## Abstract 3

### Brain Edema and Blood-Brain Barrier Leakage Influence Antiepileptic Drug Levels

**Giulia Betto, Vincent Fazio, Damir Janigro, and Chaitali Ghosh**
*Cerebrovascular Research Center, Cleveland Clinic, Cleveland, OH*

**Purpose:** Cerebrovascular dysfunction can result from cardiac events (eg, cardiac arrest) or surgical interventions (eg, coronary artery grafting). Cerebrovascular disease is a common cause of acute seizures and is characterized by loss of blood-brain barrier (BBB) permeability and extravasation of serum protein. While brain penetration of antiepileptic drugs (AEDs) in chronic epileptics has been extensively studied, comparably little is known about AED pharmacokinetics under conditions of pronounced BBB leakage. We studied the effect of BBB disruption (BBBD) on brain-to-plasma distribution of hydrophilic (deoxyglucose and sucrose) and lipophilic (phenytoin, doxorubicin, and phenobarbital) molecules. Specifically, we wished to test the hypothesis that lipophilic and hydrophilic drug distribution is differentially affected by BBBD.

**Methods:** In vivo BBBD was performed in rats by intracarotid injection of hyperosmotic mannitol. Radiolabeled drugs or unlabeled phenytoin were measured and correlated to brain water content and protein extravasation. In vitro hippocampal slices were exposed to different osmolarities; drug penetration and water content were assessed by analytical and densitometric methods, respectively.

**Results:** BBBD resulted in a rapid extravasation of serum protein and radiolabeled drugs independently from brain edema. In contrast, large shifts in water content in in vitro brain slices had a small effect on drug penetration. In both cases, the total drug permeability increase was greater for lipophilic than hydrophilic compounds. BBBD reduced the amount of free lipophilic drug in the brain parenchyma.

**Discussion:** Our data show that damage of the BBB as seen after cerebrovascular failure due to cardiac arrest or extracorporeal circulation results in a dramatic increase in serum protein extravasation and reduced free AED levels. This may represent a new mechanism contributing to poor efficacy of AEDs in acute patients affected by postoperative seizures or seizures following cardiac arrest or stroke.