Fluid compartment and renal function alterations in the rat during 7 and 14 day head down tilt

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Exposure to conditions of microgravity for any extended duration can modify the distribution of fluid within the vascular and interstitial spaces, and eventually intracellular volume. Whether the redistribution of fluid and resetting of volume homeostasis mechanisms is appropriate for the long term environmental requirements of the body in microgravity remains to be fully defined. The event that initiates the change in fluid volume homeostasis is the cephalad movement of fluid which potentially triggers volume sensors and stretch receptors (atrial stretch with the resulting release of atrial natriuretic peptide) and suppresses adrenergic activity via the carotid and aortic arch baroreceptors. All these events act in concert to reset blood and interstitial volume to new levels, which in turn modify the renin-angiotensin system. All these factors have an influence on the kidney, the end organ for fluid volume control. How the fluid compartment volume changes interrelate with alterations in renal functions under conditions of simulated microgravity is the focus of the present investigation which utilizes 25-30° head-down tilt in the rat.

A previous investigation by our laboratory studied the effects of head-down tilt (HDT) during the first seven days of suspension utilizing both chronic cannulation, thereby allowing repeated measures in the same rat, and renal micropuncture methods (1). In this study we examined the changes in extracellular fluid volume and renal function during the time course of HDT in the rats. The measurements of extracellular fluid volume and whole kidney function were performed in awake rats, thus permitting evaluation of the time course alterations in renal function in conscious non-surgically stressed rats. The HDT group was compared to suspended but non-tilted controls. In addition to the awake

studies, renal micropuncture techniques were utilized to ascertain the changes in the determinants of glomerular ultrafiltration at the single nephron level in rats exposed to seven days of HDT (1). Plasma renin activity, plasma catecholamine concentrations, and urinary catecholamine excretion were also measured to ascertain whether any of the changes in glomerular dynamics observed could be correlated with these factors which regulate systemic and renal vascular resistance (1).

In this first study, extracellular fluid space (ECF) significantly increased within 24 hr after the onset of HDT and then returned gradually to pre-tilt values by the end of the 7 day HDT (figure 1). Glomerular filtration rate (GFR) also increased significantly (19±8%) within 24 hours with a gradual decline and finally a significant reduction (-7±1%) by day 7 of head-down tilt (figure 1). The changes in GFR were most likely renal plasma flow dependent since the GFR changes paralleled the alteration in renal plasma flow except after seven days HDT where GFR was reduced and renal plasma flow was not different from control values (figure 1). In general, urine flow increased by 24 hours of HDT and remained elevated throughout the 7 days of simulated microgravity (figure 2). Both urinary sodium and potassium excretion changes were less consistent during the seven day HDT (figure 2).

At the end of seven day HDT another group of rats were submitted to renal micropuncture studies to ascertain which of the determinants of glomerular filtration contributed to the reduction in filtration rate. In superficial nephrons, single nephron glomerular filtration rate (SNGFR) decreased from 43±2 to 31±3 nl/min which was due solely to reductions in the glomerular ultrafiltration coefficient (1). These data are

consistent with the awake rat renal function measurements in which parameters other than renal plasma flow were responsible for the reduction in glomerular filtration rate. This first study was successful in delineating some of the specific alterations in renal function that occur in this model of cephalad fluid shift and relative hypokinesia, findings which are similar to human studies in situations of simulated microgravity (2).

In more recent studies, initiated this year with the start of NAG 2-659, two separate groups of rats were utilized to examine blood volume changes, extracellular fluid volume, and renal function alterations during 14 day HDT and 7 days post-tilt recovery. The major focus of this study was to further define the applicability of this model for longer term studies simulating the changes that occur in humans under conditions of microgravity and recovery and to correlate the changes in fluid compartment volumes to alterations in renal function to ascertain if the kidneys were responding to maintain volume homeostasis.

In the first group of rats, chronic cannulation of the femoral artery and vein was performed and the animals were allowed one week to recover. The rats were separated into four subgroups (n=6 in each group) and either tail suspended for 1, 7, or 14 days or left in the normal orthostatic position. Blood volume was measured in each of the four subgroups of awake rats utilizing ^{51}Cr labeled endogenous erythrocytes and the changes in volume with duration of HDT was compared to non-tilted controls. Although not significant, blood volume tended to increase from 5.4±0.1 to 5.6±0.1% of body weight after 24 hrs HDT (figure 3). By day 7, blood volume significantly decreased to 5.0±1% of body weight and decreased further to 4.8±0.1% by day 14 of HDT similar to observations made in humans (figure 3). There were no differences in body weight,

systemic hematocrit, or plasma protein concentrations among the four subgroups indicating that the observed blood volume changes were independent of these factors.

In the second group of rats cannulation of the femoral artery and vein and bladder was performed as in prior studies for chronic monitoring of extracellular volume, systemic electrolytes and plasma protein concentration as well as renal function (GFR, renal plasma flow, urine flow rate, urinary sodium and potassium excretion). Serial measurements of these parameters were performed twice prior to HDT and then at 24 hrs, 3, 7, 10, and 14 days during HDT. After the 14 day HDT period was completed, all rats were returned to normal orthostatic position and, after a 45 min waiting period, the measurements were repeated. Measurements were also performed at 24 hrs, 3, and 7 days post-HDT. All values were compared to pre-tilt control measurements in the same rat on a paired basis. Similar to our previous findings, extracellular fluid volume increased from 28.2±3.1 to 31.4±3.5 % of body weight after 24 hrs of HDT and then steadily decreased to 24±2.1 % of body weight by day 7 (figure 4). By day 14, ECF returned to values not different from control (27.3±1.2 % of body weight). During post-tilt recovery, ECF did not differ from pre-tilt control values (figure 4). GFR increased during HDT from 2.1±0.1 in control to 2.3±0.2 after 24 hrs HDT and to 2.8±0.2 ml/min after 3 days HDT (figure 5). By day 7, GFR was not different from control (2.2±0.1 ml/min) and GFR at day 14 HDT was 2.3±0.2 ml/min, also not different from pre-tilt values (figure 5). It was surprising that GFR remained at values not different from control despite the decrease in blood volume and 7 and 14 days HDT. Post-tilt GFR values were not different from pre-tilt values measured in this group of rats (figure 5). Renal plasma flow increased by day 3 of HDT

but did not significantly deviate from control values at the other measurement time points (figure 6). In early HDT, there seems to be a mild volume expansion with concomitant increase in GFR and renal plasma flow, but after the initial expansion phase, ECF and renal function return to values not different from pre-tilt measurements with a decrease in blood volume.

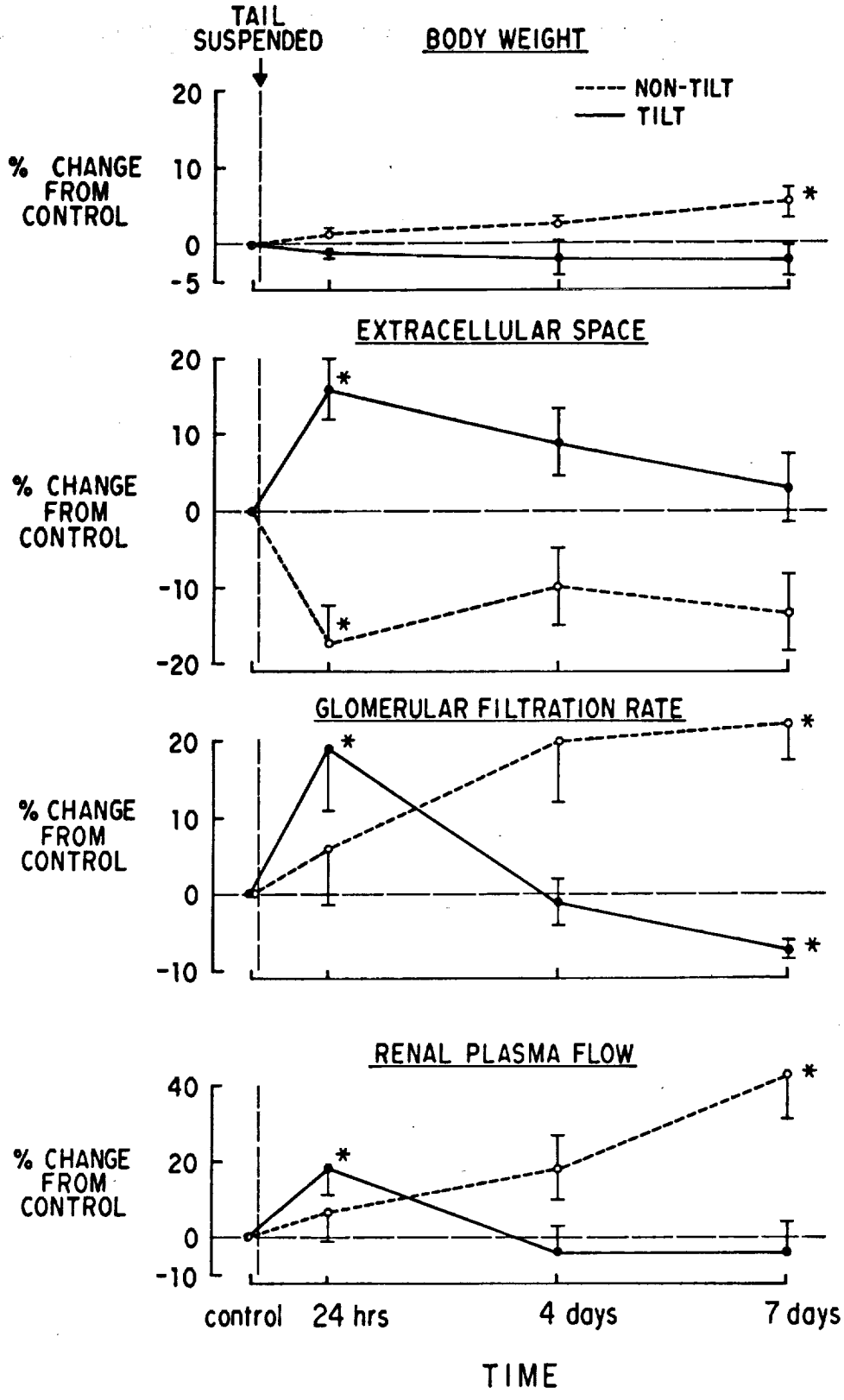
These definition phase studies provide a low cost, ground based alternative for investigation of fluid compartment volume alterations and renal function in microgravity conditions. The results are quite similar to the studies in humans where some of the same parameters were measured in HDT. However, the rat also provides a model for more invasive studies, such as renal micropuncture, as well as a vehicle for therapeutic trials to modify cardiovascular and renal response due to long term exposure to microgravity. Also, this model can easily be extended to examine volume homeostasis and renal function under conditions of 30-90 days of simulated microgravity.

REFERENCES

1. Tucker, B.J., Mundy, C.A., Ziegler, M.G., Baylis, C., and Blantz, R.C. **J. Appl. Physiol.** 63:505-513, 1987.

2. Greenleaf, J.E., Brock, P.J., Haines, R.F., Rositano, S.A., Montgomery, L.D., and Keil, L.C. **Aviation, Space and Environ. Med.** 48:693-700, 1977.

Figure 1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—— TILT
% CHANGE FROM CONTROL
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10
0
-5
*
EXTRACELLULAR SPACE
20
10
0
-10
-20
*
GLOMERULAR FILTRATION RATE
20
10
0
-10
*
RENAL PLASMA FLOW
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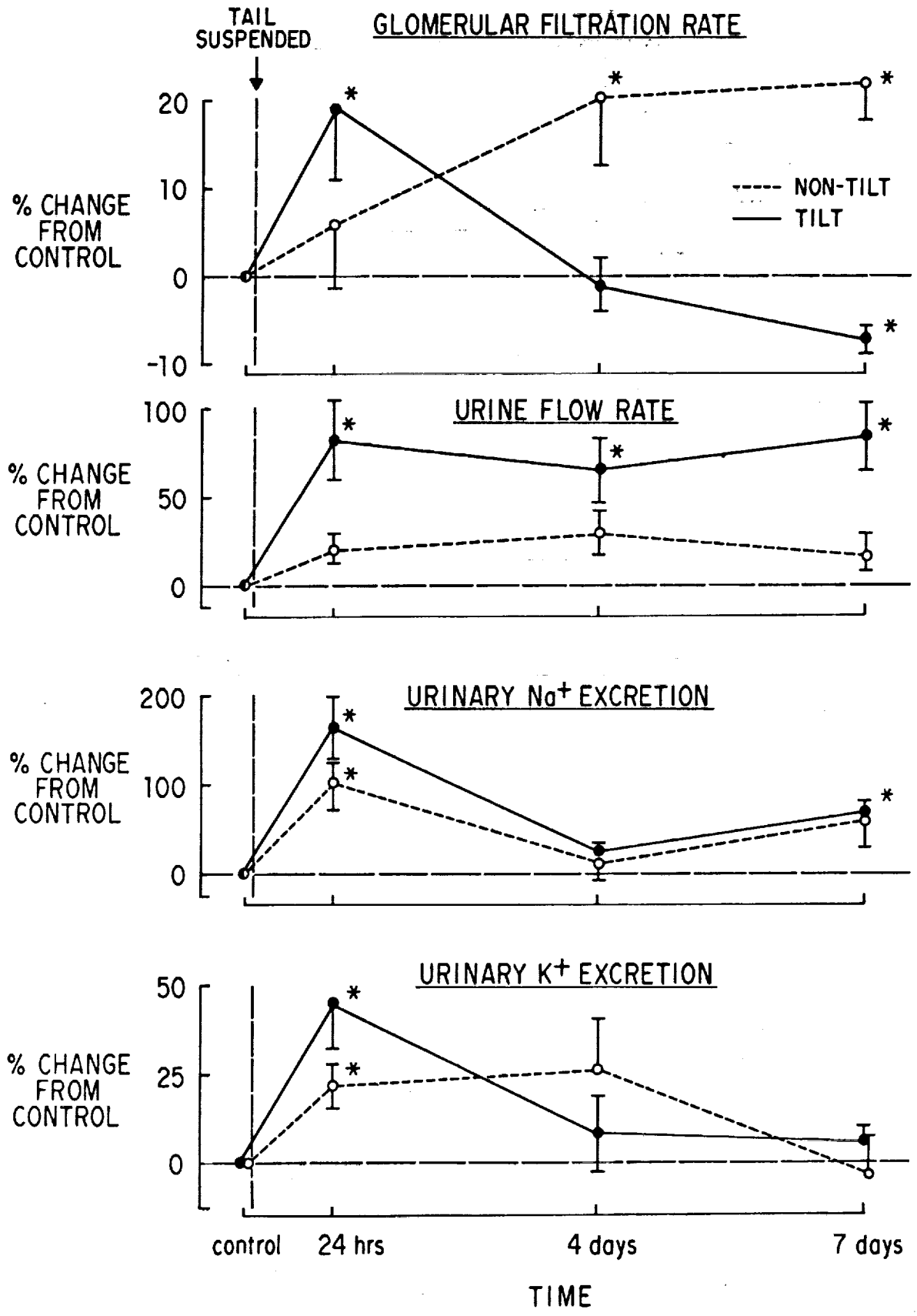
20
0
-10
control
24 hrs
4 days
7 days
TIME

Figure 2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% CHANGE FROM CONTROL
NON-TILT
TILT
URINE FLOW RATE
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50
0
% CHANGE FROM CONTROL
URINARY Na+ EXCRETION
200
100
0
% CHANGE FROM CONTROL
URINARY K+ EXCRETION
50
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% CHANGE FROM CONTROL
control
24 hrs
4 days
7 days
TIME

BLOOD VOLUME CHANGES IN HEAD DOWN TILT

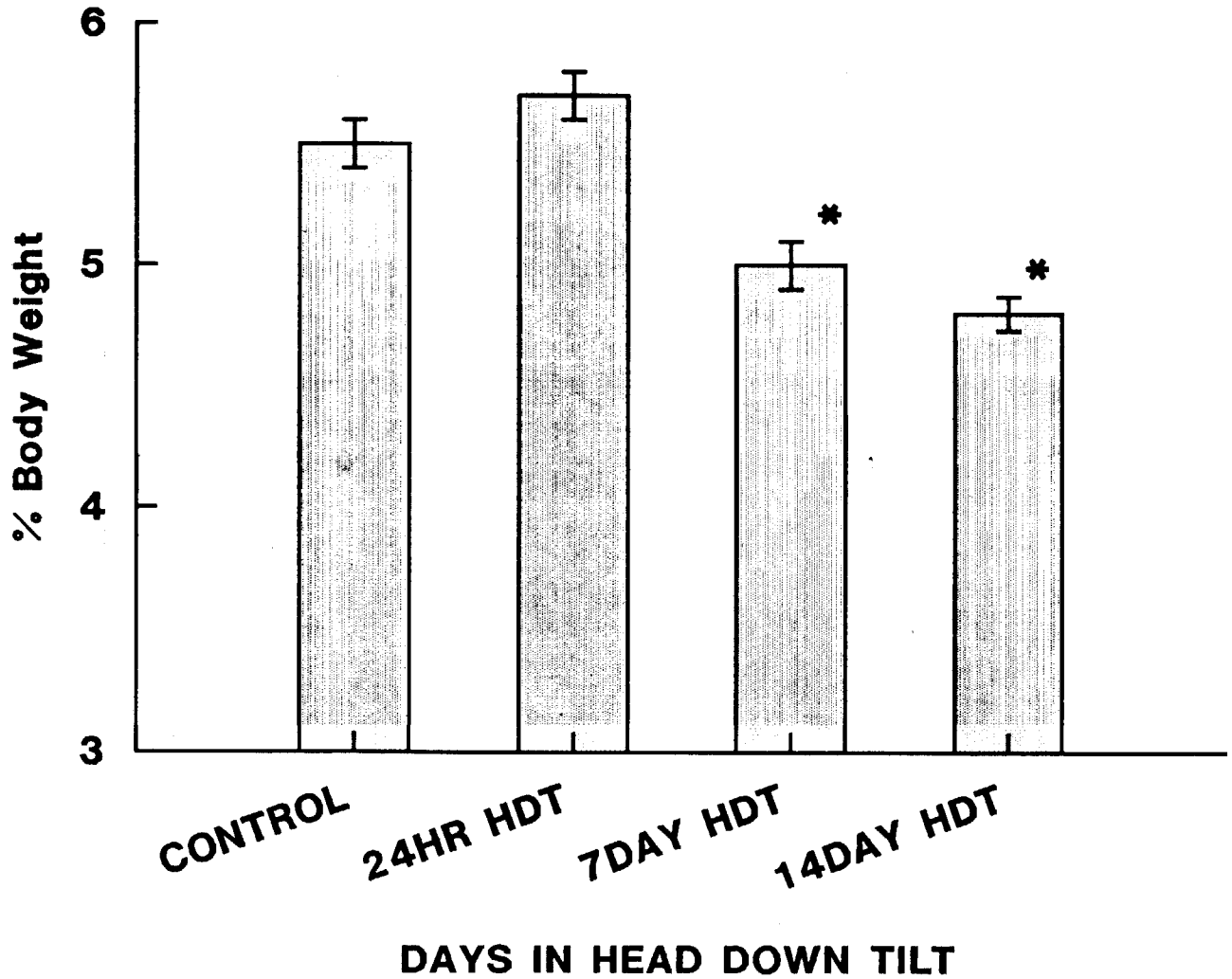

Figure 3

EFFECT OF HDT ON EXTRACELLULAR FLUID VOLUME

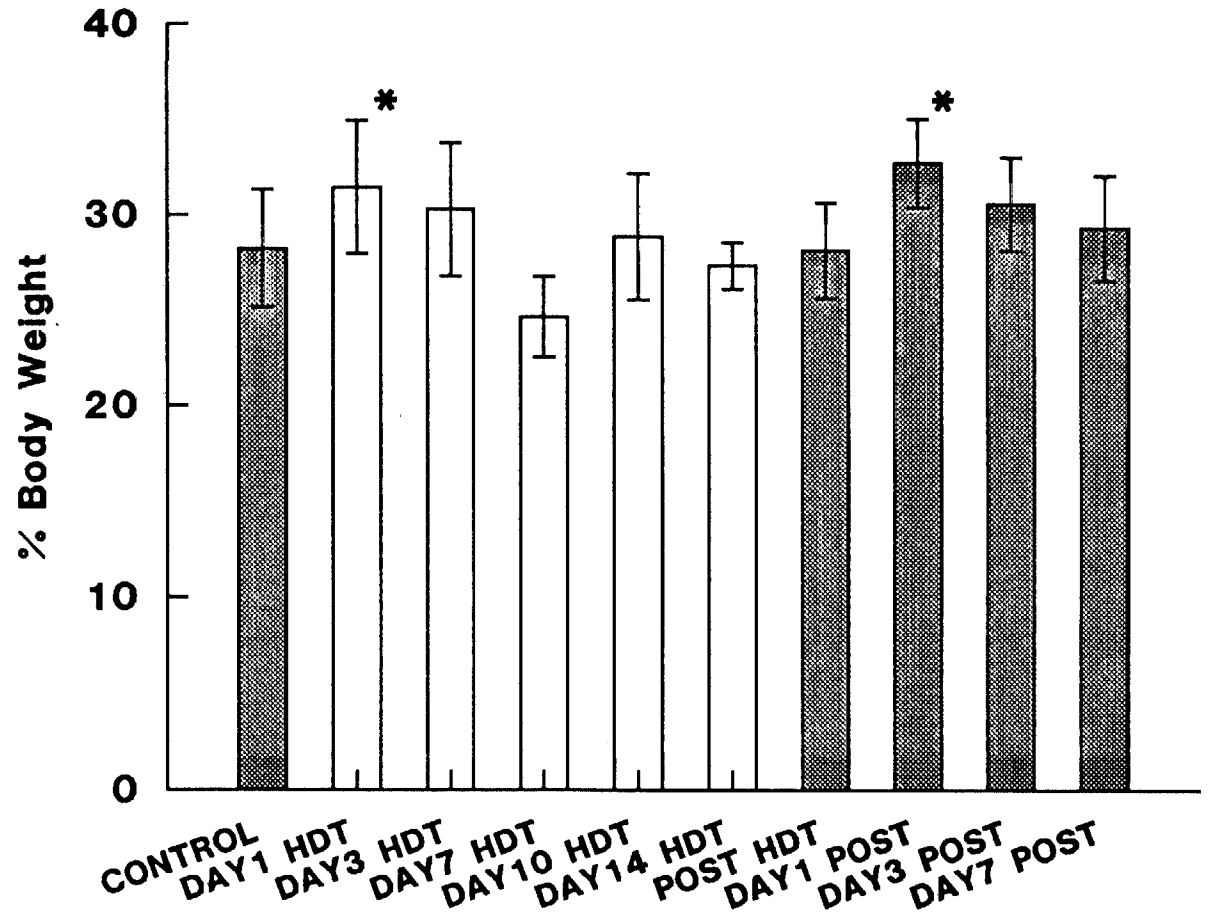

Figure 4

EFFECT OF HDT ON GLOMERULAR FILTRATION RATE

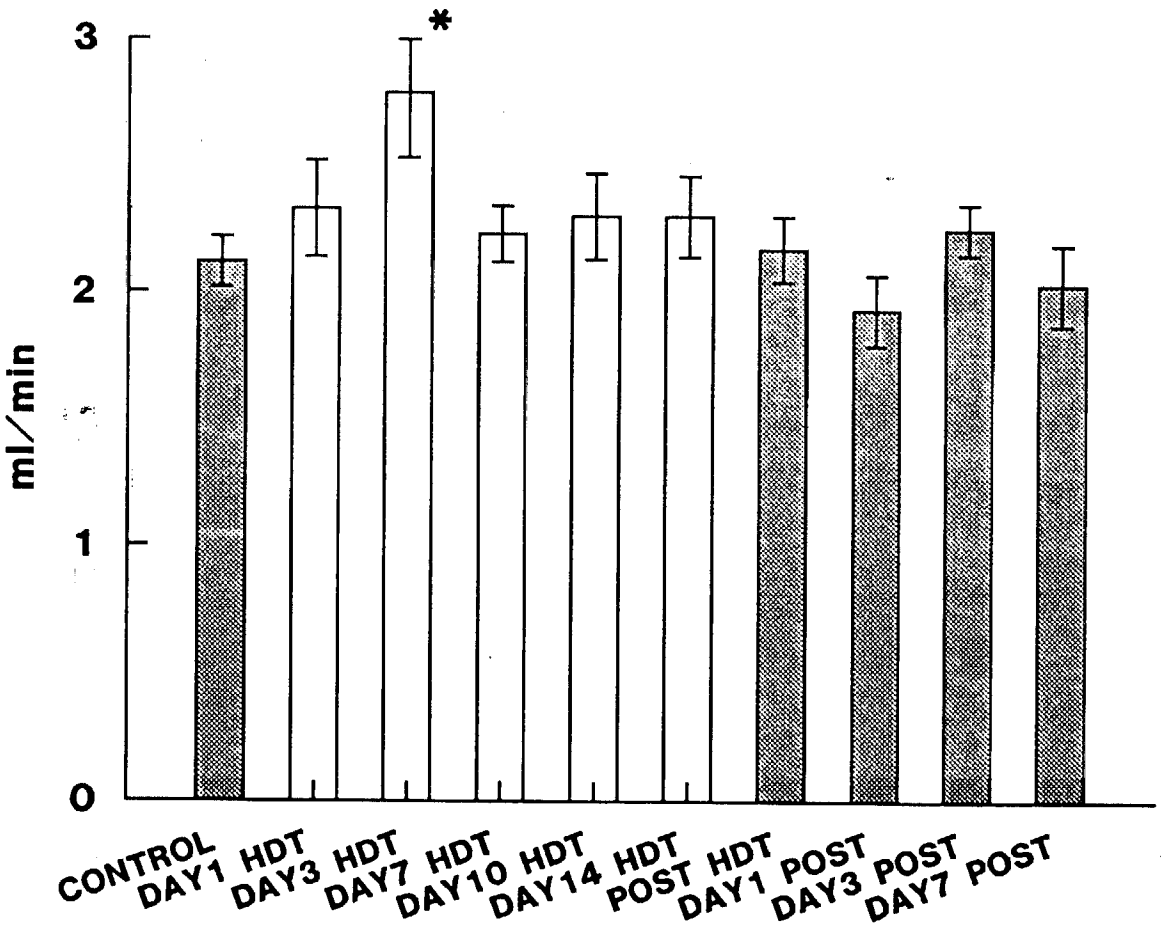

Figure 5

EFFECT OF HEAD DOWN TILT ON RENAL PLASMA FLOW

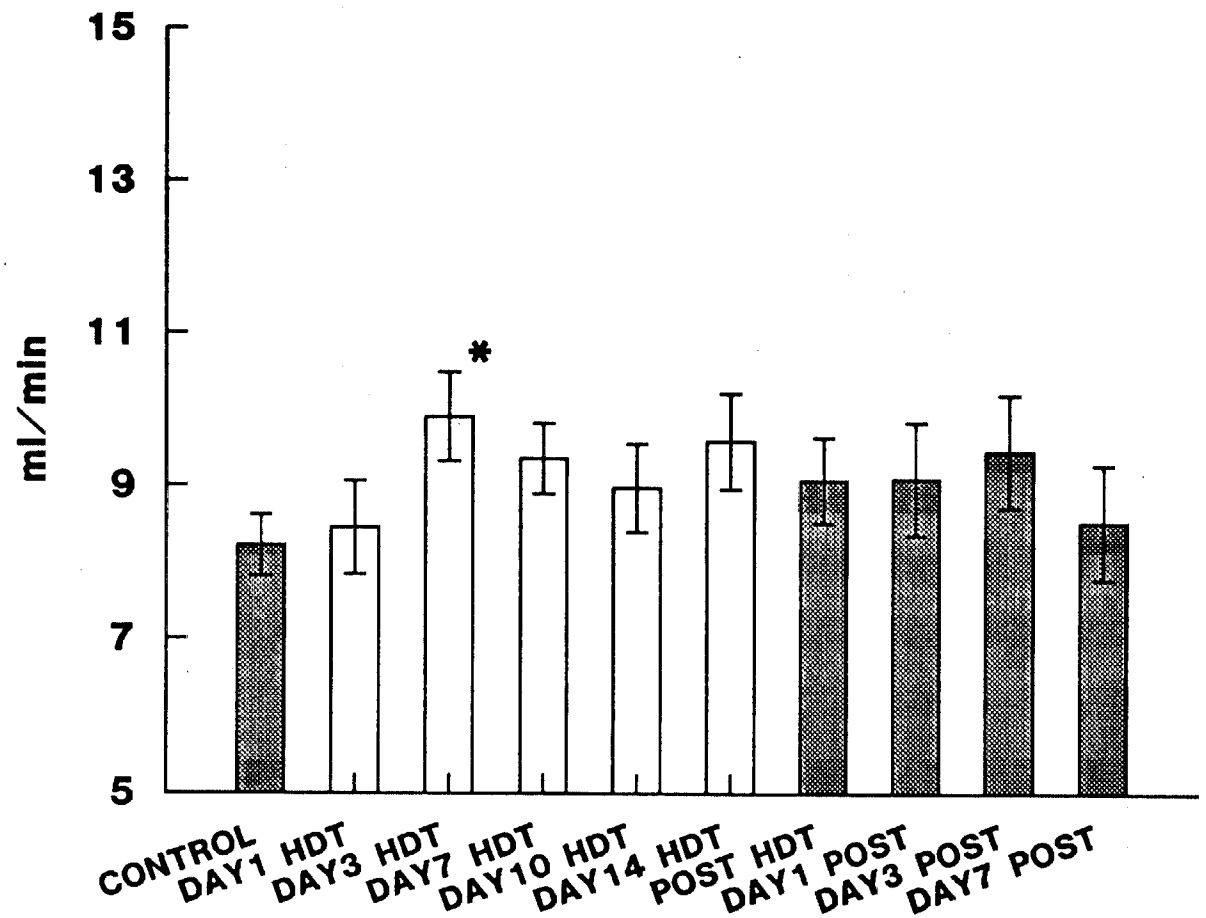

Figure 6