

Title: THE INFLUENCE OF HYPERVOLEMIA WITH AND WITHOUT INDUCED HYPERTENSION ON THE EXTENT OF ISCHEMIA FOLLOWING MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT.

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**Introduction:** With increasing complex neurovascular surgical procedures, the anesthesiologist is called upon to treat focal cerebral ischemia. One therapeutic goal involves improving collateral blood flow to the ischemic area by the following: 1) Improvement in blood rheology-hemodilution, 2) Increase in cardiac output-hypervolemia, inotropic support, or 3) Increase in cerebral perfusion pressure-hypertension. Although the above has experimental support,<sup>1,2</sup> little is known as to how any of the above variables interact with anesthetics. We evaluated the effect of the above treatment factors upon cerebral blood flow (CBF) during isoflurane anesthesia in both a 'critical' flow zone in which CBF is severely reduced and infarction is likely, and a 'penumbral' flow zone in which CBF is intermediately reduced resulting in neuronal dysfunction, yet in which the neuron is fundamentally recoverable over a limited time period.<sup>3</sup> This was achieved during middle cerebral artery occlusion (MCAO).

**Methods:** Following approval by the Animal Research Committee, male, Sprague-Dawley rats (n = 24) were intubated and anesthetized with 1.2 MAC isoflurane (1.87%) and an inspired oxygen concentration of 40%. Each rat was then randomly assigned to one of the following groups: 1) Control (C)-mean arterial pressure (MAP) and hematocrit were not manipulated, 2) Normotensive/Hypervolemic/Hemodilution (A)-5% albumin was administered over a 30 minute period to achieve a stable hematocrit of 30-33%, or 3) Hypertensive/Hypervolemic/Hemodilution (A/D)-5% albumin was administered as in group 2, and 10 ug/kg/min of dopamine was administered. The dopamine was begun 10 minutes prior to MCAO and maintained through the CBF study. Physiological parameters (pH, PaCO<sub>2</sub>, PaO<sub>2</sub>, MAP, serum glucose, hematocrit, and temperature) were monitored. The left middle cerebral artery was exposed via a subtemporal craniotomy and was occluded according to Bederson.<sup>4</sup> Ten minutes following occlusion CBF was determined with <sup>14</sup>C-iodo-antipyrine, 100 uCi/kg, as described elsewhere.<sup>5</sup> For each rat three predetermined coronal autoradiographic sections were analyzed using a Dumas Image Processing System to define the area (percentage of the infarcted hemisphere) falling within specified blood = flow ranges of: 0-15 (critical flow), and 15-23 (penumbral flow) ml/100g/min. The three sections spanned from 1.8mm posterior to the midline rostral edge of the corpus collosum to the caudal edge of the corpus collosum. Statistical analysis was performed on the physiological data and the brain data using analysis of variance, and as appropriate, mean values were compared by t-tests with a Bonferroni correction. P < 0.05 was used as significant.

**Results:** There were no differences between groups in the following physiological variables (weight, pH, PaCO<sub>2</sub>, PaO<sub>2</sub>, serum glucose, and temperature). There were differences in the hematocrit and MAP (see table 1). The critical flow and penumbral flow areas for each group are listed in table 2. There was a significant decrease in the area of critical flow for the (A) group and the (A/D) group as compared to the control group, and a decrease in the area of penumbral flow for the (A) group as compared to the control group. No other differences were observed.

**Discussion:** The results of this study indicate that the area of critical and penumbral flow was decreased with normotensive/hypervolemic/hemodilution in the rat during focal cerebral ischemia, with no additional decrease in area when the MAP was elevated with dopamine. The mechanism of the observed decrease in critical and penumbral flow zones is likely to be twofold: 1) An improvement in the blood rheology, and 2) An increase in cardiac output. The explanation as to why hypertensive/ inotropic support by dopamine failed to provide additional decreases in critical and penumbral flow zones is uncertain. Explanations may include: 1) Sensitivity of the method, 2) Insufficient elevation of the MAP, or 3) The observed cerebral vasodilation that occurs at intermediate doses,<sup>6</sup> hence if the normal cerebral vasculature was preferentially dilated, a cerebral steal may have been created. Our study raises the possibility that normotensive/ hypervolemic/hemodilution prior to short periods of focal cerebral ischemia during isoflurane anesthesia may reduce the extent of critical CBF reductions to the level where neuronal injury is less likely. Further studies are indicated to elucidate optimal hypervolemic/ hemodilution/hypertensive techniques, possible inter actions with other anesthetic regimens, and effects of beneficial treatment regimens upon functional outcome.

	MAP	HCT
Control (C)	89 ± 9	46 ± 2 <sup>+</sup>
Albumin (A)	96 ± 8	32 ± 2
A/Dopamine (A/D)	110 ± 9*	31 ± 2

Table 1-Physiological Differences (mean ±SD). \*difference from Groups A&C. †difference from Groups A & A/D. (P < 0.05.)

	0-15	15-23
<b>ANTERIOR SECTION:</b>		
Control (C)	32.1 ± 6.1	31.5 ± 5.8
Albumin (A)	8.4 ± 3.8*	18.0 ± 5.0*
A/Dopamine (A/D)	11.1 ± 4.2*	23.7 ± 3.9
<b>MIDDLE SECTION:</b>		
Control (C)	27.9 ± 5.4	27.3 ± 6.3
Albumin (A)	7.2 ± 3.0*	18.7 ± 4.1*
A/Dopamine (A/D)	8.8 ± 3.7*	23.5 ± 4.8
<b>POSTERIOR SECTION:</b>		
Control (C)	23.4 ± 5.1	24.3 ± 5.1
Albumin (A)	7.5 ± 3.4*	15.5 ± 4.3*
A/Dopamine (A/D)	9.7 ± 3.8*	19.6 ± 5.0

Table 2-Percent area of infarcted hemisphere (mean ±SD) in critical flow zone (0-15 ml/100g/min) and penumbral flow zone (15-22 ml/100g/min). \*difference from Control Group. (P < 0.05.)

**References:**

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