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MetroHealth Medical Center

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Abstract Submission Form

Poster Title: **Effect of Danegaptide on Gap Junction Preservation at the Blood-Brain Barrier after Sudden Cardiac Arrest**

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Category: **Molecular & Cellular Biology**

Objectives: Sudden cardiac arrest (SCA) is devastating and affects more than 350,000 individuals. Although rates of return of spontaneous circulation (ROSC) are improving, survivors may face devastating neurologic dysfunction due to damage to the blood brain barrier (BBB) secondary to ischemic injury. Maintaining BBB integrity may lead to improved neurologic outcomes. Gap junctions and their main protein, connexin 43 (Cx43) have been shown to be critical for BBB preservation. We recently demonstrated that SCA increased systemic proinflammatory cytokines and decreased the gap junction protein Connexin 43 (Cx43) at the BBB with associated disruption. Danegaptide, a dipeptide that specifically promotes gap junctions, has been shown to be neuroprotective in stroke but has not been tested in SCA. The purpose of this study is to determine if Danegaptide can preserve Cx43 at the BBB after resuscitation from cardiac arrest.

Methods: All experiments were approved by the Institutional Animal Care and Use Committee. We utilized a model of SCA in Sprague-Dawley rats (300-500g). Rodents were intubated and underwent rapid electrical pacing, via an esophageal electrophysiologic catheter, until ventricular fibrillation or pulseless electrical activity occurred. Rodents remained in arrest for 4-6 minutes, were resuscitated using Advanced Cardiac Life Support (ACLS) and then placed into two groups: Danegaptide (75 micrograms/kg IV after ROSC followed by 300 microgram/kg/hr IP for 3 hr, n=8) and Control (n=3). Sham experiments (n=3) without cardiac arrest were also performed. After 6 hours the rodents were euthanized and brain tissue collected. Endothelial Cx43 at the BBB in the hippocampus was identified using immunohistochemistry. The primary outcome was percent volume of endothelium colocalized with Cx43. Colocalization was performed using Huygens software (Scientific Volume Imaging, Netherlands). Statistical analysis was performed using t-test for continuous variables.

Results: Gap junction location was significantly preserved at the endothelium in the Danegaptide versus control group at 6 hours after cardiac arrest (Average Volume= 12.08±7.06% vs. 4.01 ±1.12%, p=0.014). Average volume in the Sham experiment was 9.32±6.71%. There were no differences in arrest rhythm, time in arrest, or amount of ACLS pharmacology given between groups.

Conclusion: Danegaptide significantly preserved gap junction Cx43 in the endothelium at the BBB and was comparable to nonischemic experiments. BBB preservation via gap junction promotion may be a novel therapeutic target to improve neurologic function after cardiac arrest.