Title: PHENYLEPHRINE-INDUCED HYPERTENSION DECREASES THE EXTENT OF ISCHEMIA FOLLOWING MIDDLE CEREBRAL ARTERY OCCLUSION IN THE RAT.

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INTRODUCTION: Temporary vascular occlusion may occur during both intracranial and extracranial procedures and may cause focal cerebral ischemia. Induced hypertension has been employed in these situations in an attempt to improve collateral perfusion to the ischemic region. Phenylephrine (P) is widely employed but has the theoretical disadvantage of cerebral vasoconstriction. This study examined the effect of induced hypertension with P on local cerebral blood flow (l-CBF) in and around an area of focal ischemia following middle cerebral artery occlusion (MCAO) in isoflurane anesthetized rats.

METHODS: Twenty four male, Sprague-Dawley rats (weight, 321-422 grams) were studied with prior approval by the institutional animal studies subcommittee. The rats were anesthetized with 4.0% isoflurane, orotracheally intubated and mechanically ventilated to maintain normocarbia. Two percent isoflurane in 40% oxygen, balance nitrogen was administered during the surgical preparation and throughout the experiment. Rectal temperature was servo-controlled to 37°C. Femoral vessels were cannulated for continuous blood pressure monitoring, isotope administration and blood collection. The left middle cerebral artery (MCA) was exposed via a subtemporal craniotomy and occluded with microbipolar forceps on a low power setting using continuous saline irrigation. Each rat was then randomly assigned to either the normotensive control (CTRL) group or the P-induced hypertension group. Physiological parameters (pH, $PaCO_2$, PaO_2, MAP, hematocrit (HCT), and temperature) were recorded before MCAO, after MCAO and before determination of l-CBF. In the P group, MAP was increased over 5 minutes to a level of 30-35 mmHg above the pre-MCAO MAP or to a maximum of 140 mmHg by intravenous infusion of P. MAP was maintained for 10 min prior to l-CBF determination. There was no manipulation of MAP in the CTRL group. CBF was determined as follows. ^{14}C-iodo-antipyrine (IAP), 100uCi/kg, was infused over 46 seconds. At T=45 seconds the rat was decapitated and the brain was rapidly removed and frozen. 20 micron coronal sections of brain were placed on Kodak OM-1 film with ^{14}C standards for 21 days. For each animal, four coronal autoradiographic sections were analysed using a DUMAS image processing system to determine the areas falling within specified CBF ranges: 0-6, 6-15 and 15-23 $ml \cdot 100g^{-1} \cdot min^{-1}$. The 4 sections spanned the region from 1.8 mm anterior to the midline rostral edge of the corpus callosum (CC) to the caudal edge of the CC. Statistical analysis was performed t-tests for unpaired data.

RESULTS: Data for 18 rats (P=9, CTRL=9) were available for the present analysis. There were no differences between the groups for MAP, $PaCO_2$, PaO_2, pH, HCT and temp at the time of MCAO. At the time of l-CBF determination, only MAP differed ($p<0.0001$) (see Table). Animals in the P group required phenylephrine at a rate 16.1± 4.2 $ug \cdot kg^{-1} \cdot min^{-1}$ to maintain MAP elevation. In the induced hypertension (P) group there was a trend in all 4 coronal brain sections toward smaller percentages of cross sectional area falling within the two more severe ischemic flow ranges (0-6 and 6-15 $ml \cdot 100g^{-1} \cdot min^{-1}$) (see Figure). The difference was significant for the 0-6 and 6-15 $ml \cdot 100g^{-1} \cdot min^{-1}$ ranges in Sections 3 and 4.

DISCUSSION: Phenylephrine-induced hypertension instituted after the onset of focal cerebral ischemia decreased the area over which l-CBF was reduced to levels likely to result in rapid ($0\text{-}6ml \cdot 100g^{-1} \cdot min^{-1}$) or delayed ($6\text{-}15ml \cdot 100g^{-1} \cdot min^{-1}$) neuronal death. This observation suggests that inspite of a potential vasoconstrictive effect P-induced hypertension may serve to reduce the extent of neuronal injury during short periods of cerebral vascular occlusion.

REFERENCES:1. Edvinsson L, MacKenzie ET: Amine mechanisms in the cerebral circulation. Pharmacol Rev. 28:275-348,1976.

TABLE. Physiologic data (±SD) at the time of l-CBF determination

	MAP	PaCO2	PaO2	pH	HCT (%)	TEMP (°C)
PHENYL	134±9*	38±3	125±25	7.40±.04	44±2	36.9±.3
CONTROL	86±13	37±1	130±23	7.39±.05	41±4	36.5±.8

MAP, PaCO2, and PaO2 in mmHg. * indicates p<.05 control vs phenyl

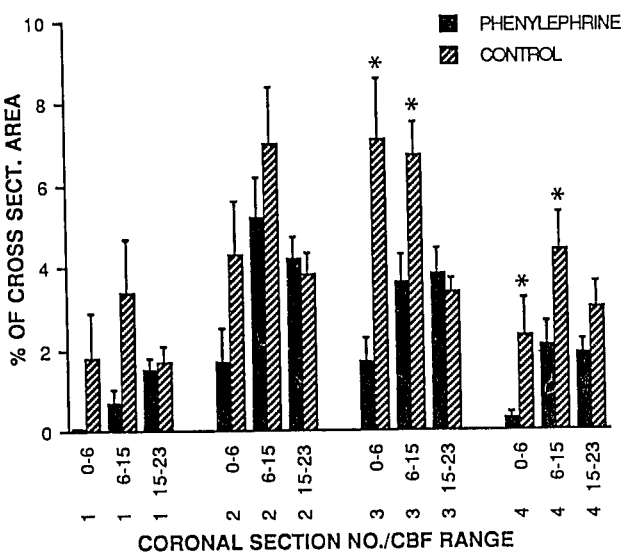

Figure. The percentage (mean±SEM) of the cross sectional area of four coronal brain sections (see text for location) falling within three l-CBF ranges (in $ml \cdot 100g^{-1}.min^{-1}$) 15 min after MCAO in rats anesthetized with isoflurane with (PHENYLEPHRINE) and without (CONTROL) induced hypertension.