The Effects of Phentolamine on Cerebral Hemodynamics During Selective Cerebral Perfusion at Deep Hypothermia in the Neonatal Pig Model

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Introduction

The mortality rate of neonates undergoing cardiac surgery for repair of congenital heart defects has decreased recently due to surgical technique advancements. However, these patients remain vulnerable to brain injury during surgery due to cerebral ischemia that may lead to manifestations of neurological dysfunction post-operatively. Patients undergoing cardiopulmonary bypass (CPB) and hypothermic circulatory arrest (HCA) followed by selective cerebral perfusion (SCP) are at a greater risk for neurological injury, with an incidence reported to be as high as 25%.[1] Vasoconstriction due to CPB can cause decreased blood flow to vital organs of the body. To counteract these effects, vasodilators that block the adrenergic response have been used clinically.[2] Phentolamine has been used as a peripheral vasodilator.[3] It is classified as a α_1 and α_2 catecholamine receptor blocker that causes vasodilation and hypotension.[2] However, whether phentolamine impedes or improves cerebral circulation remains unknown. The goal of this pilot study was to determine the effect of phentolamine on cerebral blood flow (CBF), cerebral vascular resistance (CVR), and cerebral oxygen extraction ($CMRO_2$).

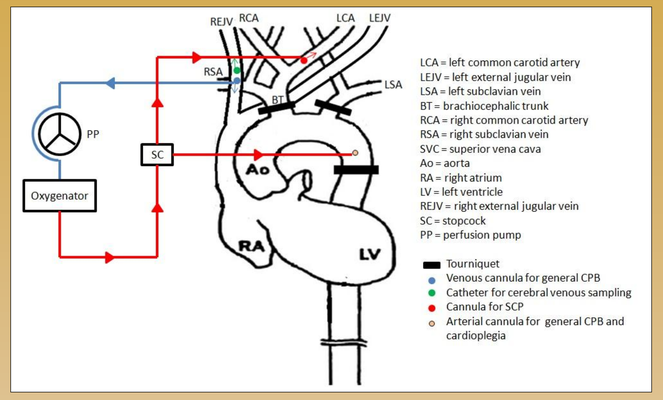


Image 1. A schematic diagram of the circuit during SCP and CPB.

$$CVR\ (mm\ Hg/mL/100\ g/min) = \frac{(MAP - MVP)}{CBF}$$

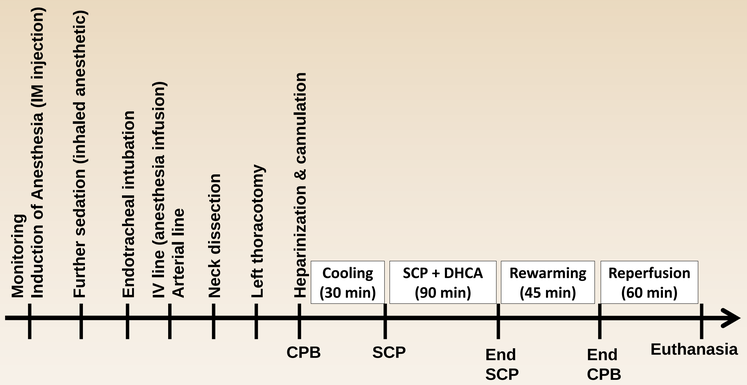
$$CMRO_2\ (mL/100g/min) = CBF \times \frac{(CaO_2 - CvO_2)}{100}$$

$$C_aO_2 = 1.36 \times Hgb \times \frac{S_aO_2}{100} + (0.0031 \times P_aO_2)$$

$$C_vO_2 = 1.36 \times Hgb \times \frac{S_vO_2}{100} + (0.0031 \times P_vO_2)$$

Materials & Methods

Experiment protocol:



The animals in the experimental group received a continuous IV infusion of phentolamine at the start of SCP; the other group did not receive any phentolamine during SCP. Eight samples were collected: a baseline, seven samples during SCP at 15 minute intervals, and a post-SCP sample. Cerebral arterial and venous samples collected from the perfusion pump and the external jugular vein, respectively, were obtained simultaneously for calculation of $CMRO_2$ (arteriovenous oxygen content difference).[4] CBF was measured from the perfusion pump during SCP. The other variables that were measured included arterial oxygen saturation, arterial oxygen pressure, external jugular venous oxygen saturation, arterial pH, external jugular venous oxygen pressure, venous pH, cerebral mean arterial pressure, cerebral mean venous pressure, and hemoglobin. These variables were gathered from monitors and blood gas analysis using the iSTAT machine.

Results

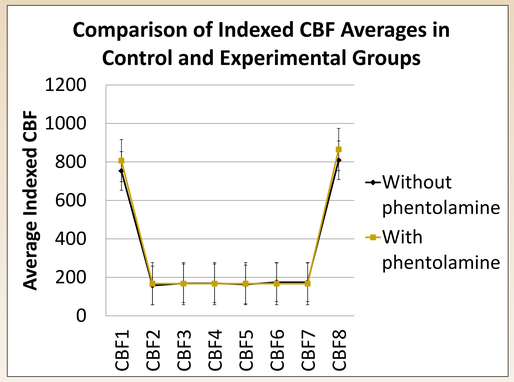


Figure 1. These are the averages of the indexed measurements for CBF for the control and experimental groups over time. Standard error bars are shown for the control and experimental groups.

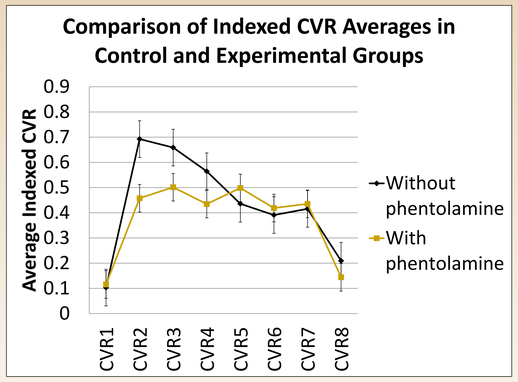


Figure 2. These are the averages of the indexed calculations for CVR for the control and experimental groups over time. Standard error bars are shown for the control and experimental groups.

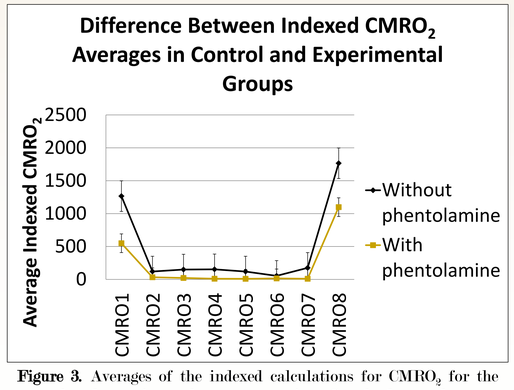


Figure 3. Averages of the indexed calculations for $CMRO_2$ for the control and experimental groups over time. Standard error bars are shown for the control and experimental groups.

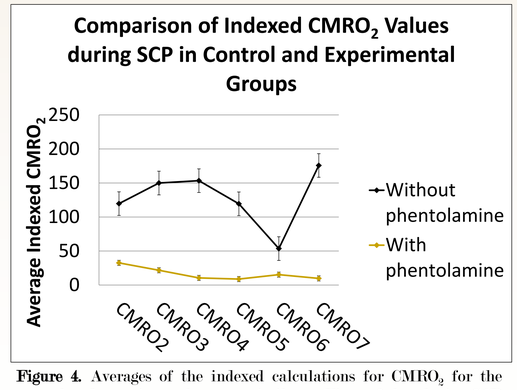


Figure 4. Averages of the indexed calculations for $CMRO_2$ for the control and experimental groups, similar to Figure 3, but during SCP only. Standard error bars are shown for the control and experimental groups.

Conclusion

In this pilot study, we determined the effects of phentolamine administration during SCP on three parameters of cerebral hemodynamics – CBF, CVR, and $CMRO_2$ – in a neonatal piglet model. We found that indexed values for CBF showed nearly identical trends in the control group compared to the experimental group due to the requirement of the protocol to maintain perfusion pump flow, so we expected the CBF values to be consistent between groups. In addition, we determined the CVR was reduced in the experimental group for approximately the first 70 minutes of SCP compared to the indexed CVR values in the control group. This implies that phentolamine may have had an effect for the first 70 minutes of SCP, and then wore off for the remainder of the SCP period. Comparison of indexed $CMRO_2$ values showed that the metabolic rate of the brain tissue in experimental cases was maintained at a lower rate for the duration of SCP compared to the control group, implying that phentolamine provided some protection against ischemic injury. Our hypothesis was supported for the CVR and $CMRO_2$ measurements, although the multivariate test of differences for intervention was not statistically significant for either of these variables. This study will be expanded in the future to include nine more piglets to achieve a final sample size of eighteen. The implications of this study include expansion to clinical trials after more rigorous experimentation to determine if patients' neurologic outcomes with phentolamine are improved compared to the surgical protocol currently in use to correct congenital heart defects in neonates.

References

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