

# Cerebral Blood Flow Levels During Experimental Ischemic Stroke Influence the Magnitude of Post-Reperfusion Blood-Brain Barrier Opening but Reperfusion After 3 Hours Does Not Reverse the Damage

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**Introduction:** Reduced cerebral blood flow (CBF) to a brain region due to the occlusion of a cerebral artery is a primary cause of human stroke. To minimize injury to the affected brain tissue, rapid reinstatement of CBF must occur as quickly as possible after ictus. It has been shown that damage to the neurovascular unit, including the blood-brain barrier (BBB), increases with later reperfusion times [1]. However, the dependency of BBB damage on CBF levels during the ischemic and reperfusion periods has not been studied. This report tests the hypothesis that the degree of the initial drop in CBF in stroke and the extent of later reperfusion determine the ensuing damage to the BBB. Arterial spin labeling (ASL)- [2] and dynamic contrast-enhanced (DCE)-MRI [3,4] techniques were used to localize and quantify CBF and BBB damage, respectively, in the same subjects.

**Materials and Methods:** Cerebral ischemia was induced in male Wistar rats (~300 g; N=22) by the occlusion of right middle cerebral artery (MCA) using a heat-blunted 4.0 nylon suture. Reperfusion was initiated 3 hours post-occlusion via suture withdrawal. CBF was measured by ASL-MRI during MCA occlusion and the first 2 h of reperfusion. Pixel-by-pixel maps of CBF during stroke and after reperfusion were made from these images [2]. Measures of CBF are also reported as a percentage of contralateral values assuming contralateral CBF to represent control or normal values. At approximately 2.5 h post-reperfusion, the blood-to-brain influx rate constant ( $K_i$ ) for the MR contrast agent, gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), was assessed by DCE-MRI [4]. Pixel-by-pixel maps of  $K_i$ , indicating regions with BBB opening (regions of interest or ROIs), were produced using Patlak plots of the DCE-MRI data [3]. Scatter plots with Pearson correlation coefficients ( $r$ ) were used to compare separately CBF values from the two sets of flow maps to  $K_i$  in the same ROIs. Significance was inferred at  $P<0.05$ .

**Results:** All rats showed decreased CBF in the right hemisphere as a result of the MCA occlusion-induced stroke. There were two primary brain regions that were affected, viz., preoptic area (PoA) and striatum (Str). The extent of CBF reduction as well as its reinstatement after reperfusion, however, varied among these brain regions. During the period of MCA occlusion, CBF (mean $\pm$ SD) was  $42\pm18$  and  $26\pm15$  ml/100g/min (20-25% of contralateral side) in the PoA and Str, respectively. After reperfusion, CBF was  $78\pm27$  and  $99\pm50$  ml/100g/min (45-55% of the contralateral side) in the PoA and Str, respectively. The ROIs defined by Gd-DTPA leakage were located mainly within the ipsilateral PoA (n=21) and Str (n=17). In many cases, BBB lesions were seen in both PoA and Str in the same rat. The  $K_i$  values were  $0.26\pm0.07$  and  $0.24\pm0.07$  ml/100g/min, respectively, in the PoA and Str. Scatter plots of  $K_i$  vs. CBF during MCA occlusion showed an inverse relationship (negative ' $r$ ' values; see Figure), i.e.,  $K_i$  was greater for the regions with lower CBF values during this period ( $r = -0.48$ ,  $P = 0.03$  for PoA;  $r = -0.53$ ,  $P = 0.03$  for Str). Conversely, plots of  $K_i$  and post-reperfusion CBF indicated no such relationship ( $r = 0.27$ ,  $P = 0.24$  for PoA;  $r = 0.38$ ,  $P = 0.13$  for Str).

**Discussion and Conclusions:** These data suggest that the severity of the acute BBB lesion in reversible cerebral ischemia is determined mainly by the drop in CBF during the first several hours of occlusion and partly support the hypothesis. Reperfusion after 3 h of occlusion, however, did little to alleviate the damage. This observation supports the suggestion that rapid recanalization of an occluded vessel and restitution of CBF is of utmost importance in acute stroke [5]. It is noteworthy that acute CBF measurements seemed to be predictive of impending BBB damage in stroke and, thus, may also prefigure its possible consequences such as a potentially lethal hemorrhagic transformation. Quantitative ASL-MRI might, therefore, be a useful tool for such predictions and for selecting thrombolytic treatment options in acute stroke.

## References:

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