NASA Grant NAG2- 1340

FINAL REPORT: SUMMARY OF RESEARCH
ADAPTATIONS OF VISCERAL AND CEREBRAL RESISTANCE ARTERIES TO SIMULATED MICROGRAVITY
PI: MICHAEL DELP, PH.D., TEXAS A&M UNIVERSITY
JULY 1, 1999 – JUNE 30, 2003

SPECIFIC AIMS

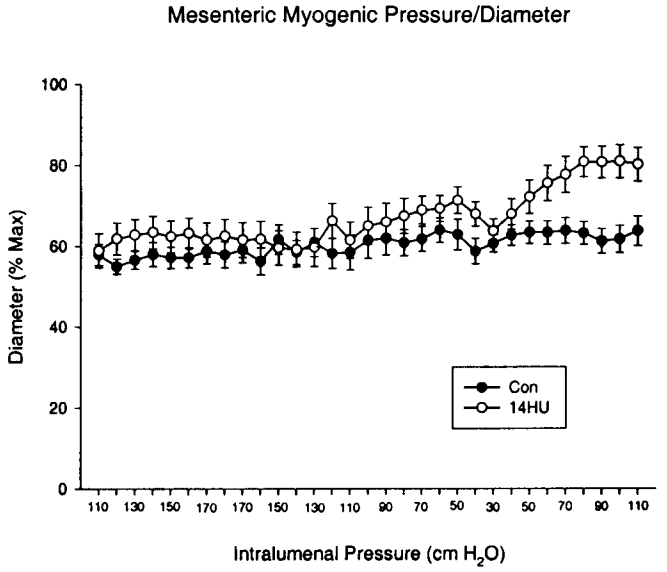
The proposed studies were designed address the effects of simulated microgravity on vascular smooth muscle and endothelial cell function in resistance arteries isolated from visceral tissues (spleen, mesentery and kidneys) and cerebrum. Alterations in vascular function induced by microgravity are particularly relevant to the problems of orthostatic intolerance and reduced exercise capacity experienced by astronauts upon re-entry into the earth's gravitational field. Decrements in contractile function or enhanced vasodilatory responsiveness of peripheral resistance arteries could lead to decreased peripheral resistance and orthostatic hypotension. Alternatively, augmentation of contractile function in cerebral resistance arteries could lead to increased cerebral vascular resistance and diminished perfusion of the brain.

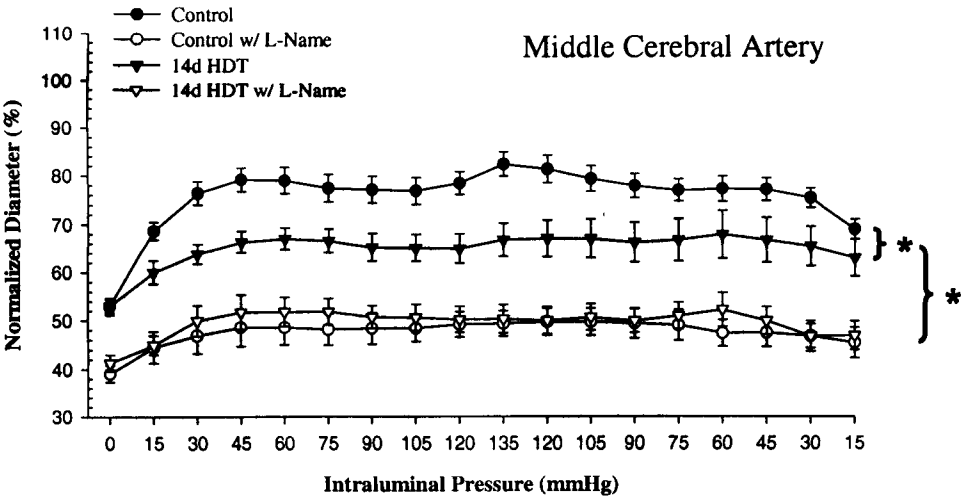
The following Specific Aims and hypotheses were proposed in this grant. Following each of the Specific Aims, progress toward addressing that specific aim is presented. With the exception of Specific Aim VI (see aim for details), all aims have been experimentally addressed as proposed. The final six months of the granting period will be used for manuscript preparation; manuscripts in preparation will contain results from Specific Aims I-IV. Results from Specific Aims V and VI have been published.

NASA Grant NAG2- 1340

I. Hindlimb unloading will attenuate myogenic responsiveness of resistance arteries isolated from the spleen, mesentery and kidneys, and increase myogenic responsiveness of cerebral resistance arteries. Myogenic (contractile) responses to incremental elevations in intravascular fluid pressure will be determined in visceral and cerebral resistance arteries of HU and C rats.

We found that the first-order renal arteries did not develop myogenic tone. Results of studies to determine the effects of unloading on myogenic responsiveness from cerebral and mesenteric resistance arteries are illustrated below. There was no effect of HU on myogenic responses in mesenteric arteries, but there was an increased myogenic responsiveness in the middle cerebral artery. The nitric oxide synthase inhibitor L-NAME eliminated differences between groups.

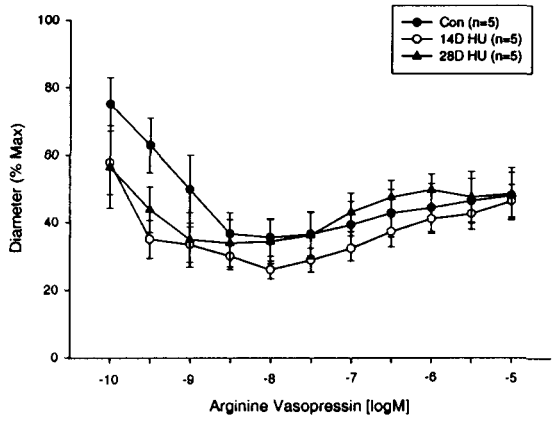




II. Hindlimb unloading will decrease responsiveness of visceral resistance arteries to vasoconstrictor agonists, and increase responsiveness of cerebral resistance arteries. Maximal contractile response and sensitivity (the agonist concentration that produces 50% of the maximal contractile response or EC_{50}) to norepinephrine (NE), arginine vasopressin (AVP), and KCl will be determined in resistance arteries from visceral tissues and to KCl in middle cerebral arteries from of HU and C rats.

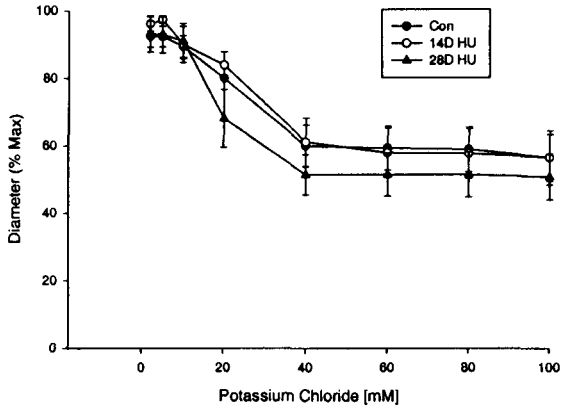
Hindlimb unloading had no effect on renal or splenic vasoconstrictor responses. However, mesenteric vasoconstrictor responses were diminished and cerebral vasoconstrictor responses were enhanced.

Renal AVP Dose Response



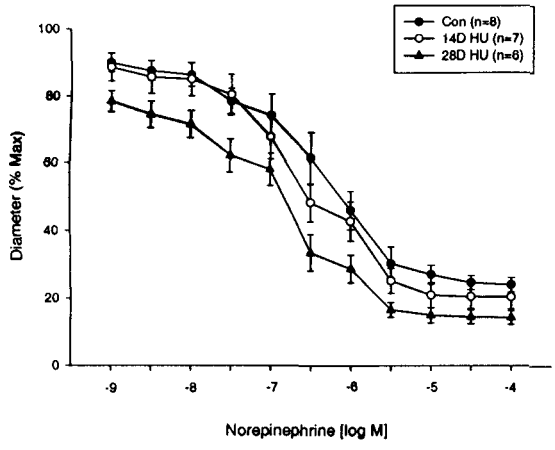
Data expressed as means ± S.E. P = 0.404

Renal KCl Dose Response

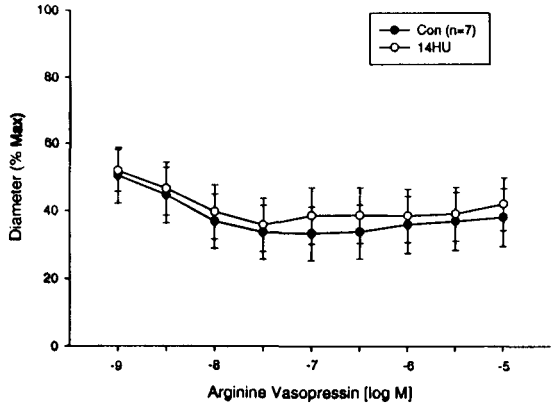


Data expressed as Mean ± S.E. P = 0.696

Renal NE Dose Response



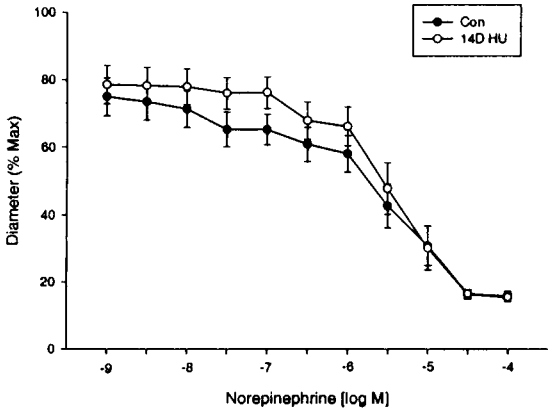
Splenic AVP Dose Response



Data expressed as Mean ± S.E. P = 0.217

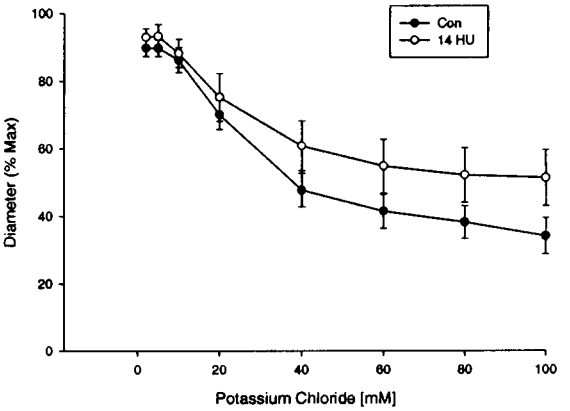
NASA Grant NAG2- 1340

Splenic NE Dose Response



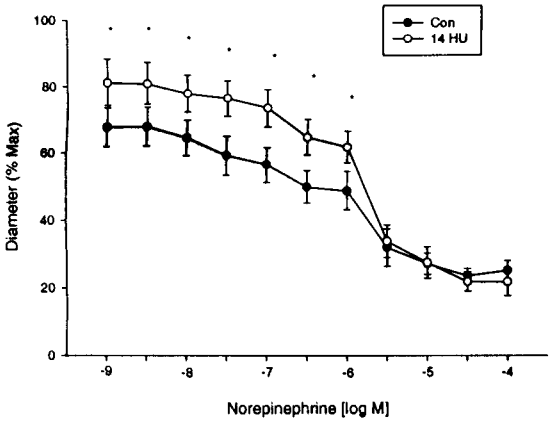
Data expressed as Mean ± S.E. P = 0.388

Splenic KCl Dose Response



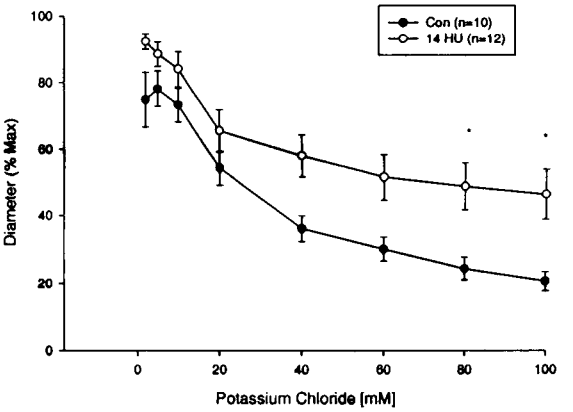
Data expressed as Mean ± S.E. P = 0.215

Mesenteric NE Dose Response



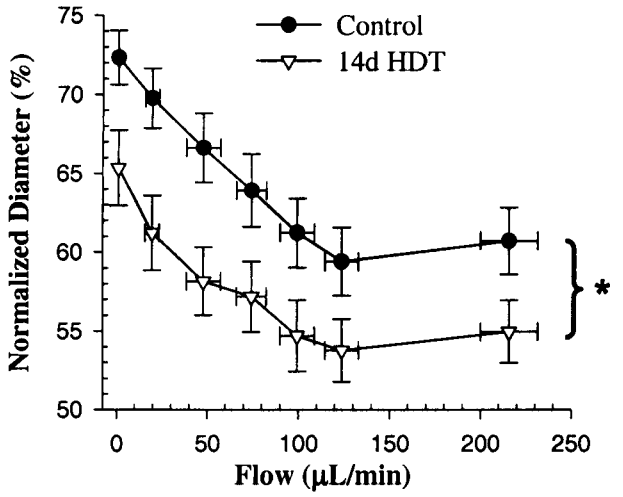
Data expressed as Mean ± S.E. * Significantly different than control, P = 0.006

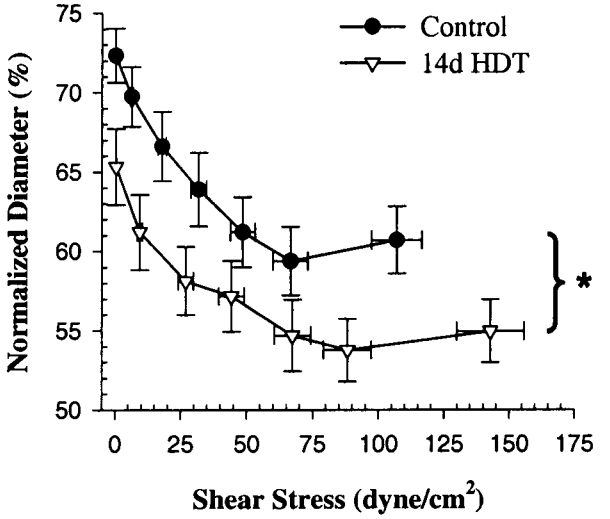
Mesenteric KCl Dose Response

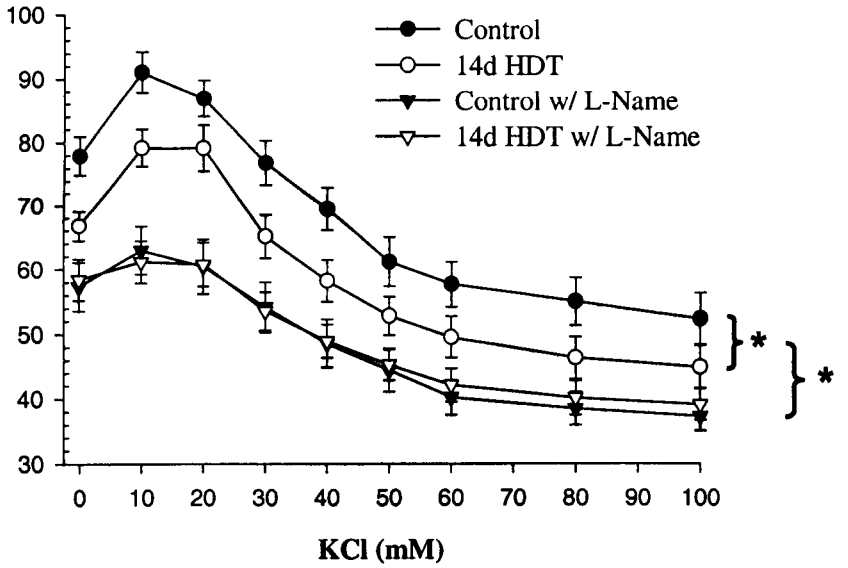


Data expressed as Means ± S.E. * Significantly different than control, P = 0.013

Constrictor responses of the middle cerebral artery:

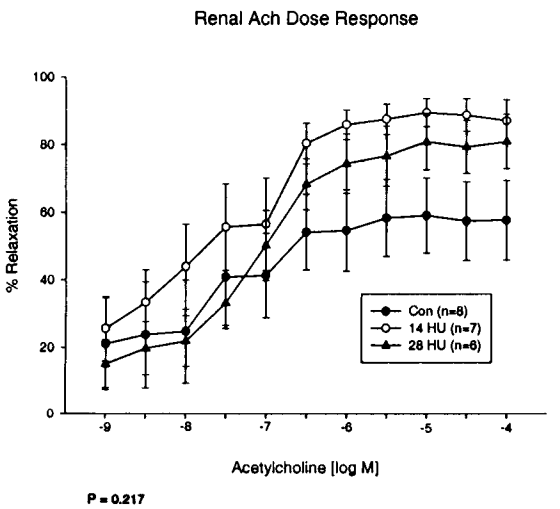


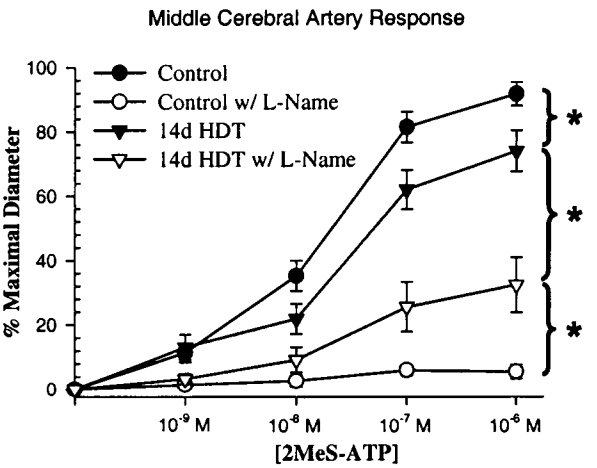




III. Hindlimb unloading will increase and decrease visceral and cerebral resistance artery responsiveness, respectively, to either endothelium-dependent or endothelium-independent vasodilator stimuli. Maximal dilatory response and sensitivity (the agonist concentration that produces 50% of the maximal dilatory response or IC_{50}) to endothelium-dependent (acetylcholine) and endothelium-independent (sodium nitroprusside) stimuli will be determined in resistance arteries from visceral tissues and the cerebrum of HU and C rats.

Responses of renal, splenic and mesenteric vessels to neither acetylcholine nor sodium nitroprusside were different between groups (only renal acetylcholine data illustrated). However, endothelium-mediated vasodilation elicited through 2-methylthio-ATP (2MeS-ATP) was lower in middle cerebral arteries from HU rats. 2MeS-ATP was substituted for acetylcholine in these studies because acetylcholine was such a poor vasodilator in cerebral vessels. There was no difference in cerebral artery responses to sodium nitroprusside.





IV. Hindlimb unloading will increase and decrease nitric oxide synthase (ecNOS) mRNA expression in visceral and cerebral resistance arteries, respectively. Expression of ecNOS mRNA will be determined in resistance arteries from visceral tissues and the cerebrum of HU and C rats using semiquantitative PCR.

Nitric oxide synthase expression was not altered by HU in any of the vessels. Because endothelium-mediated vasodilation was lower in cerebral arteries of HU rats, we expanded the times of unloading to include 1 day, 7 days, 14 days and 28 days. Again, we found no significant changes in ecNOS expression.

V. Hindlimb unloading will induce alterations in visceral and cerebral resistance artery morphology. Isolated resistance arteries of HU and C rats will be pressurized and fixed for histological analysis of arterial morphology. Transverse sections of resistance arteries will be cut and stained with hematoxylin. Vessel wall thickness and smooth muscle cell cross-sectional area will be measured to determine whether atrophy of the smooth muscle has occurred.

Results from this aim can be found in published form:

Wilkerson, M.K., J.M. Muller-Delp, P.N. Colleran, and M.D. Delp. Effects of hindlimb unloading on cerebral, splenic, and mesenteric resistance artery morphology. *J. Appl. Physiol.* 87: 2115-2121, 1999.

VI. High-intensity sprint training used as a counter-measure to hindlimb unloading will attenuate or reverse arterial adaptations. The effects of five 1-min bouts of daily, high-intensity treadmill running on visceral and cerebral resistance artery adaptations induced by hindlimb unloading will be determined.

We were unable to obtain satisfactory high-intensity treadmill running performances from the unloaded rats. After approximately one week of unloading the animals could not run at a high intensity. Therefore, Specific Aim VI was altered and redesigned as a follow-up Specific Aim V, i.e., to determine the stimulus for the change in cerebral artery morphology with hindlimb unloading. To do this, we measured blood flow and calculated vascular resistance in the brain of rats during control standing and after 10 min, 7 days and 28 days of head-down tilt (HDT, a.k.a., hindlimb unloading). In addition, regional alterations in perfusion and vascular resistance within the brain were determined.

Results from this aim can be found in published form:

Wilkerson, M.K., P.N. Colleran, and M.D. Delp. Acute and chronic head-down tail-suspension diminishes cerebral perfusion in the rat. *Am. J. Physiol. Heart Circ. Physiol.* H328-H334, 2002.

NASA Grant NAG2- 1340

Other publications acknowledging supported from this NASA grant:

Research Publications:

Delp, M.D., R.B. Armstrong, D.A. Godfrey, M.H. Laughlin, C.D. Ross and M.K. Wilkerson. Exercise increases blood flow to locomotor, vestibular, cardiorespiratory, and visual regions of the brain in miniature swine. *J. Physiol. (Lond.)* 533: 849-859, 2001.

Ray, C.A., M. Vasques, T.A. Miller, M.K. Wilkerson, and M.D. Delp. Effects of short-term microgravity and long-term hindlimb unloading on rat cardiac mass and function. *J. Appl. Physiol.* 91: 1207-1213, 2001.

Miller, T.A., L.A. Lesniewski, J.M. Muller-Delp, A.K. Majors, D. Scalise, and M.D. Delp. Hindlimb unloading induces a collagen isoform shift in the soleus muscle of the rat. *Am. J. Physiol. Reg. Int. Comp. Physiol.* 281: R1710-R1717, 2001.

Muller-Delp, JM, SA Spier, MW Ramsey, LA Lesniewski, A Papadopoulos, JD Humphrey, and MD Delp. Effects of aging on vasoconstrictor and mechanical properties of rat skeletal muscle arterioles. *Am. J. Physiol. Heart Circ. Physiol.* 282: H1843-H1854, 2002.

Muller-Delp, JM, SA Spier, MW Ramsey, and MD Delp. Aging impairs endothelium-dependent vasodilation in rat skeletal muscle arterioles. *Am. J. Physiol. Heart Circ. Physiol.* 283: H1662-H1672, 2002.

Papadopoulos, A, and MD Delp. Effects of hindlimb unweighting on the mechanical and structural properties of the rat aorta. *J. Appl. Physiol.* 94: 439-445, 2003.

Reviews:

Delp, M.D. Control of skeletal muscle perfusion at the onset of dynamic exercise. *Med. Sci. Sports Exerc.* 31: 1011-1019, 1999.

Delp, M.D. Microgravity-induced orthostatic intolerance: An arterial microvascular mechanism. In J Moravec, N Takeda and PK Singal (Eds.). *Adaptation Biology and Medicine* (Vol. 3). New Delhi, India: Narosa Publishing House, p. 144-155, 2002.

Figure 1. RENAL ARTERIOLE

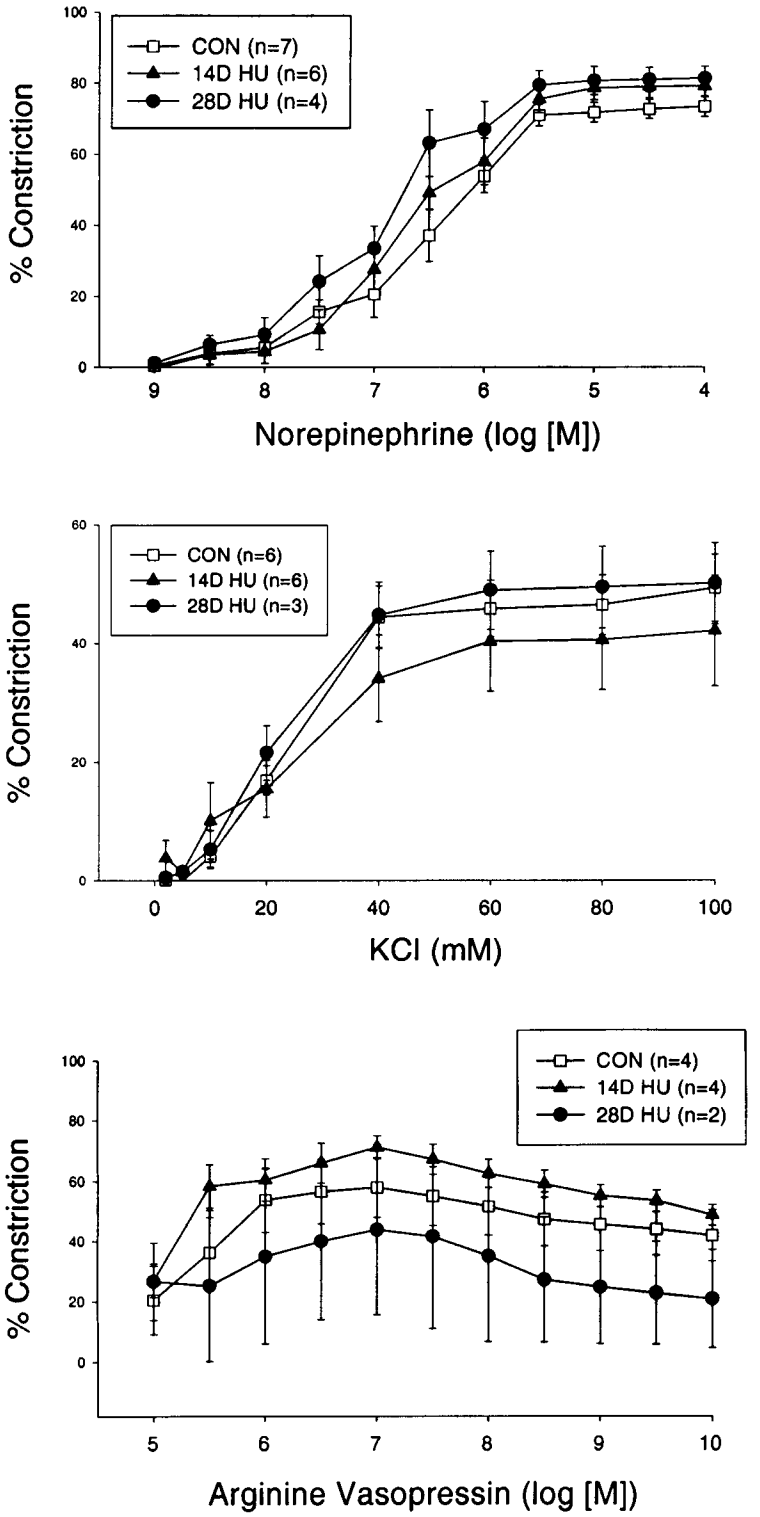
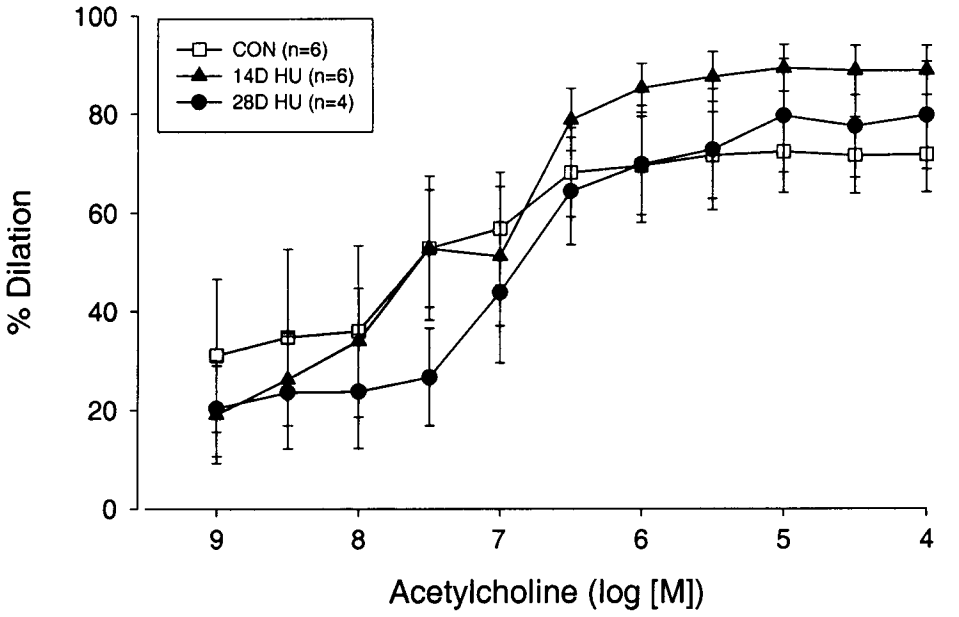


Figure 2. RENAL ARTERIOLE



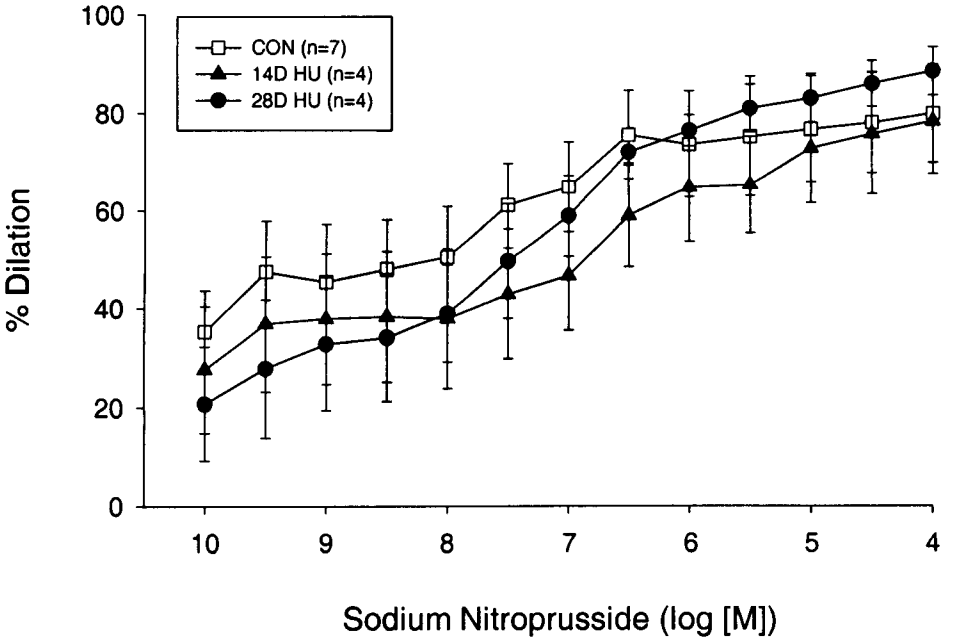


Figure 3. Brain Blood Flow and Vascular Resistance