TITLE: HALOTHANE ANESTHESIA ATTENUATES SYMPATHETIC ADRENERGIC REGULATION OF THE PULMONARY CIRCULATION FOLLOWING HYPOTENSION AND HYPOPERFUSION.

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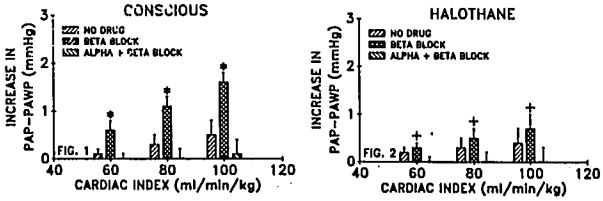
Our objective was to investigate the extent to which halothane anesthesia modifies sympathetic adrenergic regulation of the pulmonary circulation during a period of increasing cardiac index following 15 minutes of hypotension and hypoperfusion (defined as reperfusion) compared to that measured in the conscious state. The pulmonary vascular pressure gradient (PAP-PAWP) was measured at multiple levels of cardiac index ($\dot{Q}$) by stepwise inflation and then deflation of a hydraulic occluder chronically implanted around the inferior vena cava to generate baseline and reperfusion plots, respectively. Baseline and reperfusion plots were obtained on separate days in 8 conscious and halothane-anesthetized (~ 1.2% end-tidal) dogs in the intact condition (no drug), during sympathetic ß block (propranolol 1 mg/kg, iv), and during combined sympathetic α (prazosin 1 mg/kg, iv) and ß block. Controlled ventilation during halothane allowed matching of blood gases to conscious values. Two-way ANOVA and Duncan's multiple range test were used to assess the effects of reperfusion on the baseline plots. In conscious dogs (Fig. 1), no increase in PAP-PAWP was observed during reperfusion in the intact (no drug) condition. However, a marked reperfusion vasoconstriction (*$p<0.01$) was noted during ß block in conscious dogs. Moreover, this response was entirely abolished by combined α and ß block. During halothane anesthesia (Fig. 2), a reperfusion vasoconstriction (+<0.05) was also unmasked during ß block, and abolished by combined α and ß block. However, the magnitude of the vasoconstriction was less ($p<0.05$) than that observed in conscious dogs.

These results indicate that sympathetic ß adrenergic vasodilation offsets α adrenergic vasoconstriction during reperfusion in both intact conscious and halothane-anesthetized dogs. However, the absolute magnitude of sympathetic regulation is attenuated during halothane anesthesia.



TITLE: CARBOXYPEPTIDASE N (CPN) DURING CARDIOPULMONARY BYPASS (CPB)

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INTRODUCTION: Protamine given to neutralize heparin after extracorporeal circulation can trigger a catastrophic reaction characterized by increased capillary permeability, interstitial fluid and leukocyte accumulation, fever, pulmonary hypertension, bronchoconstriction and systemic hypotension. This syndrome has been attributed to activation of the complement system by the protamine-heparin complex (resulting in the release of anaphylatoxins) and the synthesis of thromboxanes. It may also involve the activation of factor XII which can activate plasma kallikrein leading to the production of the hypotensive peptide bradykinin. We previously found that protamine is a potent inhibitor of the inactivator of anaphylatoxins and kinins, human CPN. Because of the importance of this enzyme in protecting the circulation from the deleterious systemic effects of anaphylatoxins and kinins, we decided to investigate whether CPN is destroyed during CPB.

METHODS: Thirteen patients ASA III-IV, aged 46-85 scheduled to undergo cardiac surgery utilizing CPB were studied prospectively after obtaining informed consent. The study was approved by our IRB. Patients were premedicated with morphine and scopolamine. General anesthesia was achieved with sufentanil and vecuronium. The extracorporeal circuit was primed with 2,000 ml of crystalloid solution containing 5% albumin. Blood samples for CPN and alkaline phosphatase (Alk P) measurement were drawn before induction of anesthesia (B I), 10 min post induction (P I), 10 min post heparin (P H), 1,10 and 30 min after the start of CBP, and 10 min after protamine infusion (P P). The activity of CPN in plasma was measured by hydrolysis of FA-Ala-Lys in a continuous spectrophotometric assay and expressed in millioptical density units (mOD)/min/30µl of plasma. The activity of Alk P in plasma was measured by hydrolysis of p-nitrophenylphosphate in a photometer at 410 nm and expressed in normalized units (NU)/dl. Results are in mean ± SD.

RESULTS: CPN and Alk P in plasma during CPB.

	BI	PI	PH	1'in CPB	10'in CPB	30'in CPB	PP
CPN	23.2	21.8	19.9	11.4*	11.6*	11.3*	11.6*
(mOD/min/30µl)	±3.3	±3.4	±3.7	±2.3	±2.6	±2.7	±1.8
Alk P	66.7	68.5	62.8	38.5*	35.1*	33.0*	31.9*
(NU/dl)	±8.9	±13.5	±9.0	±11.3	±13.9	±12.7	±14.3

(* = $p < 0.05$ vs PI)

DISCUSSION: The concentration of CPN decreases dramatically upon initiation of CPB and remains constant throughout the procedure. Based on a similar decrease seen in the Alk P values, this reduction in activity is primarily due to dilution and not selective inactivation of CPN. Regardless of the mechanism, the decreased activity of CPN could lead to a slower inactivation of anaphylatoxins and kinins, if they were released after protamine administration. Additional inhibition of CPN activity by an excess of protamine would further compromise the ability of the patient to inactivate these mediators. This could contribute to the catastrophic reaction seen in some patients, especially if they have an initial low level of CPN.