Improved Hypoxic Ventilatory Response and Survival following Cardiac Arrest and Resuscitation in Diet-induced Ketotic Rats.

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Introduction: There is high morbidity and mortality after an initially successful cardiopulmonary resuscitation from cardiac arrest. Post-resuscitation mortality may be due to an impairment of brainstem function. Hypoxic ventilatory response (HVR) is a natural response to decreased environmental oxygen levels and can be used to reflect brainstem function with respect to regulation of respiration. The brain is normally completely dependent on glucose, but is capable of using ketones as an alternate energy source under the conditions of extreme starvation or feeding of high fat, low carbohydrate (ketogenic, KG) diet. This diet has been used successfully in treatment of epilepsy. Our group has previously reported that ketosis was neuroprotective in focal ischemia through succinate-mediated increased accumulation of hypoxic-inducible factor-1 alpha (HIF-1_).

Hypothesis: Diet-induced ketosis improves brainstem function, as exemplified by the hypoxic ventilatory response, and survival following cardiac arrest and resuscitation.

Methods: Male Wistar rats (2-month old) were fed ketogenic diet to induce ketosis, and matched controls were fed standard (STD) diet for 3 weeks before undergoing12-minute cardiac arrest and were allowed to survive for 4 days following resuscitation. Hypoxic ventilatory response, the ratio of minute volumes (10% oxygen vs. normoxic baseline), was measured using plethysmography, and overall survival rates were determined.

Results: Our data showed that HVR in KG-diet group (3.0_0.5, mean_SD, n_3) was similar to STD-diet group (2.9_0.2, n_9) before cardiac arrest. During 1- 4 days of resuscitation, HVR was significantly decreased (30–36%) compared to the pre-arrest value in the STD-diet group, and the lower HVR was associated with poorer recovery. However, HVR was improved in the KG-diet group at 1–3 days of recovery, and overall survival rate was improved in the KG-diet group compared to the STD-diet group (80% and 50%, respectively).

Conclusion: Our data show that diet-induced ketosis improves hypoxic ventilatory response in the early recovery period as well as the overall survival rate following cardiac arrest and resuscitation. Analogous to the neuroprotection in focal ischemia, diet-induced ketosis may confer protection after cardiac arrest and resuscitation via increased accumulation of HIF-1_.