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Neuroprotection by selective endovascular brain cooling - the TwinFlo™ Catheter

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Short Title: Neuroprotection by selective endovascular brain cooling - the TwinFlo™ Catheter

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Abstract

The neuroprotective effects of hypothermia have been demonstrated in experimental models and clinical trials. Experimental studies indicate that improved efficacy and broadened indications can be achieved with moderate to deep hypothermia. The TwinFlo™ Catheter was designed to provide very rapid, deep and selective brain cooling with faster cooling rates, and temperatures much lower than what can be achieved by any other hypothermia device and technique. This report describes the experimental in vivo studies and initial clinical experience with the TwinFlo™ Catheter.

Introduction

Neuroprotection — protecting the brain from the devastating effects of ischemia and reperfusion injury — remains as an important unmet clinical need today. The neuroprotective effects of hypothermia following acute stroke and cardiac arrest have been demonstrated in numerous experimental models and clinical trials[1-5]. In the laboratory, hypothermia has been shown to be the most robust neuroprotectant identified to date, because it acts on many of the pathways that lead to cell death, and its role in mitigating reperfusion injury is of particular importance. In the clinical setting, although questions regarding degree of temperature reduction and other procedural matters still remain, therapeutic hypothermia is currently recommended for most out-of-hospital cardiac arrest (OHCA) patients; however, in acute stroke, the hypothermia techniques that have been attempted failed to demonstrate benefit[6], probably because they were unable to safely cool the brain to temperatures shown to be efficacious in experimental models. The TwinFlo™ Catheter was designed to address and potentially reverse these serious health problems by

providing a means to very rapidly, deeply and selectively cool the brain, with faster cooling rates, and temperatures much lower than what can be achieved by any other hypothermia device and technique.

Methods

The TwinFlo™ Catheter

The TwinFlo™ Catheter (ThermopeutiX, Inc. San Diego, USA) was introduced by standard percutaneous transfemoral technique, and was used to isolate and selectively perfuse the carotid artery with cold blood (Figures 1-3). It comprises two concentric tubular shafts (8.5F and 14F, respectively) that define inflow and outflow lumens, and an atraumatic occlusion balloon positioned at the distal end of the inflow lumen. Figure 2 illustrates operation of the catheter.

In Vivo Studies

In vivo studies were performed in 47 pigs weighing 50-72 kg. All procedures and care of animals were in accordance with institutional guidelines. All animals were anesthetized, intubated and heparinized. They were placed on a water-heating mattress preset to 38℃ and covered from the neck to the feet with either a forced-air heating blanket or warmed blankets (Figure 4a). Temperature was measured in bilateral frontal lobes, nasopharynx, ear, esophagus, rectum, jugular vein and descending aorta. Standard cardiopulmonary perfusion circuits and equipment, or alternatively a standard dialysis pump plus a stainless-steel heat exchanger coil in a bucket of ice water, were used to cool and pump the blood. Three series of studies evaluated selective cerebral cooling and parameters, surrogate non-

invasive brain temperature measurement, and the effect of selective endovascular cooling in a focal stroke model. Hemodynamic parameters (heart rate, mean arterial blood pressure) and arterial blood gases (oxygen, hemoglobin, glucose, pH) were continuously evaluated. Outflow blood was cooled to 5-20°C, and reperfused at rates of 80-250 ml/min for 30-180 minutes. Animals were euthanized at the end of each study. In a porcine stroke model, focal ischemia was created by surgically clipping one of the middle cerebral arteries[7]. After 3 hours of ischemia, the clip was removed, and a 3-hour period of reperfusion followed. During the 3-hour reperfusion period, 25 pigs were randomized to receive selective hypothermia with the TwinFlo™ Catheter or serve as a normothermic control. After sacrifice, the brain was fixed and removed for MRI and histological analysis, which was performed by experts who were blinded to the study groups.

Results

The TwinFlo™ Catheter was successfully positioned in the common carotid artery in all animals. In the ipsilateral hemisphere, temperatures to as low as 15°C were attained, and passive rewarming did not result in rebound hyperthermia (Figure 5). Initial cooling rates up to 1.8°C/min were reached, and were dependent on the flow rate and temperature of the perfused blood (Figure 6). No hemolysis was observed for any of the blood temperatures and flow rates used in these studies. There was a strong temperature correlation between the two hemispheres, with contralateral hemispheric temperature reaching equivalence to the treated side within 60 minutes in most animals (Figures 7a-b). Systemic temperature did not fall below mild hypothermic levels; in a sub-study of 9 pigs, covering with an additional warming blanket reduced the systemic temperature drop from a mean of

3.9±1.9°C to only 2.0±1.0°C during selective cerebral cooling to 28-30°C (Figures 7a-b). Results of the brain temperature surrogate investigation (Figures 8a-b.) showed strong correlations with both cerebral hemispheres and all surrogate measurement sites. Nasal temperatures tracked the respective cerebral hemispheric temperatures, measuring 1-3 degrees warmer than cerebral temperature.

In the porcine stroke study, nasal temperatures were used as a surrogate for brain temperature. The mean ipsilateral nasal temperature decreased from 38°C to 26.5°C during selective hypothermic perfusion. By MRI imaging, the ratio of stroke volume to hemispheric volume was 10 times lower in the hypothermic group compared to the control group (0.005±0.011 vs. 0.050±0.059; $p<0.05$), and the mean histological stroke volume of the hypothermic group trended to nearly half that of the controls (0.57±0.76 cm^3 vs. 0.99±1.00 cm^3; $p=0.256$). With the exception of a decrease in pH in the hypothermia group (7.34±0.18 vs. 7.44±0.03; $p<0.001$), systemic parameters including mean arterial pressure, blood oxygenation and hemoglobin remained stable and did not differ from the normothermic cohort.

First-in-Human Usage of the TwinFlo™ Catheter

Our initial human experience with TwinFlo™ was in the setting of neurosurgery where prolonged occlusion time was required to surgically repair a giant aneurysm of the middle cerebral artery in a 59-year-old man. TwinFlo™ selectively cooled the brain to 26°C providing neuroprotection, while maintaining systemic normothermia (36.7°C). Cooling was initiated 65 minutes before temporary arterial occlusion, continued during the 39

minutes of occlusion and 16 minutes after, for a total selective cooling time of 2 hours. The patient's recovery, with no neurological deficit, appeared to be much quicker than we have typically seen in this setting.

Discussion

The challenge in protecting the brain from the effects of hypoxia is that there are numerous pathways that lead to cell death. Hypothermia addresses and prevents cell death through many mechanisms, including a lowering of the metabolic rate, reduction of excitotoxic neurotransmitters, prevention of blood-brain barrier disruption, decrease in the destructive oxygen free radical production, reduction in inflammatory markers, mitigation of reperfusion injury, and an overall up regulation of cell survival mechanisms[1,3-5]. Experimental studies of hypothermia in acute ischemic stroke showed greatest efficacy when cooling to below 31°C, suggesting that there is a potential temperature threshold in acute stroke[3]. Unfortunately, in the clinical setting to date, hypothermia did not improve recovery or mortality, and it was associated with more complications[6]. The techniques employed could only cool to a median target temperature of 33°C (range 32-35), and the time to reach target temperature was median of 4 hours[6]. The inability of these techniques to effect cooling times and temperatures that were shown to be most efficacious in the experimental studies would provide a reasonable explanation to the discrepancy between bench and bedside.

Use of TwinFlo™ addresses the time and temperature issues, and by perfusing cold autologous blood, not only is the metabolic demand decreased, but an adequate supply of oxygen and nutrients to the brain is ensured. In the setting of refractory cardiac arrest, Wang et al demonstrated that infusing cold blood with TwinFlo™ for 12 hours was not only safe, but highly efficacious in improving survival and neurological outcomes[8-9]. The authors reported that adding selective cerebral hypothermia at 27±3°C to their standard extracorporeal cardiopulmonary resuscitation (ECPR) protocol increased survival from 35% to 75%, and the rate of Cerebral Performance Category 1 (CPC 1 — no neurological deficit) increased from 12% to 50%. The encouraging outcome from this difficult patient population provides optimism that TwinFlo™ may be effective in acute ischemic stroke and other cerebral ischemic conditions.

Limitations

Findings from the in vivo studies will need to be verified in the clinical setting. The First-in-Human clinical reports include very small sample sizes, and although the preliminary data is encouraging, larger studies, and studies in acute stroke indications will be required.

Conclusion

Selective endovascular cooling of the brain with the TwinFlo™ Catheter shows promise in providing rapid, selective, deep cerebral hypothermia, and may offer an improved method for neuroprotection during neurosurgery, cardiac arrest, acute stroke and other ischemic

insult. Larger clinical investigations in these most challenging and important clinical settings are warranted.

Impact on daily practice

The ability of hypothermia to reduce brain injury is well established in animal models and in some human scenarios of global ischemia. Cerebral metabolism reductions, thought to be the mechanism behind observed neuroprotection in robust animal models, are substantial with moderate hypothermia, but the systemic complications have limited clinical applications to only very mild temperature reductions. Selective endovascular cooling via the TwinFlo™ Catheter represents a more efficient and effective application of therapeutic hypothermia specific to the organ of interest, e.g. the brain. With this technology, rapid and substantial temperature reductions may finally allow clinicians to realize the potential neuroprotective benefits of therapeutic hypothermia in global ischemia (cardiac arrest) and focal ischemia (ischemic stroke and aneurysm). Questions regarding the optimal depth and duration of hypothermia now may be relevant in the human clinical realm as lower temperature limits appear to be circumvented through the percutaneous selective approach provided by the TwinFlo™ Catheter.

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Conflict of interest statement

R. Solar and D. Meerkin are shareholders of ThermopeutiX, Inc. The other authors have no conflicts of interest to declare.

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Figure Legends

Figure 1. The TwinFlo™ Catheter. The warm blood outflow is identified by the blue marker band, and the cooled blood inflow is identified by the red marker band. The yellow band denotes the pressure measurement lumen. Ports at the proximal ends of the inner and outer catheter shafts provide means for flushing, contrast injection, and selective delivery of diagnostic and therapeutic agents.

Figure 2. Schematic of operation in selective cerebral cooling. Using standard percutaneous technique, TwinFlo™ is introduced into the femoral artery, and under fluoroscopic control advanced to the common or internal carotid artery. Blood is withdrawn from the distal end of the outer catheter located in the aortic arch, directed to an extracorporeal circuit where it is cooled, and then pumped directly to the brain through the inner catheter beyond a very atraumatic occlusion balloon, so that the brain only receives cold blood. The counter-current blood flow design (arrows in center insert) very effectively insulates the body from the cold blood during the prolonged perfusion through the aorta to the brain. As such, significantly lower temperatures can be achieved in the brain with minimal or no systemic reduction of temperature.

Figure 3a. TwinFlo™ Catheter positioned in right common carotid artery. The outer shaft of the catheter is situated in the aortic arch.

Figure 3b. Occlusion balloon inflated in the right common carotid artery.

Figure 4a. General procedural setup during in vivo studies. In this study, the extracorporeal circuit comprised a standard dialysis pump and a stainless-steel heat exchanger coil in a bucket of ice water.

Figure 4b. TwinFlo™ Catheter setup during in vivo studies.

Figure 5. Illustrative case demonstrating passive rewarming of the brain upon cessation of cold blood perfusion and deflation of occlusion balloon. Temperature of the cooled hemisphere equilibrated to systemic temperature in approximately 25 minutes.

Figure 6. Rate of cooling of the treated hemisphere as a function of flow rate of the perfused blood normalized by subject body weight for 2 ranges of temperature of the perfused blood (n=8 pigs). Higher flow rates and lower temperatures of the perfused blood resulted in faster rates of cooling.

Figure 7a. Sub-study of 9 pigs designed to evaluate further minimalization of systemic cooling. Selective cerebral cooling was performed for 3 hours, with a target ipsilateral cerebral temperature of 28-30ºC. Each data point is an average of the temperatures at that site at that time point in all animals of the study group. There was a strong correlation between the two hemispheres over the 3-hour study period ($R=0.830$, $p<0.0001$). Systemic temperatures, as measured by a rectal thermistor, fell by a mean of 3.9±1.9°C to 34±1.6°C.

Figure 7b. Brain and systemic temperatures of 4 pigs who were covered with an additional blanket during cerebral cooling. Systemic temperatures fell by only 2.0±1.0°C to a mean of 35.5± 0.9°C compared with the standardly warmed animals (n=5) that fell by 5.4± 0.6°C to 32.4± 0.5°C $p<0.005$).

Figure 8a. Brain temperature surrogate study (n=9 pigs; same subjects as in sub-study shown in Figure 7a). Ipsilateral cooled hemisphere.

Figure 8b. Brain temperature surrogate study (n=9 pigs; same subjects as in sub-study shown in Figure 7a). Contralateral cooled hemisphere.