1. Randomized Controlled Study Comparing High Dose Insulin (HDI) to Vasopressors or Combination Therapy in Refractory Toxin-Induced Cardiogenic Shock (TICS)

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**Background:** Cerebral perfusion (PBrO2) during TICS has not been formally studied. In an animal model of TICS, HDI was superior to vasopressors from a cardiovascular standpoint. However, the effects of HDI, vasopressors, or combination therapy on PBrO2 in TICS are unknown.

**Hypothesis:** In a porcine model of refractory TICS, addition of norepinephrine (NE) after maximizing HDI therapy increases PBrO2 when compared to HDI-alone or to vasopressor (NE + Epinephrine (Epi)) therapy alone.

**Methods:** Using an established porcine model of propranolol toxicity, fifteen pigs were randomized to three groups (HDI, HDI+NE, or NE+Epi). At primary toxicity, defined as a 25% reduction in heart rate (HR) * mean arterial pressure (MAP), HDI and HDI+NE groups were started on HDI (10 U/kg/hr) and NE+Epi group started on NE (titrated to 0.5 mcg/kg/min). At secondary toxicity (PoT#2), defined as a sustained MAP < 50 mmHg, the HDI group received normal saline (NS), the HDI+NE group received NE, and the NE+Epi group received Epi (titrated to 0.5 mcg/kg/min). Changes in PBrO2 after PoT#2 were compared using a linear mixed model with repeated measures within pig. Time from PoT#2 to death or censoring after 4 hours was analyzed using proportional hazards regressions.

**Results:** The mean decrease in PBrO2 was minimal in pigs with HDI+NE (0.4 mmHg/hr) but substantial in pigs with HDI-alone (10.4 mmHg/hr). Poor survival in the NE+Epi group prevented PBrO2 comparisons. The mean (SD) time to death, in hours, was 1.9 (0.4) in the HDI-alone group, 2.9 (1.4) in the HDI+NE group and 0.1 (0.1) in the NE+Epi group. Moderate evidence supported supplementing HDI with NE (HR=0.31; 95% CI 0.06 to 1.65; p=0.15).

**Discussion:** PBrO2 was better preserved in the HDI+NE group than in HDI-alone. A substantial and significant mortality benefit was demonstrated with HDI-alone compared to NE+Epi.

**Conclusions:** In a model of refractory TICS, HDI+NE treatment was superior to HDI-alone and vasopressors alone, at preserving PBrO2 over time. If MAP sustained at < 50 mmHg after maximizing HDI, adjunctive treatment with NE should be considered to preserve PBrO2. Our data suggests vasopressors alone should not be used due to significantly increased mortality.

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