B4

TITLE: ABNORMAL VASCULAR REACTIVITY IN THE ob/ob MOUSE

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Obesity is an increasing health problem in the United States. While the association between obesity and hypertension has long been recognized, the underlying mechanisms have not been well characterized. The neuroendocrine peptide leptin has been shown to have a critical role in modulating metabolism and leptin receptors have been recently demonstrated in endothelial and vascular smooth muscle cells. We hypothesize that leptin is an important modulator of vascular tone and that abnormalities in leptin signaling may contribute to increased vasomotor tone and hypertension. To test this hypothesis, we examined vascular responses to vasoconstrictors and both endothelial depending and independent dilators in the leptin deficient obese (ob) mouse and wild type (wt) controls. Aorta and mesenteric microvessels (150 um) were isolated. Aortic rings were suspended in organ baths on wire stirrups and stretched to their optimal load (500 mg) in Kreb's buffer (pH = 7.4) equilibrated with 95% O_2/5%CO_2. Microvessels were cannulated on micropipettes in a microchamber and maintained in a no flow state at a constant pressure in Kreb's. Intraluminal diameter was monitored by a video dimension analyzer. Dose response curves to vasoconstrictors (NE, Phe and the thromboxane A2 analogue U46619) and vasodilators (SNP and ACH) were generated for both vessel types. Aorta from the ob mouse showed significantly enhanced vasoreactivity as compared to wt to a variety of adrenergic and non-adrenergic vasoconstrictors (Phe: ob/ob log EC50 = -6.7, Emax = 215%; wt log EC50 = -5.6, Emax = 43.4%. U46619: ob/ob log EC50 = -7.9, Emax = 355%; wt log EC50 = -7.1, Emax = 266%) ($p<0.05$). Inhibition of endothelial NO production with L-NAME resulted in maximal responses similar to wt, but continued enhancement of reactivity as evidenced by a one-half log left shift. In microvessels, we found no difference between the ob and wt mice with regards to their response curves to vasoconstrictors, however, responses to ACH stimulated endothelial dependent vasodilation were profoundly attenuated in the ob mouse as compared to the wt controls (ob/ob log EC50 = -6.5, Emax 41% vs wt log EC50 = 8.0, Emax 79% ($p<0.05$). Maximal response to SNP, an NO donor, was the same but the EC50 was shifted by an order of magnitude. Ob mice were then repleted with leptin (or PBS) using 14-day osmotic infusion pumps set to deliver physiological doses of leptin. Microvessels were tested as described above. ACH dose responses in the leptin repleted mouse were the same as the wt, while the PBS controls continued to demonstrate severely impaired endothelial dependent vasodilation. These results suggest a role for leptin in vasomotor regulation and represents the first evidence for impaired endothelial function and enhanced vasoconstrictor responses in this model of obesity. Because of the effect of leptin on factors such as insulin sensitivity and lipid metabolism, the observed vascular effects need to be interpreted in the context of these changes. The direct modulating effect of leptin in pathways involved in vasoregulation remains to be tested.

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TITLE: LONG TERM SURVIVAL AND QUALITY OF LIFE IN CARDIAC SURGICAL PATIENTS WITH PROLONGED ICU LENGTH OF STAY

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Patients with prolonged ICU length of stay (LOS) after cardiac surgery represent a substantial burden on ICU resources and hospital cost. We sought to determine the impact of prolonged ICU LOS on survival and/or quality of life.

We retrospectively reviewed the charts of all adult patients admitted for at least 14 consecutive days after their primary procedure in our cardiac surgical ICU in 1998. Data were analyzed to generate a modified Multiple Organ Dysfunction Score[1] (MODS, range 0-24). Discharged patients were contacted to evaluate quality of life as determined by an activity of daily living score (ADL), defined as normal (ADL=12), impaired (12<ADL>6) or severely impaired (ADL≤6).

49 of 1280 patients remained in the ICU for at least 14 days. This represented only 3.8% of all patients but 28% of ICU patient-days. Mean hospital LOS was 68.9 days when ICU LOS was ≥ 14 days, compared with 13.8 days when ICU LOS was < 14 days ($p<0.05$). In-hospital mortality for this group was 28.5% compared with 5.3% for patients with an ICU stay < 14 days ($p<0.05$). Patients who died in hospital had a significantly longer mean ICU stay (43 v. 29 days, $p<0.05$) than those who survived. At the time of this survey (6-18 months after hospital discharge), 8 of the 35 discharged patients had already expired. Of the 28 surviving patients, quality of life (ADL score) was normal in 19 (38% of the initial group of long ICU LOS patients), impaired in 6 (12%) and severely impaired in 2 (4%). Compared with patients who regained normal quality of life, MODS at day 14 was significantly higher (5.84 v. 3.06, $p<0.05$) and mean ICU LOS was significantly longer (39 v. 24 days, $p<0.05$) in patients who subsequently died or who survived with impaired ADL.

In our units, an ICU LOS ≥ 14 days was predictive of an in-hospital mortality five times greater than that for ICU patients with LOS < 14 days. In the former group, 62% of patients died in hospital or within 18 months of discharge, or had an impaired quality of life. A high MODS at 14 days was associated with a poorer outcome- either death or survival with impaired quality of life. In-hospital mortality and an impaired quality of life after discharge are more likely with longer overall ICU LOS.

Reference: 1. Crit Care Med 1995;23:1638.

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