A MRI Investigation of Cerebral Perfusion Response to Hypothermia in Ischemic Rats with a MR Compatible Regional Brain Temperature Manipulation System

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Introduction

A wealth of reported results has demonstrated that hypothermia is neuroprotective while hyperthermia exacerbates ischemic injury. However, most of the reported studies have employed rather simplistic whole body surface cooling approaches to manipulate temperatures, which could result in side effects, including pneumonia, arterial hypotension, thrombocytopenia, bradycardia, infection and myocardial infarctions. Selective brain cooling has been proposed as an alternative approach to provide neuroprotection while minimizing these side effects. In this study, we have devised a MR compatible temperature manipulation system, which is able to regulate brain temperature consistently and accurately while maintaining a normal core body temperature for a desired period of time in rats. Subsequently, the effects of brain temperature on cerebral blood flow (CBF) in both normal and ischemic rats were investigated.

Method

The MR compatible temperature manipulation device includes two parts to control the brain and body temperatures separately and simultaneously. The brain temperature manipulation component consists of a tubing coil, which wraps around the head of the rat, a feed-back control unit and an MR-compatible peristaltic pump (SCI400D/U1, Watson Marlow Inc.). Water circulating in the tubing coil was driven by the peristaltic pump. Hypothermia and hyperthermia were induced by using either icy (4°C) or warm water (52°C), respectively. Brain temperature measured with a fiber-optic thermo-probe (Luxtron Inc, Santa Clara, CA) inserted into the brain at a depth of 4mm was utilized by the feedback control unit to adjust the flow rate of the pump so as to induce or maintain the targeted temperature. The body temperature was maintained through a separate feed-back control of the heating pad, which wrapped around the animal body, and a pump. The core body temperature reading from a thermo-probe inserted 5-6 mm into the rectum was used as the feedback signal to maintain the desired body temperature at 37.5±0.5°C by switching the pump on or off. Normothermic condition in brain was achieved by adjusting the core body temperature to the normal physiological range with the heating pad.

A total of 11 rats were studied and these rats were divided into three groups. Rats in the first group (n=4, 300±25g) were employed to determine the effectiveness of brain temperature manipulation using the devised system. Four different brain temperature manipulations, hyperthermia (39°C), normothermia (37°C), hypothermia (32°C) and a three-phase hypothermia (29°C, 32°C and 35°C) were conducted with one manipulation in each rat. For the three-phase hypothermic condition, the brain temperature was first cooled down to 29°C, maintained for 30 minutes, rewarmed to 32°C, maintained for another 30 minutes, rewarmed to 35°C and maintained for 30 minutes. For the second group of rats (n=5, 300±25g), cerebral ischemia was induced using an intraluminal suture middle cerebral artery occlusion (MCAO) model under the normothermic condition for 40 minutes, followed by the induction of three different hypothermic conditions, including 35°C, 33°C and 31°C. In order to determine how hypothermia affects cerebral perfusion, ADC and CBF maps were acquired at each temperature point. A segmented SE EPI DWI sequence and a continuous arterial spin labeling (CASL) sequence with segmented EPI readout were used to obtain ADC and CBF maps, respectively. Finally, for the sham operated group (n=2, 300±25g), a similar experimental procedure without occluding MCA was performed. The imaging parameters for the segmented SE DWI EPI were as follows FOV= 45 x 45 cm, 114 x 128 matrix, TR= 1200 ms, bandwidth 592Hz/pixel, slice thickness 2mm and the imaging parameters for the CASL were: FOV= 45 x 45 cm, 60 x 64 matrix, TR= 3000 ms , bandwidth 1116Hz/pixel, slice thickness 2mm.

For the ischemic rats (Group 2), three ROIs (core, mismatched and contra) were manually determined based on ADC and CBF maps. The core region was defined as the regions with ADC abnormalities (<mean-3*SD of the contra-lateral hemisphere). The mismatched region was defined as the hypoperfused region without the ADC lesion in the ipsilateral hemisphere. A mirror ROI in the contralateral hemisphere was chosen as the contra ROI. In contrast, an ROI encompassing both hemispheres excluding the region at a proximity to the temperature probe was outlined as sham ROI for rats in Group 3.

Results

As demonstrated in Figure 1, the targeted temperatures can be rapidly achieved (< 10 minutes) for all four rats at different temperatures. In addition, the devised system is capable of maintaining the targeted temperatures throughout the entire experimental condition (90 minutes). Furthermore, results obtained from the three phase manipulation (blue line, Fig 1) demonstrate our ability to easily regulate the brain temperature to any desired temperature. The body temperature is kept within 37±0.5°C and no significant changes in the heart rate (HR) and mean arterial blood pressure (MABP) are observed when compared to that in the normothermic condition throughout the entire experiment duration.

The relations between CBF and the brain temperature under ischemia are shown in Fig. 2. A highly linear relationship is observed between CBF and the brain temperature independent of the brain perfusion status; a reduction in brain temperature results in a reduction in CBF. However, the rate of CBF reduction in response to hypothermia differs among different ROIs. The CBF in the contra ROI (triangles, Fig 2) drops most rapidly, followed by the mismatched region (squares, Fig 2) and the core area (diamonds, Fig 2) has minimal changes in CBF. Interestingly, the rate of CBF reduction in the contra ROI of the ischemic rats appears to be slower than that of the sham operated rats (circles, Fig 2).

Discussion and Conclusions

The MR compatible local brain temperature manipulation device can achieve the targeted brain temperature quickly and maintain it for a long period of time under both hypothermic and hyperthermic conditions, while maintaining the body temperature, MABP and HR within the normal ranges. A highly linear relationship is observed between CBF and temperature. However, the rate of CBF reduction differs among different ROIs. Although many physiological underpinnings may account for the observed different relations between CBF and the brain temperature, it is plausible that the status of autoregulation plays a critical role on how CBF will respond to brain temperature manipulation; the autoregulation is dysfunctional in the core area while may be slightly impaired in the mismatched regions, leading to different CBF characteristics in responses to temperature manipulations. More studies are needed to further investigate whether or not brain metabolism under hypothermia also responds in a similar manner as that of CBF.

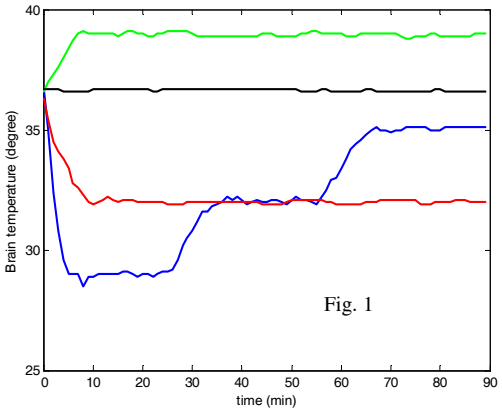

Fig. 1

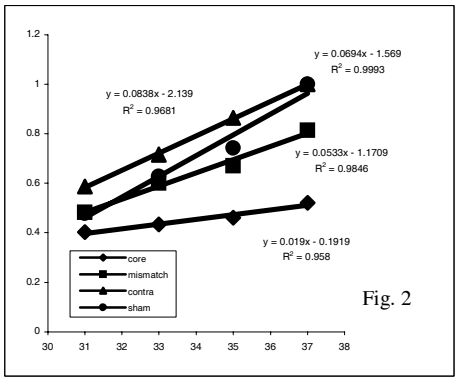

Fig. 2