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Temperatures Achieved in Human and Canine Neocortex During Intraoperative Passive or Active Focal Cooling

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Focal cortical cooling inhibits seizures and prevents acquired epileptogenesis in rodents. To investigate the potential clinical utility of this treatment modality, we examined the thermal characteristics of canine and human brain undergoing active and passive surface cooling in intraoperative settings. Four patients with intractable epilepsy were treated in a standard manner. Before the resection of a neocortical epileptogenic focus, multiple intraoperative studies of active (custom-made cooled irrigation-perfused grid) and passive (stainless steel probe) cooling were performed. We also actively cooled the neocortices of two dogs with perfused grids implanted for 2 hours. Focal surface cooling of the human brain causes predictable depth-dependent cooling of the underlying brain tissue. Cooling of 0.6–2°C was achieved both actively and passively to a depth of 10–15 mm from the cortical surface. The perfused grid permitted comparable and persistent cooling of canine neocortex when the craniotomy was closed. Thus, the human cortex can easily be cooled with the use of simple devices such as a cooling grid or a small passive probe. These techniques provide pilot data for the design of a permanently implantable device to control intractable epilepsy.

Introduction

Although a number of novel antiepileptic drugs have been introduced in recent years, they remain inadequate for the control of focal neocortical epilepsy in many patients (Yang *et al.*, 2002; Grosso *et al.*, 2013). Even with advancements in the surgical technique, many patients remain poor candidates for potentially curative surgical intervention (Fujii *et al.*, 2010). Additional palliative modalities, including vagal nerve stimulation, deep brain stimulation, and transcranial magnetic stimulation, have also not dramatically reduced the occurrence of seizures (Theodore and Fisher, 2007; Bagic *et al.*, 2008; Fisher *et al.*, 2010; Chambers and Bowen, 2013; Liu *et al.*, 2013).

Brain cooling is another nondestructive technology that is known to have antiepileptic properties in both animal models (Bricolo *et al.*, 1966; Gasteiger *et al.*, 1985; Hill *et al.*, 2000; Yang and Rothman, 2001; Javedan *et al.*, 2002; Yang *et al.*, 2002) and humans (Pásztor and Tomka, 1969; Karkar *et al.*, 2002; Karlov, 2003). Several clinical studies have demonstrated the utility of systemic cooling as an adjunct for the treatment of intractable epilepsy (Vastola *et al.*, 1969; Sourek and Travnicek, 1970; Corry *et al.*, 2008; Guilliams *et al.*, 2013). We first investigated the effect of focal brain cooling on seizures after initial observations that the intraoperative irrigation of exposed cortex with iced saline (4°C) reduced or abolished the interictal activity. The efficacy of irrigation with iced saline has made its use a standard clinical practice for the control of seizures or active discharges during cortical stimulation mapping procedures for epilepsy or tumor resection (Sartorius and Berger, 1998; Karkar *et al.*, 2002).

We have been exploring the use of focal cooling to rapidly terminate other types of *in vitro* and *in vivo* seizures (Hill *et al.*, 2000; Yang and Rothman, 2001; Burton *et al.*, 2005), and we recently reported that cooling by just 2°C prevents the development of epileptic seizures in a fluid percussion injury model of post-traumatic epilepsy (D'Ambrosio *et al.*, 2013). In the latter study, passive cooling by 2°C for 5.5 weeks persistently prevented nearly all ictal activity, and this effect lasted for at least 10 weeks after the cooling ended.

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On the basis of our intraoperative experience with focal cooling and the finding that fluid percussion injury-induced epileptic seizures respond to small brain temperature changes, we would like to begin the translation of mild focal brain cooling to the clinical setting. However, before this occurs, the quantification of the brain's response to surface cooling is necessary for assistance with the device design. In this study, we describe the spatial and temporal characterization of temperatures achieved during the intraoperative direct focal surface cooling of human and canine neocortex.

Methods

Patient selection

Institutional review board approval was obtained from the Washington University Human Research Protection Office (IRB No. 201105440). Patients who planned to undergo intracranial epilepsy procedures in which tissue was to be resected were invited to participate. If pediatric patients were to be enrolled, informed consent was obtained from both parents by the neurosurgeon (M.D.S.). In addition, if at any time the additional 20 minutes of operating room time required to carry out the experiments would jeopardize the well-being of the patient, then that patient was excluded from the study; the clinical team would then proceed with standard clinical care. Data were ultimately successfully collected from a total of four patients.

Human cooling modalities

Three distinct cooling modalities were tested to achieve a range of surface cooling temperatures. Active cooling was achieved with the use of a sterile electrocorticography (ECoG) grid constructed with an integrated cooling bladder over the central electrodes (PMT Corporation, Chanhassen, MN; Fig. 1A. A Non-Significant Risk pre-Investigational Device Exemption (pre-IDE NSR No. I090851) was granted by the FDA for intraoperative use of the modified grid). This allowed for the circulation of sterile iced normal saline (4°C) through the center of the grid over the exposed neocortex.

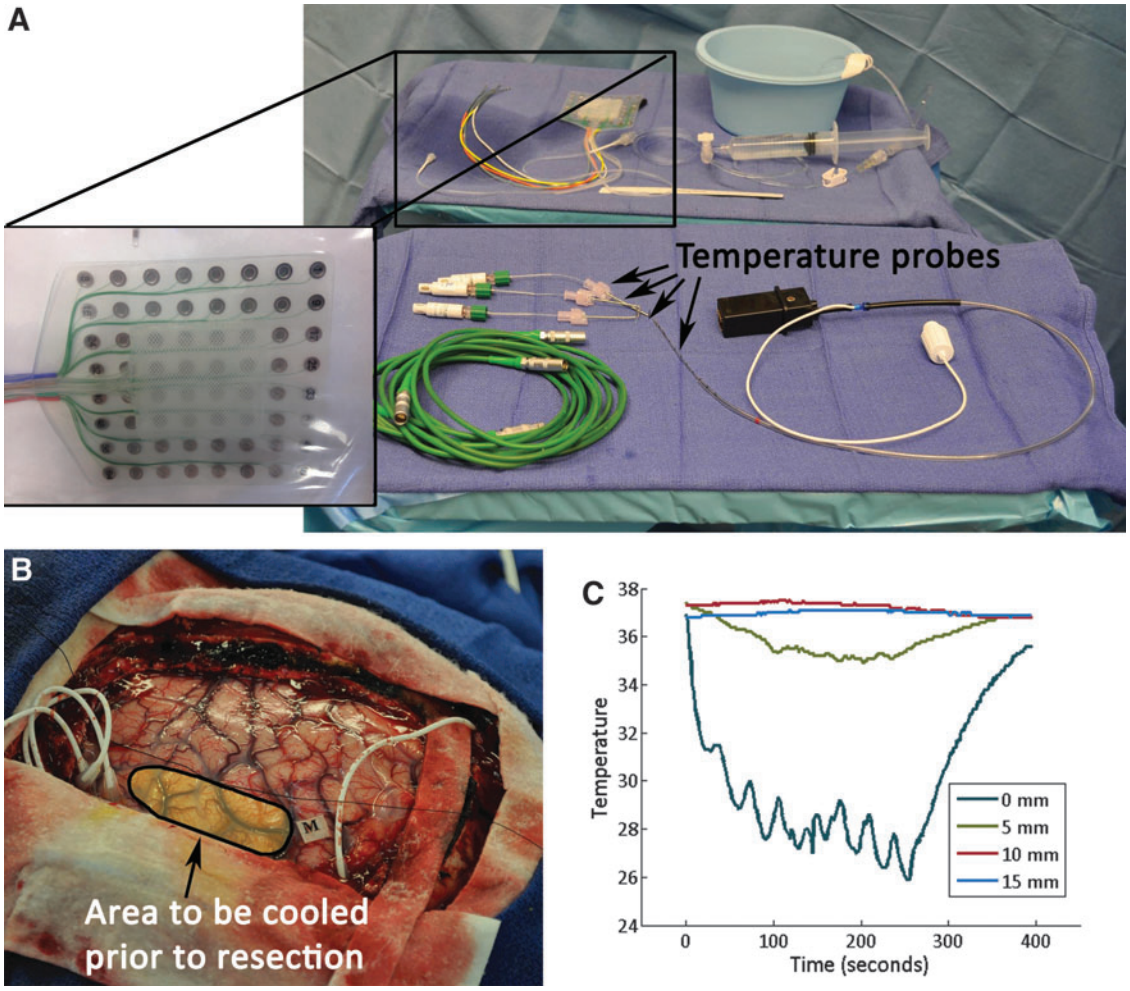


FIG. 1. Intraoperative techniques for active cooling and temperature measurement in humans. **(A)** Sterile cooling grid (*inset*), temperature probes, and the method for the use of the iced saline-perfused cooling grid are shown. **(B)** An intraoperative picture showing exposed neocortex with the cooling grid removed before cortical resection. **(C)** Data gathered from temperature probes at various depths during cooling through the means demonstrated in **(A)**. The *sawtooth pattern* seen at the 0 mm grid–brain interface was caused by the pulsatile pumping of the chilled saline through the bladder of the grid.

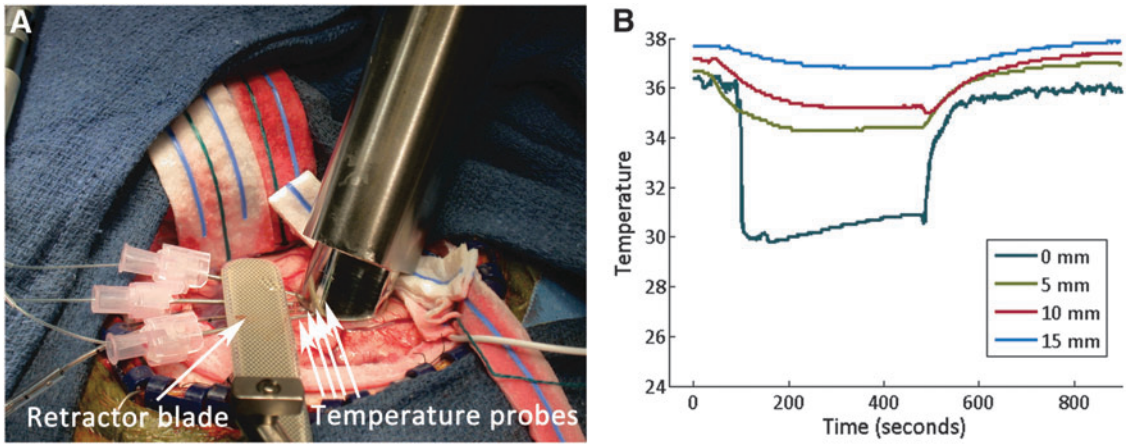


FIG. 2. Intraoperative techniques for passive cooling. **(A)** Demonstration of the intraoperative use of a heat sink for passive cooling with concurrent temperature measurement. **(B)** Data gathered with the use of the heat sink for cooling followed by a period of rewarming after the removal of the device.

The area of contact of the cooling portion of the grid was a 1600 mm^2 (4 cm × 4 cm). Passive cooling was accomplished by placing a room-temperature (22°C) surgical-grade stainless steel probe (the University of Washington, Scientific Instruments Laboratory) onto the brain's surface in the region of interest. The body of the probe had a length of 130 mm and a diameter of 30 mm (Fig. 2A). The area of contact with the brain was a 546 mm^2 ellipse (29 mm × 24 mm). The brain was also cooled through the direct application of iced saline cortical irrigation (4°C) in the same region in a similar manner as that used to terminate induced seizures during standard intraoperative cortical stimulation procedures (Sartorius and Berger, 1998; Karkar *et al.*, 2002).

Electrocorticography

ECoG was part of the standard clinical care for the selected patients. It was performed with the standard grid or strip subdural clinical electrodes (PMT or Ad-Tech Medical Instrument Corporation, Racine, WI), which were placed on the brain surface. Standard clinical ECoG equipment (Stellate, Montreal, Quebec, Canada, and XLTEK, London, Ontario, Canada) was used to record the electrical activity throughout the procedure.

Human protocol

The full set of focal cooling experiments involved an additional 20 minutes in the operating room for each patient; it was scheduled at some point after standard clinical ECoG was performed and before cortical resection. The intraoperative experiments were limited to a 20-minute duration because such a window of time should not add increased risk or morbidity in the context of an operation that typically lasts 4–7 hours. The temperature probes were placed only in the brain tissue that was to be resected to eliminate any risk to the surrounding uninvolved cortex. Iced saline (4°C) was used because of its ready availability, documented clinical utility and safety, ease of use, and stable temperature without the need for refrigeration devices.

After clinical ECoG was performed and the area of proposed resection was verified by the epilepsy team, a thermocouple array was inserted into the cortex that was designated for resection. The thermocouple array comprised four sterile clinical brain temperature probes (Integra LifeSciences Corporation, Plainsboro, NJ): three Licox brain tissue temperature probes (Catalog No. C8B) that were inserted into the cortex and one 110-4BT probe that was placed on the brain surface. The depth–temperature probes were placed at depths of 5, 10, and 15 mm. They were placed vertically, perpendicular to the brain surface, as close to each other as practicable, and at the center of the region to be cooled. Finally, the thermocouples were connected to standard clinical temperature monitors (Category No. AC3.1; Integra LifeSciences Corporation).

At the beginning of the 20-minute window, baseline ECoG and brain temperature measurements were recorded. The 20-minute time window did not allow for trials of each of the cooling modalities in each patient, so one or two cooling modalities were tested in each of the four patients (Table 1). In Patient 1, surface cooling with iced saline irrigation was performed for 5 minutes and this was followed by a 5-minute rewarming period. Similar to its clinical use for the termination of intraoperative seizure activity during cortical stimulation procedures, the iced saline was irrigated directly on the brain surface with a syringe over the implanted thermocouples. Next, the active cooling grid was placed over the temperature probes, and the area was actively cooled for 5 minutes; this was also followed by a rewarming period. The cooling was performed by the manual irrigation of fluid through the grid, with the cooling bladder portion of the grid placed directly over the thermocouples. The fluid temperature was measured at the iced saline supply reservoir (4°C), but some ambient warming occurred as a result of the fluid moving through the tubing before reaching the cooling bladder portion of the grid. Patient 2 underwent similar iced

TABLE 1. COOLING MODALITIES TESTED ON EACH PATIENT

Patient no.	*Cooling modality 1*	*Cooling modality 2*
1	Iced saline	Active
2	Iced saline	Passive
3	Passive	—
4	Passive	Iced saline

saline surface irrigation and rewarming, but this was then followed by the application of the passive cooling probe for 5 minutes and another rewarming period. Patient 3 underwent a more prolonged passive cooling period and rewarming period, and Patient 4 underwent iced surface saline irrigation after the passive cooling trial. Temperature and ECoG were recorded for the entire cooling and rewarming periods in all patients. After the cooling experiments, the passive cooling probe or grid was removed from the operative field, the temperature monitor array was withdrawn from the brain, and the standard operative technique was used for the completion of the surgical procedure.

Human data analysis

All data were analyzed offline after the completion of the patient's clinical procedure. Cooling and rewarming periods for the various cooling modalities were identified in the raw temperature–time data for all four probes and saved separately. Each cooling or rewarming period was fitted by way of regression to Newton's Law of Cooling, which states that

$$\frac{dT(t)}{dt} = -r\Delta T(t) \qquad \text{(Eq. 1)},$$

with the solution

$$T(t) = T_{ss} + (T(0) - T_{ss})e^{-rt} \qquad \text{(Eq. 2)}.$$

Here, $T(t)$ is the temperature at time t, $T(0)$ is the initial temperature, T_{ss} is the steady-state or final temperature, and r is a positive rate constant. The rate constant has units of $time^{-1}$, and $\frac{1}{r}$ is a time constant that can be interpreted as the amount of time required to reach 63.2% of the temperature change achieved at steady state. The time constants were plotted separately for the cooling and rewarming processes as a function of temperature probe depth (Fig. 3).

Next, the steady-state temperature change ($\Delta T(00)$) was defined as

$$\Delta T(00) \equiv T(0) - T_{ss} \qquad \text{(Eq. 3)},$$

which is the difference between the initial and steady-state temperatures for each temperature probe and cooling process. Furthermore, the final surface temperature ($T_{ss,0\ mm}$) was defined as the steady-state temperature achieved at the 0 mm depth for each cooling process. With these definitions in mind, steady-state temperature changes were plotted against the final surface temperatures of the three temperature probes at depths of 5, 10, and 15 mm. Although the passive cooling probe itself is slightly warmed by the brain during the 5 minutes of direct contact (Fig.

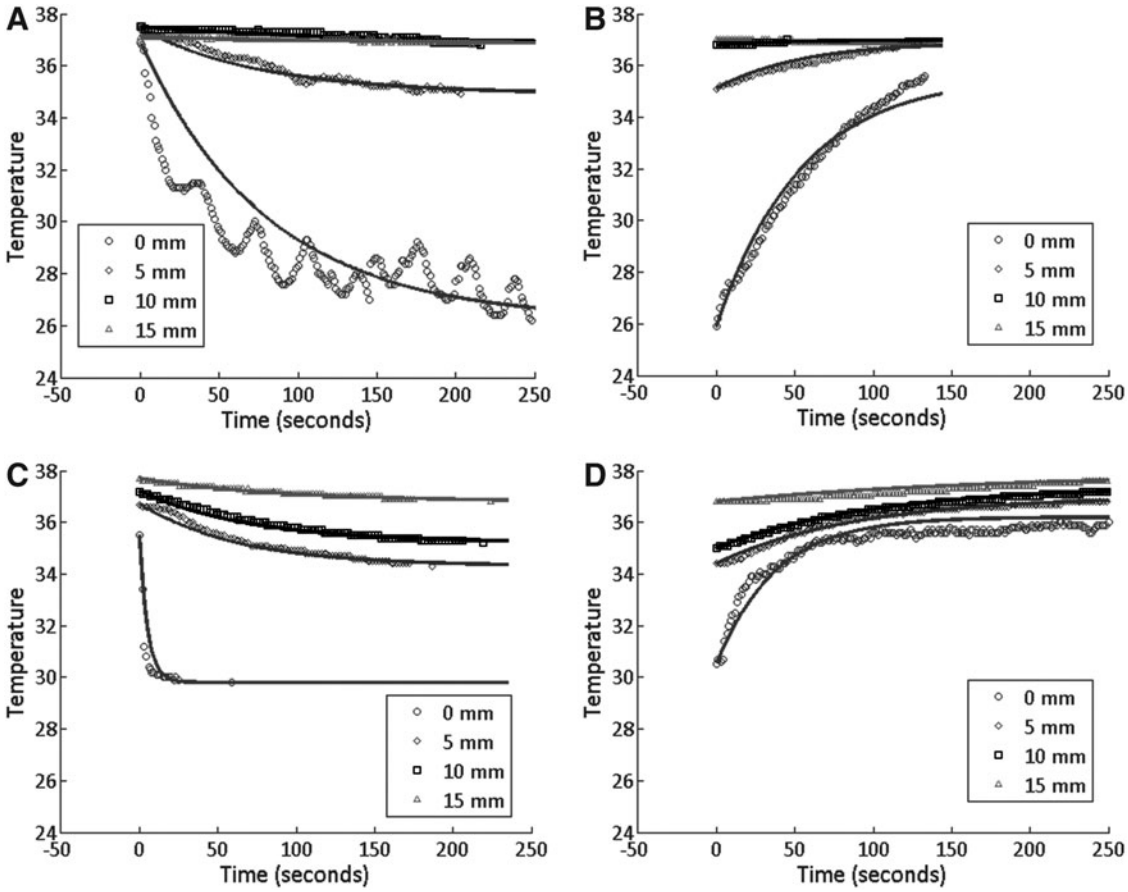


FIG. 3. Sample regression curves. **(A)** Temperature–time data for Patient 1 undergoing active cooling with the use of a grid. **(B)** Temperature–time data for Patient 1 undergoing rewarming after active cooling with the use of a grid. **(C)** Temperature–time data for Patient 3 undergoing passive cooling with the use of the heat sink. **(D)** Temperature–time data for Patient 3 undergoing rewarming after passive cooling. The *solid lines* in **(A–D)** represent best-fit curves.

2B), for the purposes of modeling, the effect was considered negligible.

Canine brain cooling

Because we did not have the institutional review board approval to fully implant an active cooling grid into a human patient with the bone replaced and the scalp closed, and because the human experiments were limited to 20–30-minute periods, we also performed large animal experiments to verify that mild cooling can conveniently be implemented for hours with a fully implanted fluid cooling grid. These grids were tested in two dogs as surrogates for humans at the University of Minnesota College of Veterinary Medicine. These experiments had approval from the University of Minnesota's Institutional Animal Care and Use Committee. Each dog was premedicated with midazolam and butorphanol; anesthesia was induced with thiopental and maintained with isoflurane given through an endotracheal tube. After the establishment of stable general anesthesia, a craniotomy was performed and a bone flap was removed to expose the dura.

A standard Silastic ECoG grid with a 4×2 recording electrode array was inserted over the neocortex and covered with dura before the control ECoG (XLTEK) was obtained. The grids were positioned laterally in the subdural space, underneath intact dura, bone, muscle, and skin. The bone flap itself was not replaced due to the configuration of the electrode wires and ingress/egress cooling tubing. After initial recording, the standard grid was then replaced with the grid/cooling bladder; this was similar to the one shown in Figure 1A, but it was smaller, with a $4\,\text{cm} \times 2\,\text{cm}$ cooling/electrode surface rather than a $4\,\text{cm} \times 4\,\text{cm}$ cooling surface within an 8×8 electrode array. The cooling grid was positioned laterally under the dura, bone, muscle, and scalp and the scalp incision was reapproximated. The perfusion tubing was then connected to a standard clinical peristaltic pump. The tubing flowed through a cooling chamber placed within 2 feet of the head to minimize the temperature drop between the cooling chamber and the grid/cooling bladder. Temperature was measured within the bladder and at the interface between the bladder and the neocortex with standard thermocouples. The electrodes on the cooling grid were connected to the same ECoG amplifier, with the output archived on a laptop computer. Each of these experiments lasted ~ 2 hours, during which, 20-minute periods of baseline, cooling, and rewarming were performed using two different cooling temperatures per animal.

Results

Human cooling

We tested three focal cooling modalities (passive, active, and iced saline irrigation) on four patients with brain tissue that was to be resected for intractable epilepsy (Figs. 1 and 2). Temperature–time curves for probes positioned at depths of 0, 5, 10, and 15 mm in the neocortex were obtained for each cooling and rewarming period. We used Newton's Law of Cooling (Eq. 1) to approximate the cooling and rewarming processes. We found that we could analyze the data under the assumption that the brain comprises slices with boundaries at each of the temperature probe depths so that the temperatures within each slice are approximately uniform.

We used the regression analysis to separately fit cooling and rewarming data from each probe, and we drew the resulting curves over the original temperature–time data (Fig. 3). The time constants determined for each depth and method were obtained and compared (Fig. 4). This analysis demonstrated a direct relationship between the depth of the brain tissue from the surface and the time constant, which supports the internal consistency of the experiment (i.e., the positions of the temperature probes and cooling devices or possible changes in regional cerebral blood flow did not significantly affect the results).

We were interested in determining the degree of surface cooling required to achieve 1–2°C of steady-state cooling deep in the sulci of the neocortex (Fig. 5). This was estimated by plotting steady-state temperature changes during cooling against final surface temperatures for temperature probe

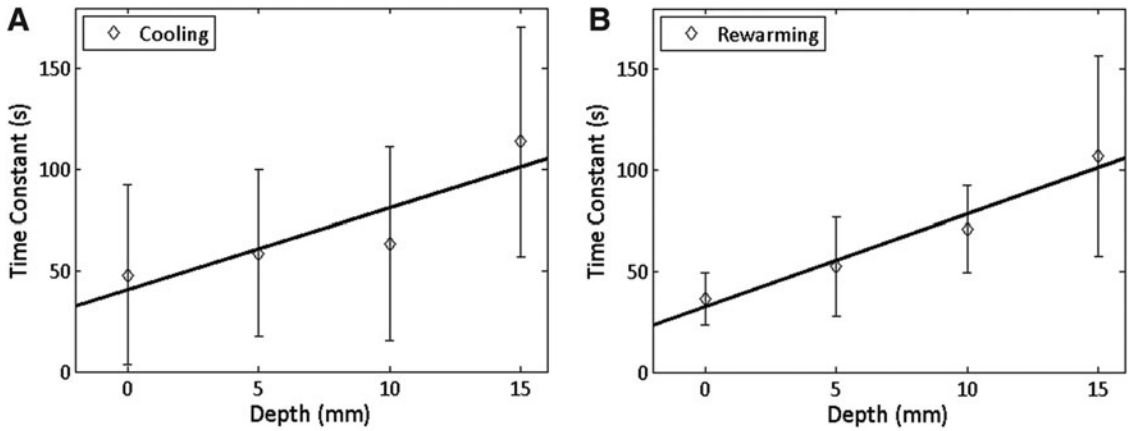
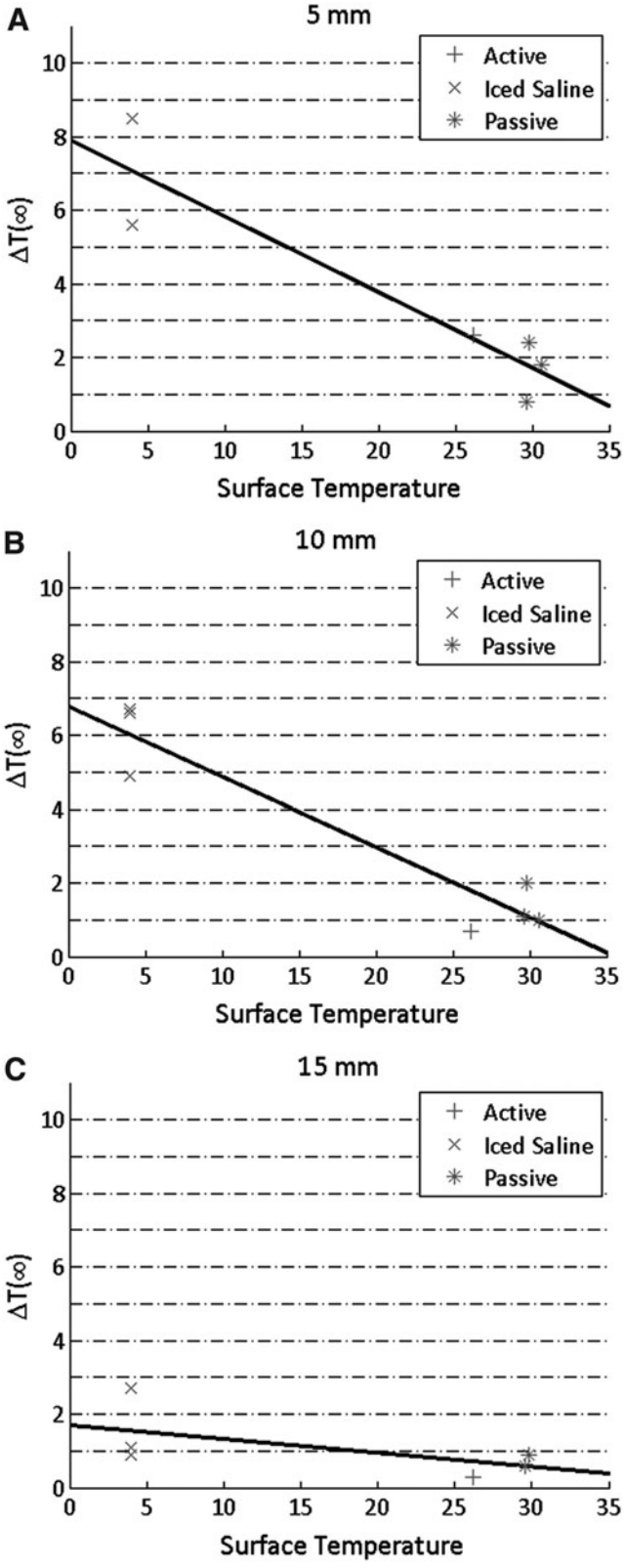


FIG. 4. Time constants as functions of temperature probe depths. Regression constants from the fitting of the temperature data were converted into time constants. **(A)** Time constants for all cooling processes analyzed in the patients. **(B)** Time constants for all rewarming processes analyzed in the patients. Error bars are shown at one standard deviation above and below the mean time constant at each depth. The time constant can be interpreted as the amount of time required to reach 63.2% of the temperature change achieved at steady state.

depths of 5, 10, and 15 mm (Fig. 5). We used the final surface temperature as the measure of the degree of surface cooling in response to the rapid equilibration of the surface temperature to the applied cooling temperature, which was observed during the experiments.



The difficulty of cooling deeper regions of the brain can be explained by the anatomic changes that occur with depth and the rapid heat dissipation that is facilitated by robust cerebral blood flow. The results of our experiments involving direct brain cooling agree with those of a previous theoretical simulation and with several clinical trials of localized external head cooling in patients with traumatic brain injuries (Zhu and Diao, 2001; Wang *et al.*, 2004; Forte *et al.*, 2009; Harris *et al.*, 2009). In those trials, external cooling was applied with cooling helmets or ice packs to achieve a comparable change in temperature within the brain of about 2°C.

Although one of the goals of the study as initially designed was to evaluate the effects of surface cooling on baseline human ECoG, as a result of difficulties with obtaining artifact-free ECoG data during the short 20-minute time window allowed for each patient, we did not obtain enough human ECoG data for analysis.

Canine cooling

The fluid-cooled grid was tested in two dogs for 2 hours each to determine if perfusing the bladder with cold saline at a steady rate with a peristaltic pump would safely cool the underlying neocortex. For these experiments, the grid was covered with dura and scalp and placed along the lateral parietal cortex between the cranial vault and the brain, covered by dura, skull, muscle, and skin; time-stamped cooling was then performed during continuous ECoG. This configuration is similar to the way the grid would have to be positioned if it was left in place for several days during invasive monitoring to localize the human epileptogenic cortex. The results achieved in the dogs reflected the temperature reductions described previously for the human tests. When the cooling bath was held at $\sim$10°C, the lowest temperature reached inside the grid was 21°C (This was the average of the minimum temperatures found in both dogs at perfusion rates of 10 and 20 mL/min; see the green lines in Fig. 6.). Reducing the cooling bath temperature to 0°C decreased the grid temperature to 17°C. At both cooling bath temperatures, the temperature at the grid–cortex interface was 4–5°C higher (see the red lines in Fig. 6). Cooling reached a steady state and was maintained during 20-minute cooling periods with each temperature. We did not see a dramatic effect of the perfusion rate on the grid or interface temperature.

ECoG was recorded with the use of a standard grid and again after the cooling grid was inserted. There was no qualitative difference in the appearance of the ECoG results

FIG. 5. Steady-state temperature changes. **(A)** The differences between the initial and final temperatures achieved during cooling at a temperature probe depth of 5 mm are plotted as functions of the final surface temperatures. The desired 1.2–2°C of cooling can be achieved at this depth with the use of an applied surface temperature of 28–33°C. **(B)** An identical analysis is shown for a temperature probe depth of 10 mm. The desired cooling can be achieved at this depth with the use of an applied temperature of 22–27°C. **(C)** An analysis identical to that given in part A is shown for a temperature probe depth of 15 mm. The desired cooling can be achieved at this depth with the use of an applied temperature of less than 12°C. The *solid black lines* in **(A–C)** represent the linear fittings of all data points.

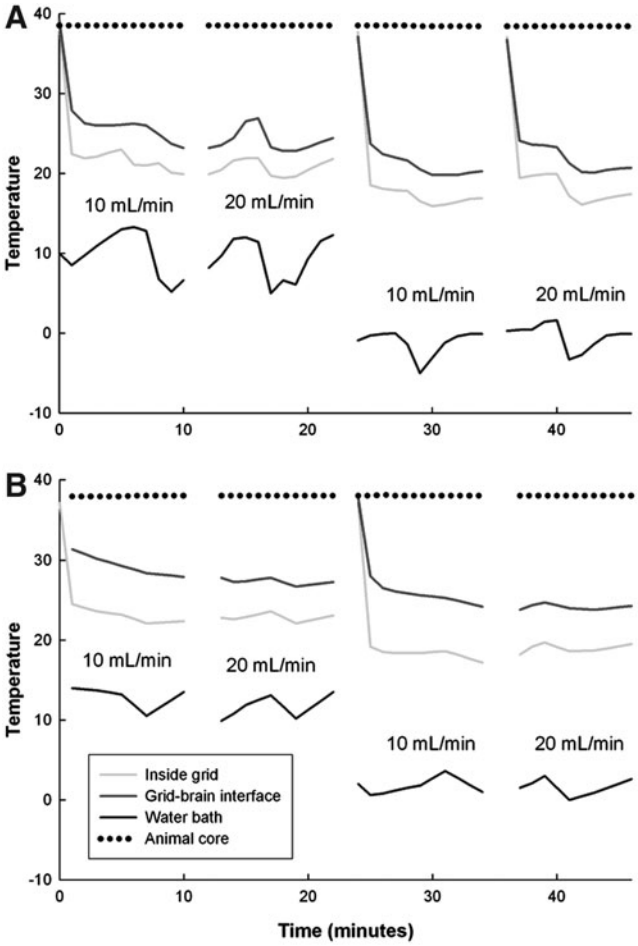


FIG. 6. Canine neocortical cooling. **(A, B)** Results obtained in two separate dogs in which the brain was focally cooled with the modified grid. In both dogs, the lowest temperature achieved was not dramatically affected by increasing the grid perfusion rate from 10 to 20 mL/min. Not surprisingly, reducing the temperature of the cooling chamber from 10°C to 0°C did have a noticeable effect on cooling. There was a 15–20°C temperature gradient between the cooling chamber and the grid as a result of the warming of the saline as it left the chamber and entered the grid. The cooling chamber had to be adjusted during the trials, which explains the temperature instability (*black line*). The interval between the separate cooling trials was not always identical, although the parts of this figure show them as equal.

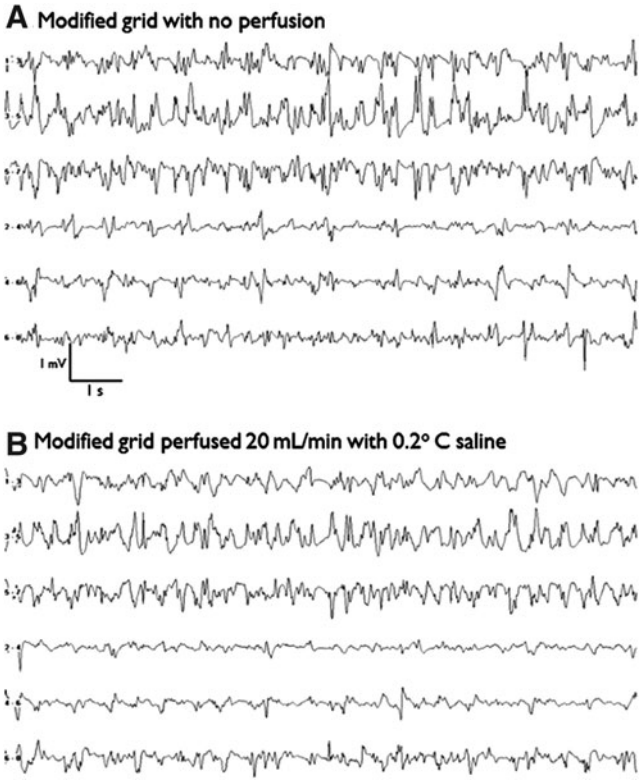


FIG. 7. Canine sample electrocorticography (ECoG). Sample ECoG tracings created with the use of a modified 4×2 ECoG grid (PMT Corporation, Chanhassen, MN). **(A)** ECoG with the grid in place but no perfusion. **(B)** The same grid and the same animal with 20 mL/min of perfusion with 0.2°C saline. There is no pulse artifact degrading the ECoG. The scales for (**A** and **B**) are identical.

with the standard grid compared with the cooling grid. Moreover, the quality of the ECoG recorded with the modified cooling grid was not noticeably altered by perfusion as rapid as 20 mL/min (Fig. 7). This makes us optimistic that the modified grid will allow for simultaneous cooling and ECoG without any loss of fidelity if it is used for invasive human monitoring. This amount of cooling did not have a significant effect on baseline normal ECoG in the canine model, and the effect of this cooling on an epileptiform activity was not evaluated.

Discussion

In this article, we presented data obtained through the intraoperative cooling of human and canine neocortex with the use of active and passive methods. In four patients, intraoperative data that reflect cooling at the surface and multiple depths of the cortex were recorded and analyzed. In our data, focal neocortical brain cooling ($\Delta T(00)$) depended primarily on the surface temperature ($T_{ss,0\ mm}$) and the depth of the probe relative to the cortical surface. In addition, the time required to achieve steady-state cooling was directly related to depth in relation to the cortical surface (Fig. 3A, C). In accordance with previously published data from studies of animal models, a therapeutically effective temperature decrease was found to be achievable and predictable to a depth of 10–15 mm from the cortical surface (Fig. 5).

Cooling has been investigated in many clinical scenarios, and systemic cooling is commonly used to manage patients with cardiac arrest and neonatal hypoxic–ischemic encephalopathy. Improved neurologic outcomes have been documented, although they are not without certain shortcomings (e.g., infection risk, thromboembolic phenomena). The risk for the development of seizures after neonatal hypoxic–ischemic insults may be decreased by mild systemic cooling (Srinivasakumar *et al.*, 2013). However, systemic cooling can only be used for short time periods in an intensive care setting. The antiepileptic effects of systemic hypothermia have been reviewed in detail elsewhere (Motamedi *et al.*, 2013).

Despite previous investigations that have focused on cortical cooling, the depth to which the cortex must be cooled for

therapeutic effect has not been extensively studied. In fact, it may only be several millimeters from the cortical surface. This is clearly a major unanswered question that could be resolved by clinical studies that involve invasive monitoring during possible cortical resections for epilepsy. Radiographic studies suggest an average sulcal depth in adults of ~ 7 mm (Yun *et al.*, 2013). We have demonstrated that potentially therapeutic cooling can reach between 10 and 15 mm from the cortical surface, a depth that would include cooling of gray matter in the majority of the sulci. For deeper seated lesions such as the insula or mesial temporal structures, a depth cooling probe with a superficial heat dissipation would be required to achieve therapeutic cooling below the surface and sulci. Such a device concept has been described by the members of our group (Smyth and Rothman, 2011).

The goals of this line of research include the potential development of an implantable cooling device for therapeutic benefit. The possible uses of such a device include the preoperative confirmation of the accurate localization of an epileptogenic focus, the identification of neurologic deficits that could result from the removal of epileptogenic cortex, and the possible treatment (Smyth and Rothman, 2011) or prevention (D'Ambrosio *et al.*, 2013) of epilepsy. As a next step, a subdural grid with a cooling bladder could be used during multistage epilepsy surgery to establish the therapeutic efficacy of cooling for the prevention of neocortical seizures and to determine the threshold cortical temperature necessary for seizure termination. The cooling grid that was tested intraoperatively could also be implanted temporarily in patients undergoing multistage epilepsy surgery. Such a patient would undergo standard craniotomy and placement of the modified grid per standard clinical techniques. The grid would be anchored to the dura and the electrode tails anchored to the scalp as per routine. The cooling tubing would be similarly secured. After a typical period of standard ECoG during which typical seizures are characterized and captured, and the second-stage surgery is planned for resection of a seizure focus, the cooling grid could then be utilized for periods of cooling. Individuals with high baseline seizure frequency could be evaluated for reduction in seizure frequency or severity during cooling periods compared with baseline rates. Other electrocorticographic features, such as epileptiform discharges and interictal spikes, and high-frequency oscillations could be evaluated. At second-stage surgery, the modified grid would be removed and standard resection carried out. Once the critical temperatures to quench human seizures are established, a permanent implant could be designed with a better knowledge of power and heat dissipation requirements. Ideally, such studies would reveal the parameters necessary for the design of compact practical thermoelectric-based cooling systems. Given the use of advanced techniques for the prediction of epileptic events (Martinerie *et al.*, 1998; Osorio *et al.*, 1998; Le Van Quyen *et al.*, 1999), the use of focal cooling on an ongoing basis as a smart device may present a unique opportunity for a breakthrough in the management of epilepsy.

In conclusion, human neocortex can be cooled by 0.6–2°C to a depth of 10–15 mm with relatively simple techniques such as passive cooling through a probe of sufficient thermal mass or the use of a cooling grid that circulates saline coolant, with a predictable change in temperature. These findings support the concept that a practicable cooling device could be designed for implantation in humans for the control of epileptic seizures.

Acknowledgments

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Disclosure Statement

Several of the coauthors (D'Ambrosio, Miller, Smyth, and Rothman) own shares in a startup company, Therma Neurosciences, with the goal of creating a prototype device for human trials of brain cooling for the treatment of epilepsy. None has received any monetary compensation. No competing-financial interests exist for the remaining authors.

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