Project Design

i) Innovative selective brain cooling method

Both intra- and extra-cranial vascular arrangements in humans and in primates offer opportunities for selective brain cooling (SBC)[4,5] while leaving the whole body temperature close to normothermia to avoid complications from hypothermia. In humans arterial inflow blood to the brain via the internal carotids and venous blood from the skin of the face and from the nasal and pharyngeal cavities come in intimate contact in the cavernous sinus. One method to selectively decrease brain temperature is to cool the nasal and pharyngeal cavities and the embedded veins therein. Another method is to rely on the bulk transfer of cooled venous blood from the skin and nasal mucosa to the dura mater which, with its high density vascularization, would cool the cerebrospinal fluid (CSF) that in turn would cool down the brain indirectly, via brain arteries that penetrate deep into the brain parenchyma. The use of both SBC methods has been amply demonstrated with a number of commercially available clinical devices for treatment of neuroemergencies (such as traumatic brain injury and stroke) as reviewed by a recent UK Health Technology Assessment.[6]

Our invention focuses on cooling the mucosa of the upper airways by blowing cold air into the nasal and pharyngeal cavities. The method is similar to the Rhinochill device (www.Benechill.com) which uses perfluorohexane, a liquid with low boiling point temperature, instead of air and was shown to decrease brain temperature, increase survival and decrease neurological deficits of resuscitated cardiac arrest patients.[7] However, our method has two advantages: (1) air is immediately available everywhere whereas perfluorohexane has to be ordered and shipped in advance; (2) compressed air costs very little vs about ~$2,800 for a 2-hr supply of perfluorohexane[8]. Since prevention of brain injury may require up to 12-24 hr of SBC[9,10], the cost for the coolant will be prohibitive if Rhinochill is used. The method for cold air generation which is the crux of our invention is particularly simple. It relies on blowing compressed air from medical air cylinders or regular hospital compressed air outlets or a compact compressed air generator through a commercially available vortex tube. The tube, measuring ~ 3 X 75 cm, separates the compressed air input into two opposing streams – one hot and one cold (Figure 1).[11] Depending on the pressure of the input compressed air and the ratio of the cold vs hot flow, a cold air temperature of -25 to -30^{o}C can be achieved. We have also designed and constructed a servo-controller of these two operating parameters to produce automatically cold air at the desired flow rate and temperature. Design targets of the servo-controller achieved are: cold air flow rate from 20 to 50 of litre per minute (LPM) in 5 LPM steps and cold air temperature control range from -10 to +10 degrees C in 1 degree steps. The vertex tube together with the servo-controller is very compact and can be easily used at the bedside of patients in hospitals or on ambulances on-route to hospitals provided compressed air is available from air cylinders or generators.

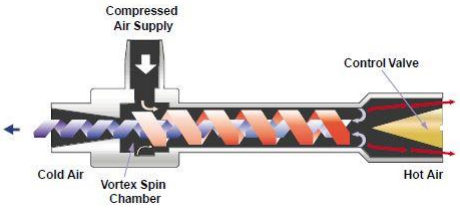

Figure 1. Schematic diagram of a vortex tube

ii) Preliminary brain cooling results

We were successful in cooling the brain of both pigs and rabbits with our method. Figure 2 shows the result of a typical 7-hr cooling experiment in pigs. The brain temperature was measured with an implanted thermocouple. By blowing -10^{0}C air at 50 L/min into the nostrils, the brain temperature decreased rapidly from 38^{0}C to 34^{0}C within 15 mins and then more slowly to 33.2^{0}C in the next 15 mins. Subsequently, the brain temperature was maintained at 33.2±0.2^{0}C for 6.3 hrs by increasing the air temperature to 0^{0}C at the same flow rate. On the other hand, the minimum whole body temperature as measured with rectal and esophageal temperature probes during the whole 7-hr cooling period was above 36^{0}C, significantly above the threshold of 34^{0}C for complications to occur[2,3]. Review of MRI of the upper airways before and after cooling showed no edema, hemorrhage or inflammation evident within the nasal cavity

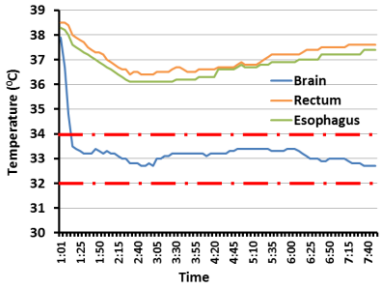

Figure 2. Cooling results obtained with our device in a pig

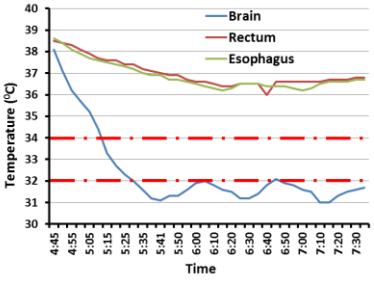

Figure 3. Cooling results obtained with our device in a rabbit

plus nasopharynx. Similar successful cooling results were obtained in another six pigs and six rabbits. Figure 4 shows cooling results from a rabbit. By blowing -7^{0}C air at 20 L/min into the nostrils, the brain temperature decreased from 38^{0}C to 34^{0}C within 30 mins and then to 31.2^{0}C in the next 30 mins. Subsequently, the brain temperature was maintained at 31.2±0.4^{0}C for 2 hrs by increasing the air temperature to 2^{0}C at the same flow rate. The minimum whole body temperature as measured with rectal and esophageal temperature probes during the whole 3-hr cooling period was above 36^{0}C.

iii) Objectives

The primary goal of this application is to demonstrate that our cooling method will minimize brain injuries resulting from cerebral ischemia and trauma by selectively reducing brain temperature to the mild therapeutic hypothermia range (32-34^{0}C) in 30 min or less and by maintaining that temperature over extended period of time, up to 12 hrs. For this goal, two sets of rabbit experiments (objectives) involving a stroke model and a fluid percussion model of traumatic brain injury will be used. Demonstration of neuroprotection in both objectives will pave the way for phase I clinical testing in patients.

iii.a) Demonstration of neuroprotection in stroke

The rabbit stroke model is based on the filament model we have previously developed.[12] All experimental/surgical procedure will be performed in the PET/CT scanner suite at St. Joseph's Hospital. A thermocouple thermometer is implanted at the back of the brain to record brain temperature throughout the experiment. After exposure of the left internal carotid artery (L-ICA) on the PET/CT scanner table, a small hole is made in the artery[13] and a 5-O nylon suture is inserted through the hole towards the brain until elastic resistance is felt (usually after 50 to 60 mm, as indicated by markers on the filament). A CT Perfusion study is done to verify ischemia in the L-ICA territory. Once ischemia is confirmed, SBC is initiated with our device under servo-control of cold air temperature and flow rate to reach brain temperature of 32^{0}C in 15 minutes and thereafter maintained at this temperature for 12 hours. After one hour of occlusion, the filament is retracted, the L-ICA repaired[13] and the neck wound sutured. The size of the infarct resulting from 1-hr occlusion and 11-hr reperfusion will be determined using PET imaging at 12 hr into cooling with the ^{18}F-FFMZ ligand that binds to viable neurons[14] and is injected at 30 min prior to imaging at a dose of 185 MBq. A similar group of control rabbits will also be studied in the same way except that SBC will not be used. The effectiveness of hypothermia in protecting the brain against ischemia will result in significantly different infarct size between the two groups of animals. Six rabbits in each of the SBC and non-SBC group will detect a 20% difference in infarct size between the two groups at 0.8 power and 95% confidence.

iii.b) Demonstration of neuroprotection in traumatic brain injury (TBI)

We will use the fluid percussion device in our lab (Figure 4) to create the rabbit TBI model[14]. A small burr hole is made in the lateral aspect of the rabbit skull; injury is produced by the rapid impact of a fluid bolus from the saline reservoir against the intact dural surface. By placing the pendulum at the same height, reproducible brain injury can be achieved in different animals with the device. There will be a SBC and a non-SBC group of six rabbits each. The sample size, study procedures and analysis methods for each group are the same as in the first objective.

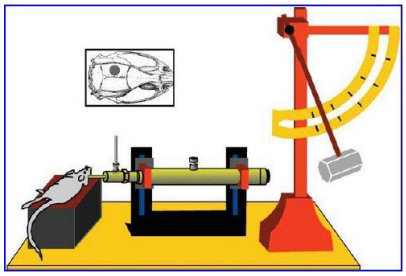

Figure 4. A fluid percussion device for creating traumatic brain injury in small animals including rats and rabbits

c) Intellectual Property Status

A provisional patent application title "Mammalian head cooling system and method" for our device has been filed by WORLDiscoveries with the U.S. Patent and Trademark Office on March 21, 2014 who assigned No. 61/968844 to the application. Furthermore, a regular patent application claiming priority from the provisional application has been filed before the deadline of March 21, 2015. We are awaiting results from the regular patent application.

d) Outcomes

The results of this project will provide proof-of-principle pre-clinical data that our selective brain cooling device can reduce brain injuries from ischemia and trauma. This is a necessary first step before clinical testing in human patients can be justified. Furthermore, the data will strengthen our presentation to medical device companies for their interest to license our technology. Throughout the project period, through our own or WORLDiscoveries' contacts, we will seek out medical device companies, particularly those in the area of non-invasive head-cooling, for their interest in our device.

References

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