

## SELECTIVE BRAIN COOLING IN SHEEP BY INTRA-VENTRICULAR CATHETERS: A 7T BIRDS STUDY

Daniel Coman<sup>1</sup>, Yuegao Huang<sup>1</sup>, John W Simmons<sup>2</sup>, James A Goodrich<sup>3</sup>, Brain McHugh<sup>4</sup>, John A Eleftheriades<sup>5</sup>, Douglas L Rothman<sup>1,6</sup>, and Fahmeed Hyder<sup>1,6</sup>

<sup>1</sup>Diagnostic Radiology, Yale University, New Haven, CT, United States, <sup>2</sup>CoolSpine LLC, Woodbury, CT, United States, <sup>3</sup>Comparative Medicine, Yale University, New Haven, CT, United States, <sup>4</sup>Neurosurgery, Yale University, New Haven, CT, United States, <sup>5</sup>Cardiothoracic Surgery, Yale University, New Haven, CT, United States, <sup>6</sup>Biomedical Engineering, Yale University, New Haven, CT, United States

**INTRODUCTION.** Selective brain hypothermia is an extremely important clinical tool because it can help alleviate damage caused by brain trauma, cardiac arrest and stroke, among other conditions [1,2]. Towards this translational goal a cerebrospinal fluid (CSF)-based cooling platform for selectively inducing brain hypothermia was developed [3]. This novel system uses cool saline circulating in a closed loop through a catheter with an expandable balloon placed in the lateral ventricles to conductively induce cooling in neighboring brain tissue. However temperature distributions during intra-ventricular cooling in the whole brain are needed to understand the cooling efficiency of the device prior its translation to humans. Therefore temperature mapping by a novel chemical shift imaging (CSI) technique, which utilizes a lanthanide macrocyclic probe like TmDOTMA, that is extremely sensitive to temperature was employed. The method, termed *Biosensor Imaging of Redundant Deviation in Shifts (BIRDS)*, is based on detection of paramagnetically shifted <sup>1</sup>H signals emanating from TmDOTMA using CSI [4,5]. Using BIRDS the time dependence of absolute temperature distribution during the cooling process was obtained.

**MATERIALS AND METHODS. Animal preparation.** Adult, male sheep (n=2, 30kg) were sedated with acepromazine (0.5 mg/kg, intramuscular) and valium (0.5 mg/kg, intravenous), followed by ketamine (2.2-2.75 mg/kg, intravenous), and then intubated. Anesthesia was maintained at an adequate level with isoflurane (< 1%) throughout the procedure. Burr holes were made bilaterally 1.5 cm anterior and lateral to the posterior fontanelle at an angle of 10° from the sagittal plane on each side. A pediatric slotted stylet was inserted into each hole, and the location in the lateral ventricle was confirmed by CSF flow and pressure differences measured by manometry. The cooling catheters were placed via the burr holes in both the right and left ventricles. These catheters were also used to inject TmDOTMA<sup>-</sup> (7mg/kg) directly into ventricles at an infusion rate of 1ml/h. A water-heating blanket was used to control and maintain normothermic body temperature (38°C). **Data acquisition.** 25x25x25 3D CSI datasets (Fig. 1A) were obtained on a Varian 7.0T/68cm horizontal-bore spectrometer (MagneX Scientific Ltd.) using a <sup>1</sup>H resonator/surface coil RF probe. A single-banded refocused 90° Shinnar-Le Roux (SLR) RF pulse of 40 kHz bandwidth and 500 μs was used for selective excitation of the TmDOTMA<sup>-</sup> methyl group. The data was acquired with a TR of 20ms and a FOV of 200x200x200 mm<sup>3</sup>. The spectra were line broadened (200 Hz), phased (zero order) and baseline corrected (first order) in a similar fashion in Matlab. The temperature maps (Fig. 1B and 1C) were calculated from the chemical shifts of TmDOTMA<sup>-</sup> methyl group  $\delta_{CH_3}$  according to the equation:  $T=(34.45\pm 0.01)+(1.460\pm 0.003)\cdot(\delta_{CH_3}+103)+(0.0152\pm 0.0009)\cdot(\delta_{CH_3}+103)^2$  [5].

**RESULTS.** The sheep brain temperature maps before cooling indicate an average temperature of 38.0±0.4°C, which is consistent with previous measurements [6]. First, we started circulating ice-cold saline via the left catheter and we observed selective cooling of left hemisphere to 33.6±0.8°C (Fig. 1D), while the average temperature in the right hemisphere was only slightly decreased to 37.7±0.9°C (Fig. 1E). However, when we started the circulation of the ice-cold saline through both catheters, we observed a slight increase in the average temperature of the left hemisphere to 34.9±0.2°C (Fig. 1D), and a decrease in the right hemisphere to 35.3±0.4°C (Fig. 1E). Increasing the flow rate from 35ml/min to 42ml/min resulted in a decrease in the average temperature to 32.3±0.2°C and 33.5±0.3°C in the left and right hemispheres, respectively (Fig. 1D and 1E). At the end of experiment, the cooling was stopped and the temperature was allowed to recover. After 10 minutes of recovery, an average temperature of 37.8±0.2°C and 38.1±0.5°C was measured in the left and right hemispheres, respectively (Fig. 1D and 1E).

**DISCUSSION.** Detection of TmDOTMA<sup>-</sup> was obtained for the first time in sheep brain by simultaneous delivery directly in each ventricle. We presume that majority of the in vivo TmDOTMA signal detected was from the extracellular space. Temperature maps calculated from the chemical shift of the methyl group were obtained every 10 minutes. A drop of ~4°C in the left hemisphere (Fig. 1D), was observed within 10 minutes of cooling. During the cooling of the left hemisphere, the temperature in the right hemisphere decreased only by 0.3°C (Fig. 1E). Efficient cooling of the right hemisphere by ~ 3°C (Fig. 1E) was achieved when the saline solution was circulated through the right catheter. The less efficient cooling of the right hemisphere compared with the left one and the slight increase in the temperature of the left hemisphere (Fig. 1D) are probably due to the circulation of the saline solution through both catheters. This hypothesis is supported by the temperature decrease in both hemispheres when the saline flow rate was increased, which suggests a more efficient cooling at higher flow rate. A fast recovery to physiological brain temperature was observed in both hemispheres within 10 minutes after cooling was stopped. In summary, we demonstrate that absolute changes and dynamics of brain temperatures in sheep during selective intra-ventricular CSF cooling can be measured by BIRDS with TmDOTMA. These measurements have a direct impact on designing selective brain hypothermia procedures in humans during brain trauma, cardiac arrest or stroke. Our results suggest that direct cooling via intra-ventricular catheters can successfully induce substantial brain hypothermia, with potential for significant mitigation of brain injury in a variety of pathologic conditions.

**REFERENCES.** [1] Holzer M. (2008) *Eur J Anaesthesiol Suppl* 42:31-38; [2] Christian E, Zada G, Sung G, Giannotta SL. (2008) *Neurosurg Focus* 25:E9; [3] Moomiaie RM, Ransden J, Stein J, Strugar J, Zhu QB, Kim JH, Eleftheriades JA. (2007) *J Cardiovasc Surg (Torino)* 48:103-108; [4] Coman D, Trubel HK, Rycyna RE, Hyder F. (2009) *NMR in Biomed.* 22:229-239; [5] Coman D, Trubel HK, Hyder F. (2009) *NMR in Biomed.* 23:277-285; [6] Moomiaie RM, Gould G, Solomon D, Simmons J, Kim JH, Botta D, Eleftheriades JA. (2012) *J NeuroIntervent Surg*, 4(2):130-3

**ACKNOWLEDGEMENTS** Supported in part by P30-NS052519 and NSF-0923928.

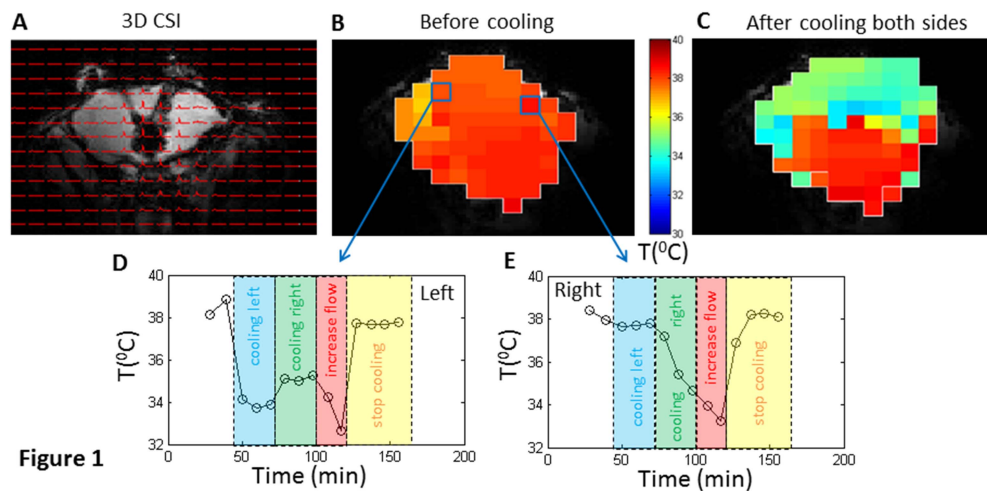


Figure 1