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Title : THE EFFECT OF HYPERTENSION ON THE BLOOD-BRAIN BARRIER

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Introduction Normal function of the brain is dependent on an intact interface between brain, CSF, and blood. Acute hypertension occurs commonly in critical care situations and may disrupt blood-brain barrier (BBB) function. In the past, studies of the BBB have been hampered by either extensive and potentially disruptive, invasive CNS instrumentation,or sacrifice of many animals at selected times. Thus it has been difficult to obtain reliable information on the rates and distribution of BBB breakdown. This study used computed tomography (CT) which allowed direct and constant visualization of the CNS in individual dogs to determine the course and distribution of BBB breakdown by acute hypertension.

Methods Mongrel dogs were anesthetised with pentobarbital (30 mg/Kg I.V.) and ventilated with 100% oxygen. The $PaCO_2$ was kept in normal range (38 ± 5 mm Hg). Intra-arterial blood pressure (BP) and ECG were constantly monitored and the dogs kept normothermic. Diatrizoate meglumine 60%,an iodinated, ionic contrast material was injected (1.3 mg I/Kg) over ninety seconds and an infusion of the dye (0.35 cc/Kg body weight/min) was begun 20 minutes after the initial dye injection to maintain steady state blood iodine levels which were determined by measurement of blood CT attenuation coefficients (AC). Twenty minutes after the initial dye injection,BP was raised from 121 ± 12 (SD) to 240 ± 14 mm Hg by phenylephrine infusion. CT scans at 3 brain levels 4 mm apart were obtained prior to the initial contrast injection and thereafter at 3,7,10,20,30,35,45,60,75 minutes. An Ohio Nuclear 2020 CT Scanner, operated at 120 Kvp and 75 ma for 4 seconds was used for all scans. Each scan was visually reviewed and selected anatomical compartments were identified from each CT picture as the Basal Ganglia (BG), Medial Cortex (MC) and Lateral Cortex (LC) in the right and left cerebral hemispheres. A representative area within these anatomical locations was chosen for analysis. These areas consisted of 50-100 pixels (1.0 mm^3 /pixel). CT attenuation coefficients from 3 scans from each time period were normalized to the control period and the mean AC for each anatomical area for each dog was calculated. Rates of change of AC (ΔAC/min) were compared using covariance analysis. Two dogs received Evans Blue dye 3% 4 cc/Kg: one control (no BP elevation) and one experimental (BP elevation) to correlate changes on CT scan with areas of staining. These dogs were sacrificed at the conclusion of the experiments, the brains removed, fixed, and serially sliced.

Results Ten minutes after the onset of hypertension, breakdown of the BBB was evident (Fig. 1). Increased densities were noted visually on CT scans at 20 minutes and took on the appearance of "fluffy snowballs" as hypertension continued. Prior to elevation of BP there was no increase in density of areas examined either visually or by measurement of AC. When different areas within a single dog were compared, there were significant ($p < 0.05$) differences between rates of breakdown between areas in 3/5 dogs as determined by covariance analysis. Rates of breakdown of these areas were variable between dogs, (ranges expressed as (Δ AC normalized/min), BG (0.001 - 0.024), MC (0.010 - 0.028), LC (0.013 -0.051)). These preliminary results suggest that the LC was more sensitive to break-of BBB by hypertension than the other anatomical areas. When these penetration rates are related to average change in mean BP over the experimental period, the trend is to more rapid penetration being correlated with greater increases in mean BP ($r = .85$). Visual comparison of CT scans with corresponding brain sections of the dog which received Evans Blue dye showed areas of CT enhancement that followed the distribution of the Evans Blue stain. The control dog showed neither enhancement on CT nor staining of cut sections.

Discussion Two problems in studying hypertensive breakdown of BBB are: (1) to determine the anatomical distribution of the breakdown and (2) to quantitate the rate at which these various areas are affected. Earlier studies to determine anatomical information were limited by the need to sacrifice each animal which precluded obtaining information on the rate of BBB breakdown and were unable to distinguish differences in breakdown rates in different anatomical compartments. In this study breakdown of BBB associated with hypertension was studied in vivo and in real time. The results correlate well with classic methods using Evans Blue dye, but extend our information by providing quantitation and anatomical localization against a time base, providing data on rate and distribution of BBB breakdown simultaneously. It can be seen that the breakdown of the BBB varies from area to area in a single dog and between dogs. The LC appears to be the most sensitive of the three areas examined. While the factors which cause BBB breakdown under hypertension are unclear, our preliminary data suggest a relationship between the change in mean BP and the rate of contrast penetration across the BBB. An in vivo, real time method such as this will allow testing of various interventions on the rate, distribution and magnitude of BBB breakdown.

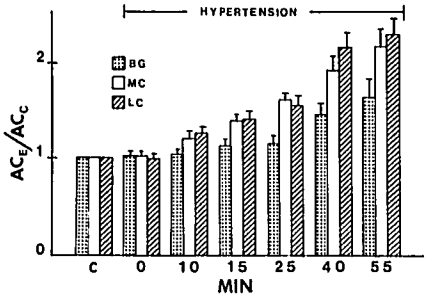

Fig. 1. Normalized CT attenuation coefficients (Mean + SEM)