

**TITLE:** POLYETHYLENE GLYCOL CONJUGATED SUPEROXIDE DISMUTASE (PEG-SOD) IMPROVES RECOVERY OF HYPERCAPNIC REACTIVITY (HYPR) FOLLOWING ISCHEMIA

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**INTRODUCTION:** HYPR is markedly diminished following cerebral ischemia in piglets. We tested the hypothesis that intravenous (IV) PEG-SOD improves recovery of HYPR in piglets exposed to 10 min global ischemia and 120 min reperfusion, independent of recovery of cerebral oxygen uptake (CMRO<sub>2</sub>).

**METHODS:** 1-2 wk old piglets (approx. 3 kg) were sedated with ketamine (10 mg/kg) and anesthetized with pentobarbital (35 mg/kg IV bolus; 4-6 mg/kg/hr IV infusion). After tracheostomy piglets were mechanically ventilated and catheters inserted for monitoring arterial blood pressure, intracranial pressure, arterial and cerebral venous blood gases and cerebral blood flow (CBF, microspheres). To determine the effect of pre-ischemic vs post-ischemic treatment with PEG-SOD, each piglet received 2 drug injections (30,000 U PEG-SOD or equal volume of PEG, IV) in a randomized, blinded fashion: first, 30 min following the end of surgery; second, at the end of ischemia. Therefore, piglets received 1 of 3 treatments: PEG at both time points (PEG/PEG); PEG first, PEG-SOD second (PEG/PEG-SOD); PEG-SOD first, PEG second (PEG-SOD/PEG). CMRO<sub>2</sub> and CO<sub>2</sub> reactivity

(CBF at PaCO<sub>2</sub> of 25, 40 and 60 mmHg) were measured 30 min after the first drug injection. Global cerebral ischemia was produced by ligating the ascending aorta. At 10 min of ischemia the ligature was removed to allow for reperfusion. CMRO<sub>2</sub> and CO<sub>2</sub> reactivity were retested at 120 min reperfusion.

**RESULTS:** There was no difference between groups for HYPR (CBF<sub>hypercapnia</sub>-CBF<sub>normocapnia</sub>/PaCO<sub>2</sub><sub>hypercapnia</sub>-PaCO<sub>2</sub><sub>normocapnia</sub>) to forebrain prior to ischemia (PEG/PEG: 1.2±0.3; PEG-SOD/PEG: 1.3±0.3; PEG/PEG-SOD: 1.5±0.4 ml/min/100g/mmHg). Following 120 min of reperfusion HYPR decreased to 0.2±0.2 ml/min/100g/mmHg in piglets treated with PEG/PEG but was not different from pre-ischemic values in piglets treated with PEG-SOD/PEG or PEG/PEG-SOD. CMRO<sub>2</sub> was not different between groups prior to ischemia (PEG/PEG: 3.2±0.2; PEG-SOD/PEG: 3.6±0.3; PEG/PEG-SOD: 3.6±0.2 ml/min/100g). Following 120 min reperfusion CMRO<sub>2</sub> decreased to 2.6±0.3 ml/min/100g in piglets treated with PEG/PEG-SOD, but was not different from pre-ischemia in the other two groups.

**DISCUSSION:** This study demonstrates that IV administration of PEG-SOD either prior to ischemia or at the time of reperfusion prevents deterioration of HYPR which occurs during reperfusion in piglets. We conclude that altered post-ischemic reactivity, in the piglet, is at least partially due to production of oxygen-derived free radicals. Our data cannot support the hypothesis that recovery of CO<sub>2</sub> reactivity is determined by recovery of CMRO<sub>2</sub>. Supported by NS20020, NS24394, NS01225.

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**Title:** THE CONTRIBUTION OF CAROTID CHEMORECEPTORS TO CHANGES IN MESENTERIC VEIN DIAMETER DURING ACUTE HYPERCAPNIA IN THE RABBIT

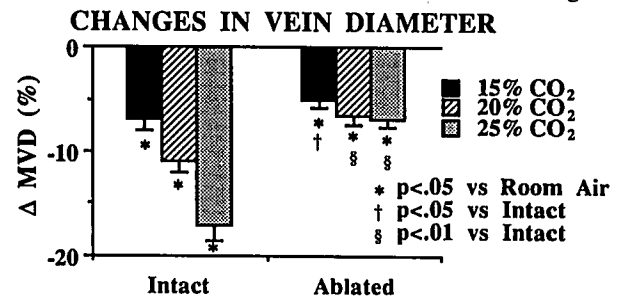
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The venous circulation of the splanchnic bed is in part controlled by changes in sympathetic efferent tone.<sup>1,2</sup> Peripheral chemoreceptors play an important modulatory role by regulating the autonomic control of the vasculature. Previously, it was shown that reflex constriction of small mesenteric veins was attenuated by denervation of carotid chemoreceptors.<sup>3</sup> Peripheral chemoreceptors are known to respond to hypercapnia and acidosis as well as to hypoxia. The purpose of the present study was to quantify the reflex mesenteric venoconstriction resulting from graded acute hypercapnia and to determine the contribution of carotid chemoreceptor activation to this response.

Six New Zealand white rabbits (1.1-1.6 kg) were anesthetized with thiamylal. Surgical preparation consisted of tracheotomy for control of ventilation, femoral venous cannulation for alpha-chloralose infusion and femoral arterial cannulation for continuous blood pressure and heart rate monitoring. A 13 cm loop of terminal ileum was exteriorized and superfused with physiological salt solution (37°C). The mesentery was transilluminated and continuous measurements of mesenteric vein diameter (MVD) via videomicrometer system were made in response to 40 sec periods of 15%, 20% and 25% inspired CO<sub>2</sub>. Mesenteric intravenous pressure was measured simultaneously at the same site using glass micropipettes and a servo-null technique.

All measurements were then repeated following bilateral dissection and surgical ablation of the carotid chemoreceptors. Arterial blood gas analyses (pH, PCO<sub>2</sub> and PO<sub>2</sub>) were performed at room air and at each level of hypercapnia. Measured PCO<sub>2</sub> were 31.9±1.9, 79.9±2.5, 98.1±2.0 and 116.1±1.4 mmHg in response to room air, 15%, 20% and 25% CO<sub>2</sub>, respectively. Percent changes in MVD before and after carotid denervation are shown in the figure.



These data indicate that there is a graded mesenteric venoconstriction in response to increasing levels of hypercapnia. This response is attenuated by carotid chemoreceptor ablation or by 1% inhaled halothane.<sup>4</sup> The observation of a greater inhibition of this response at higher levels of inspired CO<sub>2</sub> in denervated animals suggests a contribution of carotid chemoreceptor activation that is proportional to the severity of hypercapnia.

**References:**

1. *Am. J. Physiol.* 256 : H162, 1989
2. *Am. J. Physiol.* 256 : H1066, 1989
3. *FASEB J.* 4 : A1190(# 5365), 1990
4. *Anesthesiology* (abstract), 1990