. Although the rise in both CVP and AP was modest and transient, the renal response was marked and continued throughout the first 24-48 hrs of LBPP.

We observed that both CVP and AP decreased following removal of LBPP. These changes were, in fact, much more consistent and of greater magnitude than those following stimulus application. Furthermore, the persistence of AP below that of the last day of pressure should provide a strong stimulus for renal salt and water conservation. This situation is similar to the cardiovascular deconditioning present in astronauts returning from spaceflight (2). In the LBPP model as well as during spaceflight, however, it is unclear whether these

recovery effects occur secondary to a reduced circulating volume that is not being rapidly replenished or consequent to a resetting of baroreceptor or other control mechanisms produced by the prolonged central vascular congestion.

In summary, this study provides the first renal and cardiovascular data from a non-human primate model for 7-day exposure to a simulated weightless environment. We provide results indicating that chronic exposure of the squirrel monkey to a LBPP-induced central volume expansion results in a two-phase response. During the first 24-48 hrs, natriuresis and diuresis occur which reduces the effective extracellular fluid volume. As a result of the reduction of vascular volume, the animals return to salt and water balance and remain so for the duration of the stimulus. Removal of the stimulus results in a modest conservation of fluid and electrolytes and a reduction in mean arterial pressure that appears similar to the syndrome of cardiovascular deconditioning appearing in astronauts upon their return to 1g from spaceflight.

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FIGURE LEGENDS

Fig.1 Diagram of metabolism chair custom-designed for the squirrel monkey.

Fig.2 Daily urinary sodium excretion, volume, and osmolality during seven days (days 1-7 as denoted by black bars) of lower body positive pressure (LBPP) or in the absence of LBPP (control). Days 0 and 8 are pre- and post-pressure days, respectively, in the LBPP series. Values are 24 hr means $\pm$ SE for seven animals. * indicates $P<0.05$ vs. paired control day.

Fig.3 Urinary sodium excretion, volume, and osmolality one day prior to (day 0) and during the first two days of lower body positive pressure (LBPP) (days 1 and 2). Controls did not receive LBPP. Black bars denote hours of darkness. Values are means $\pm$ SE for two hour urine collection periods in seven animals. * indicates $P<0.05$ vs. paired control value.

Fig.4 Water and sodium balance during seven days (days 1-7 as denoted by black bar) of lower body positive pressure (LBPP) or in the absence of LBPP (control). Days 0 and 8 are pre- and post-pressure days, respectively, in the LBPP series. For both variables, balance was calculated as the difference between intake and urinary excretion. Values are 24 hr means $\pm$ SE for seven animals. * indicates $P<0.05$ vs. paired control day.

Fig.5 Daily urinary potassium excretion during seven days (days 1-7 as denoted by black bars) of lower body positive pressure (LBPP) or in the absence of LBPP (control). Days 0 and 8 are pre- and post-pressure days, respectively, in the LBPP series. Values are 24 hr means $\pm$ SE for seven animals. * indicates $P<0.05$ vs. paired control day.

Fig.6 Plasma aldosterone concentration during seven days (days 1-7 as denoted by black bar) of lower body positive pressure (LBPP) or in the absence of LBPP (control). Day 8 represents a post-pressure day in the LBPP series. Blood

samples used for analysis were drawn each day at 13:00 h with an additional sample being taken at 15:00 h on day 1. Values are means $\pm$ SE for seven animals.

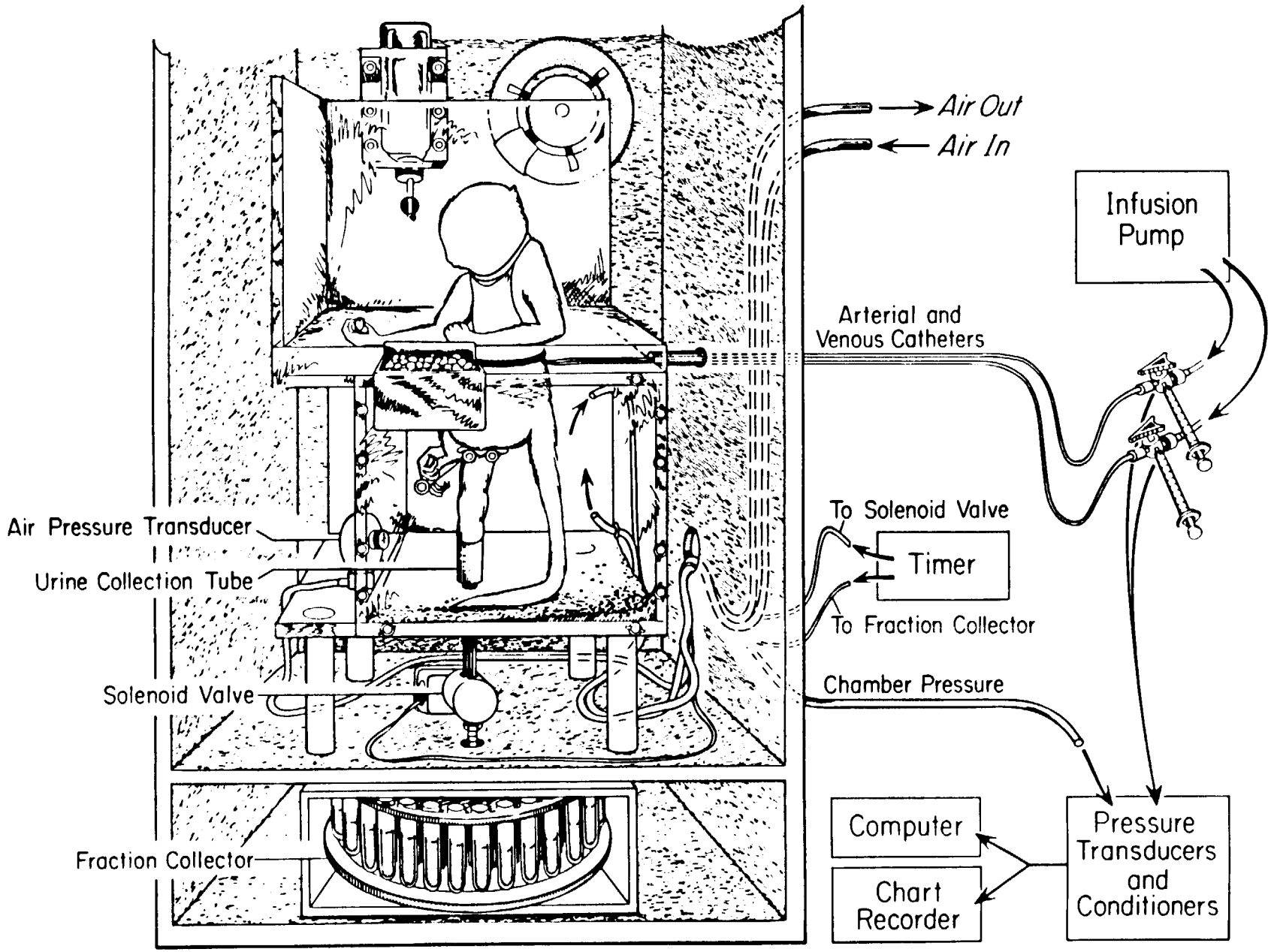
Air Out
Air In
Infusion Pump
Arterial and Venous Catheters
To Solenoid Valve
Timer
To Fraction Collector
Chamber Pressure
Air Pressure Transducer
Urine Collection Tube
Solenoid Valve
Fraction Collector
Computer
Chart Recorder
Pressure Transducers and Conditioners

FIG. 1

FIG. 2

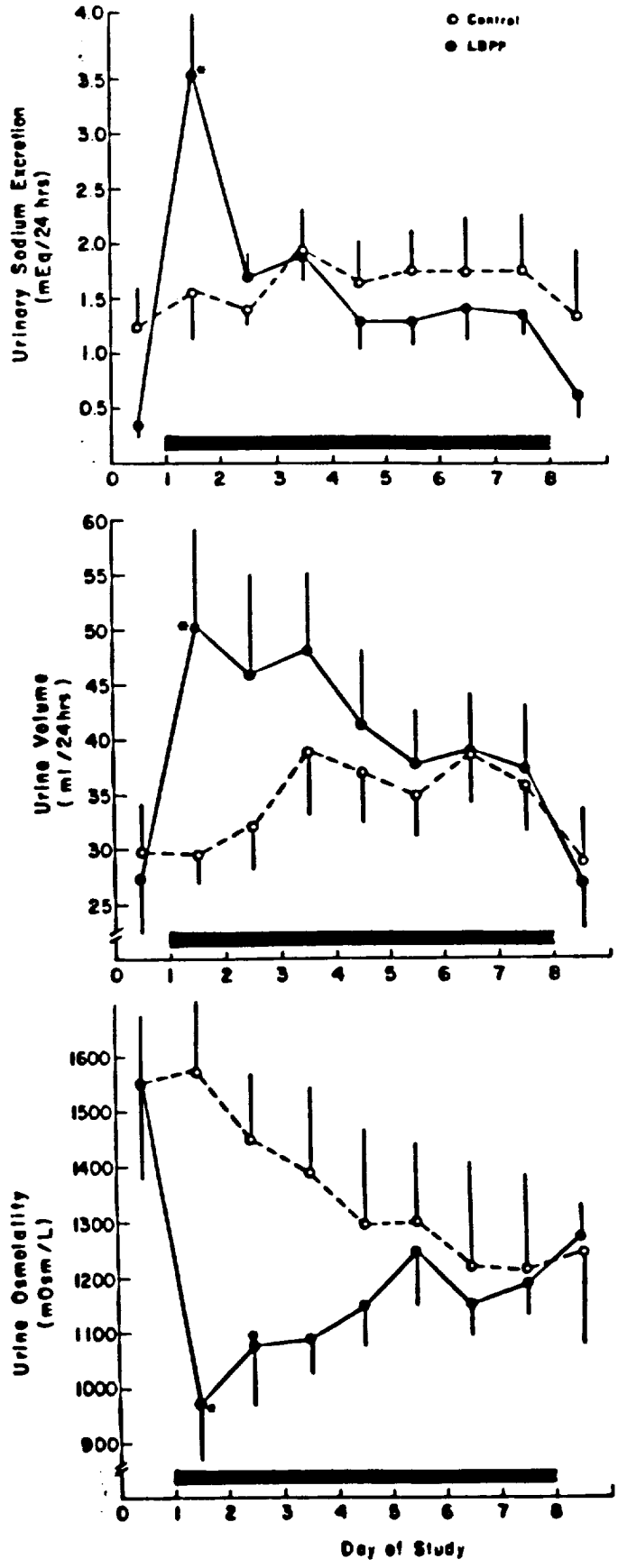
○ Control
● LBPP
Urinary Sodium Excretion (mEq/24 hrs)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
1
2
3
4
5
6
7
8
Urine Volume (ml/24hrs)
60
55
50
45
40
35
30
25
Urine Osmolality (mOsm/L)
1600
1500
1400
1300
1200
1100
1000
900
Day of Study

FIG. 3

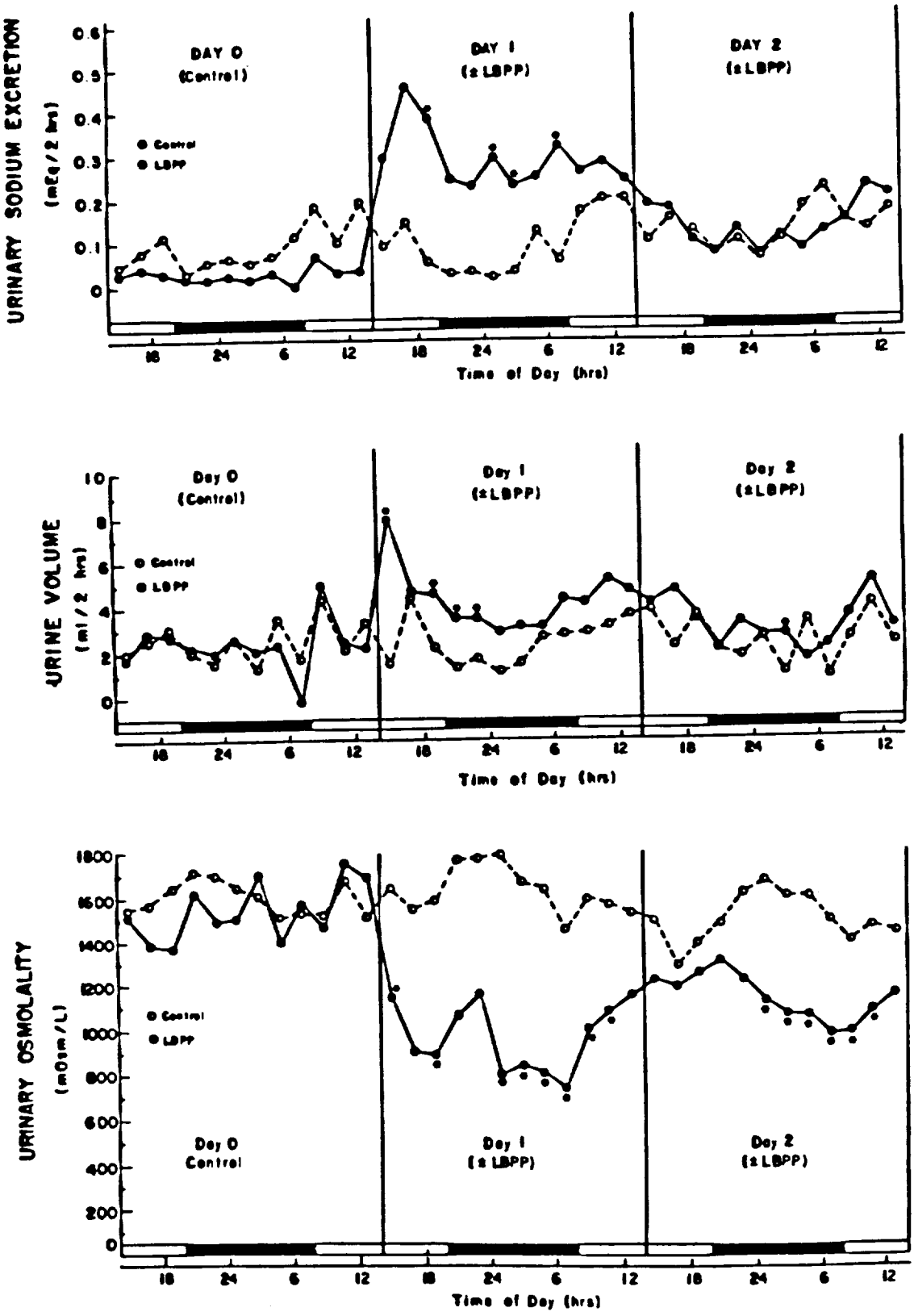
URINARY SODIUM EXCRETION
(mEq/2 hrs)
DAY 0
(Control)
DAY 1
(±LBPP)
DAY 2
(±LBPP)
Control
LBPP
Time of Day (hrs)
URINE VOLUME
(ml/2 hrs)
Day 0
(Control)
Day 1
(±LBPP)
Day 2
(±LBPP)
Control
LBPP
Time of Day (hrs)
URINARY OSMOLALITY
(mOsm/L)
Control
LBPP
Day 0
Control
Day 1
(±LBPP)
Day 2
(±LBPP)
Time of Day (hrs)

FIG. 4

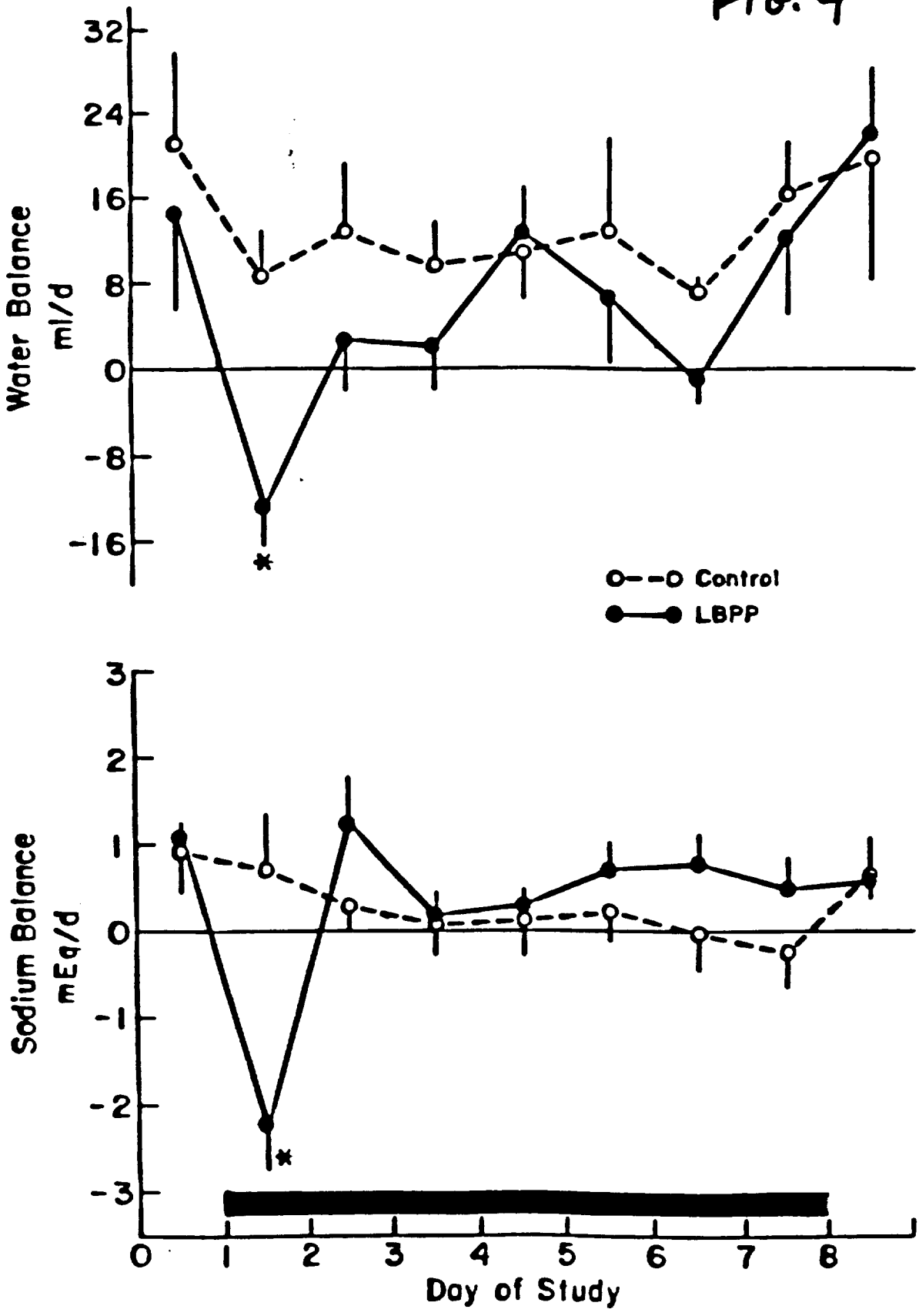
Water Balance
ml/d
32
24
16
8
0
-8
-16
*
Control
LBPP
Sodium Balance
mEq/d
3
2
1
0
-1
-2
-3
*
0
1
2
3
4
5
6
7
8
Day of Study

FIG. 5

Urinary Potassium Excretion
(mEq/24 hrs)
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
Day of Study
O Control
● LBPP

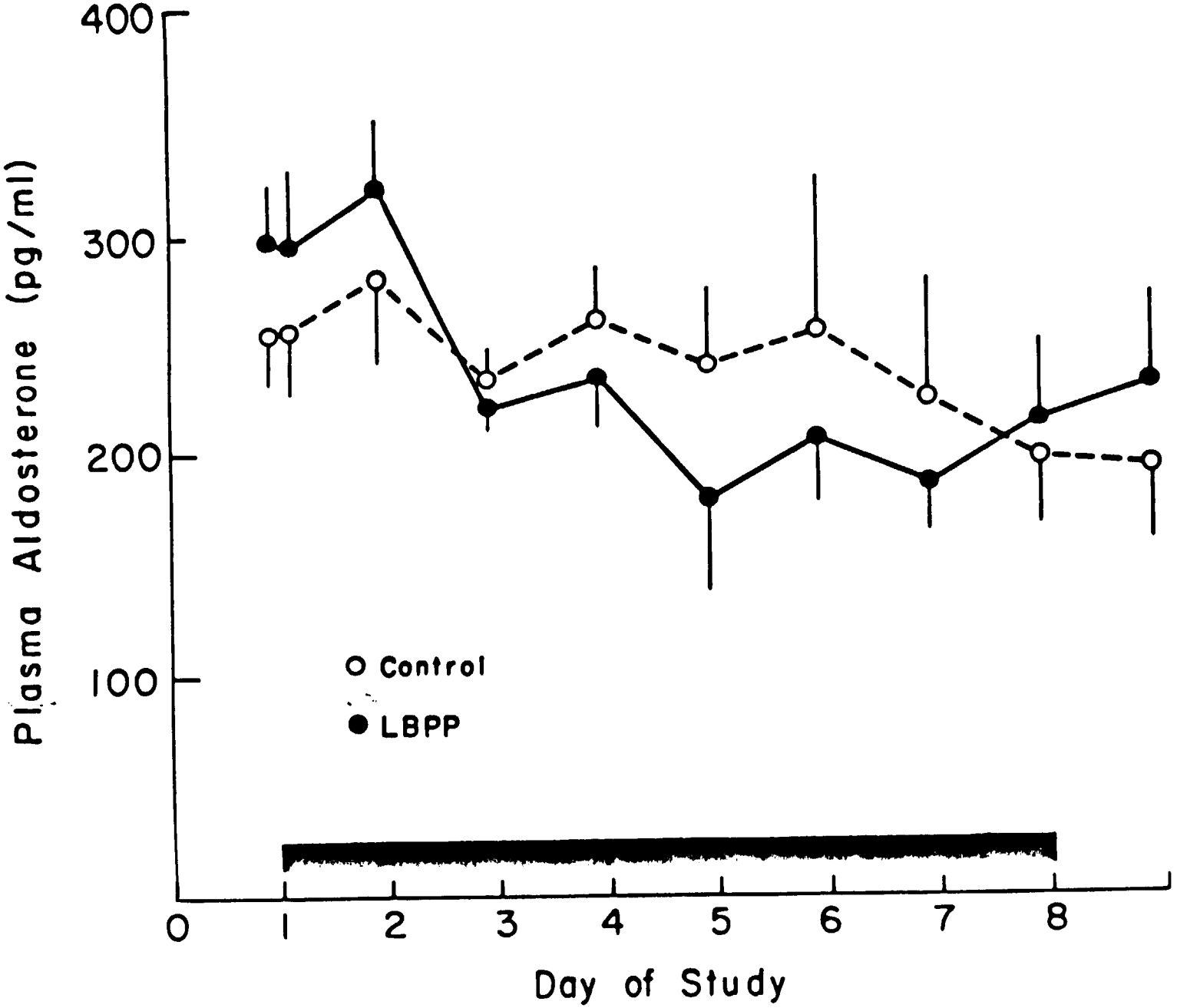
400
300
200
100
Plasma Aldosterone (pg/ml)
Control
LBPP
0
1
2
3
4
5
6
7
8
Day of Study

FIG. 6