PERFLUOROCHEMICAL NASOPHARYNGEAL COOLING INDUCES SELECTIVE BRAIN HYPOTHERMIA

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ABSTRACT

Background: Effectiveness of hypothermic brain neuroprotection depends on how rapidly cooling is initiated and the therapeutic hypothermic zone (THZ) is reached. Whole body surface (WBS) or intravascular methods are encumbered by equipment, systemic instability, and slow response. Due to proximity to the cerebral circulation, the nasopharynx is uniquely suited for selective brain cooling; however nasopharyngeal (NP) cooling with oxygen or liquid is limited by low heat capacity and/or respiratory compromise. As an alternative, high oxygen solubility, distribution, and rapid evaporative properties of nasopharyngeal aerosolized perfluorochemical (PFC) increases the heat capacity of respired gas, thus should rapidly induce brain cooling without cardiopulmonary compromise.

Objective: To compare regional cooling rates and cardiopulmonry function in juvenile sheep during WBS or NP-PFC cooling.

Design/Methods: Anesthetized and ventilated young sheep (n=22), instrumented with multiple temperature probes and vascular catheters, were randomized to WBS (cold H_2O blanket) or NP-PFC aerosol (PFC/O_2 spray device; BeneChill, Inc.) cooling. Temperatures, blood pressure, cardiac output and blood chemistry were measured for up to 2 h. Cooling rates were evaluated (ANOVA) as a function of method (WBS vs NP-PFC), PFC/O_2 flow (0.50 – 2.0 mL/kg/min; 0.20 – 2 L/kg/min), and time to reach the brain THZ (≥ 3ºC below baseline).

Results:

Cooling Rates (ºC/hr) X ± SE	Brain	Vascular	Rectal
WBS (*)	1.40 (0.12)	1.39 (0.16)	1.59 (0.13)
NP-PFC (**)	8.23 (1.10)	4.51 (0.54)	2.80 (0.36)

Independent of flow and region, cooling was faster (*p<0.001) during NP-PFC vs WBS. With WBS, brain vs systemic cooling rates were not different and brain THZ was not reached by 2 hr. With NP-PFC independent of flow, brain>vascular>rectal rates (**p<0.001) and brain THZ was reached in 24.2 ± 3.3 SE min. Brain cooling rates increased with (p<0.001) with PFC and O_2 flow.; brain to systemic temperature gradient increased with (p<0.001) with PFC flow. Blood pressure and cardiac output decreased with cooling during WBS and remained stable during NP-PFC. Gas exchange was stable with both methods.

Conclusions: NP-PFC aerosol cooling provides rapid and preferential brain hypothermia without cardiovascular compromise or cumbersome equipment.

INTRODUCTION

Cerebral hypoxic-ischemic events are the leading cause of acute neurological injury at birth, and, cause of long-term disability across age worldwide. A 2-5 ºC reduction in brain temperature after this event can improve neuropathological, cerebral energetic, and electrophysiological outcomes. The neuroprotective efficacy of cerebral hypothermia has been linked to how rapidly cooling is initiated, how quickly the brain is cooled, and the extent of tissue that reaches the therapeutic hypothermic zone. Whole body surface (WBS) or intravascular methods for brain cooling are encumbered by equipment, systemic hypothermia, slow response, and concomitant systemic instability. Selective head cooling by circulating cold water cap shows promise, though regional gradients in brain temperature remain. Due to proximity to the cerebral circulation, the nasopharynx is uniquely suited for selective and homogenous brain cooling; however, nasopharyngeal (NP) cooling with oxygen or liquid is limited by low heat capacity and/or respiratory compromise. As an alternative, the favorable distribution and rapid evaporative properties of nasopharyngeal aerosolized perfluorochemical (PFC) increases the heat capacity of respired gas, thus should facilitate rapid induction and maintenance of global brain cooling without substantial compromise in systemic temperature.

Theoretical Basis for PFC Nasopharyngeal Cooling

1. Latent Heat of Vaporization
   - Phase Change of PFC liquid to PFC vapor
   - Endothermic reaction
   - ΔHeat ∝ (Q_{PFC} x C_P x Surface Area)
2. Hematogenous Cooling
3. Conductive Cooling

HYPOTHESIS

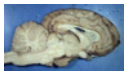
PFC nasopharyngeal cooling will rapidly induce global cerebral hypothermia

OBJECTIVES

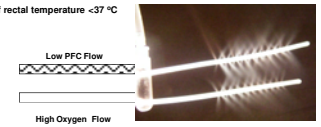
- Characterize brain cooling rates as a function of PFC/Gas flow ratio.
- Compare brain and systemic cooling rates and temperature gradients during PFC nasopharyngeal cooling to whole body surface cooling.

METHODS

- **Animal Model**
  Normal Weanling Sheep (n = 25; 21 – 25 kg)
  Ketamine (10 mg/kg) and butorphanol tartrate (1 mg/kg) pre-anesthesia (IM)
  Sodium Pentobarbital (12.5 mg/kg) supplemented by continuous infusion (1.25 mg/kg/hr)
- **Instrumentation**
  Carotid Artery, bilateral external jugular and pedal veins, trachea cannulation
  Pulmonary Artery (Thermodilution Catheter)
  ECG leads and Pulse Oximeter Probe
  Temperature Probes
  Brain (Inferior Frontal: 5 cm; 3rd Ventricle: 5 cm; Superficial Parietal: 3 cm) placement confirmed by fluoroscopy and Evans Blue
  Ear (approximating tympanic membrane)
  Vascular (High via external jugular into thoracic cavity; Low via pedal vein into abdominal cavity)
  Subcutaneous
  Intramuscular
  Rectal



- **Management**
  Mechanical Ventilation (Time-cycled, volume-controlled) with 100% O_2)
  Target PaO2 > 300 mmHg; PaCO2 = 35 - 45 mmHg; pH = 7.35 – 7.45
  Skeletal Muscle Paralysis (Pancuronium Bromide: 0.10/ mg/kg/hr)
  Maintenance Fluids (D_5 @ 7.5 mL/kg/hr)
- **Measurements**
  Temperature, systemic and pulmonary arterial blood pressure, heart rate: continuous recordings
  Arterial Blood Chemistry and Cardiac Output: Baseline, mid and final induction, serially throughout maintenance
- **Calculations and Analyses**
  Regional Cooling Rates, Time to Therapeutic Hypothermic Zone, Brain Cooling Rates as a function of PFC/Gas Flow
- **Protocols**
  Whole Body Surface Cooling induced and maintained by circumferential, cold water (0ºC) circulating blankets
  Nasopharyngeal Cooling induced and maintained by PFC/ Oxygen spray cannula device. (Perfluorohexane; F2, Ltd)
  - PFC (room temperature) and Oxygen flow are independently regulated by mass flow meters at predetermined rates
  - Nasal Temperature = 2 – 5 ºC
  - Induction: Continuous spray to target -3.5 ºC change from baseline
  - Maintenance: Intermittent spray: restart @ 0.5 ºC above target, terminate when target temperature was restored
  - External warming blanket applied if rectal temperature <37 ºC



RESULTS

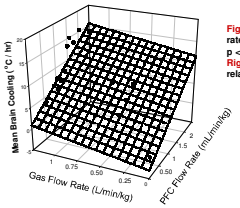
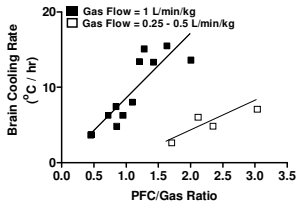


Fig 1: Left: Interrelationship between PFC flow rate, gas flow rate, and mean brain cooling rate. p < 0.0001, r = 0.88, r^2 = 0.78, r^2 adjusted = 0.75. **Right:** Mean brain cooling rate is directly related to the ratio of PFC to Gas flow rates



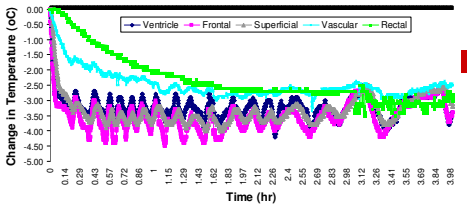


Fig 6: Regional brain and systemic temperature changes during induction and 4 h maintenance protocol with PFC nasopharyngeal cooling. Note consistency between brain regions demonstrating ability to rapidly induce and maintain hypothermia in deep and more superficial brain structures with minimal differences in cooling rates.

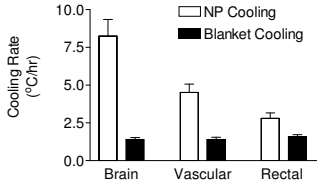


Fig 2: Absolute cooling rates (X ± SE) during nasopharyngeal (NP) (open) and blanket cooling (solid) protocols. ANOVA demonstrated significant difference (p < 0.001) between all compartments with NP > blanket and within NP rates, with brain > vascular > rectal (p< 0.001).

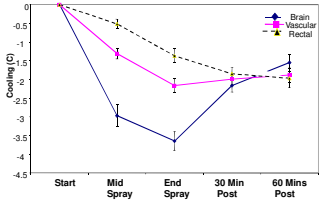


Fig 4: Brain to systemic temperature gradient increased during the nasopharyngeal cooling protocol, diminished with termination, and was no longer observed following 30 min of active cooling.

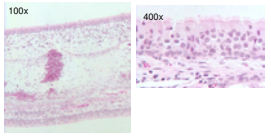


Fig 7: Histomicrographs of sections of the nasal passage following 2 h of PFC nasopharyngeal cooling. Note: intact epithelial surface.

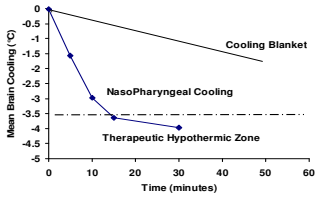


Fig 3: The therapeutic hypothermic zone was reached within 15 mins. with PFC nasopharyngeal cooling but not achieved with the whole body surface cooling blanket during the 2h protocol

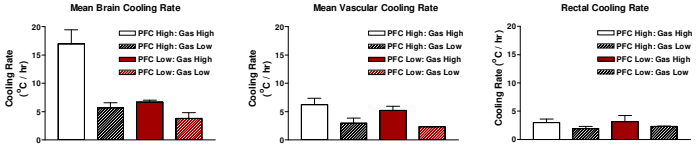


Fig 5: Compartmental cooling rates evaluated as a function of PFC and gas flow rates. PFC high flow rates = 1 – 2 mL/min/kg, PFC low flow rates = 0.5 - 1 mL/min/kg; Gas high flow rate = 0.5 - 1 L/min/kg; Gas flow rates = 0.2 - 0.5 L/min/kg.

CONCLUSIONS

- With PFC nasopharyngeal cooling , PFC / Gas flow ratio directly influenced brain cooling rates.
- With PFC nasopharyngeal cooling, absolute compartmental cooling rates and brain to systemic temperature gradients were significantly greater than with whole body surface cooling.
- With PFC nasopharyngeal cooling, brain to systemic temperature gradients demonstrated preferential brain cooling relative to vascular and rectal temperature profiles. Vascular and rectal cooling rates were approximately one-half and one-third of brain cooling rate, respectively.
- With PFC nasopharyngeal cooling, the therapeutic hypothermic zone was reached within 15 mins. whereas whole body surface cooling did not obtain this zone within 2 h.
- PFC nasopharyngeal cooling rapidly induced and maintained global cerebral hypothermia.

SUMMARY

The principle findings of this study are that the therapeutic hypothermic zone targeted for global brain neuroprotection can be rapidly reached and maintained by PFC nasopharyngeal cooling. This approach maintains brain to systemic temperature gradients with preferential brain cooling relative to vascular or rectal temperatures and requires relatively little instrumentation. On-going studies are focused at increasing the brain to systemic temperature gradient by modulating the PFC/gas flow ratio and incorporating external warming blankets commensurate the PFC nasopharyngeal cooling. Future studies are planned to evaluate the neuroprotective effect of this approach in models of cerebral compromise.

ACKNOWLEDGMENTS

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