J Neurosurg 99:604–608, 2003

A device for cooling localized regions of human cerebral cortex

Technical note

HANS E. BAKKEN, M.D., HIROTO KAWASAKI, M.D., HIROYUKI OYA, M.D., JEREMY D. W. GREENLEE, M.D., AND MATTHEW A. HOWARD III, M.D.

Department of Neurosurgery, University of Iowa, Iowa City, Iowa

Neurosurgeons use invasive mapping methods during surgery to understand the functional neuroanatomy of patients. Electrical stimulation methods are used routinely for the temporary disruption of focal regions of cerebral cortex so that the surgeon may infer the functional role of the brain site being stimulated. Although it is an efficient and useful method, modes of electrical stimulation mapping have significant limitations. Neuroscientists use focal cooling to effect a more controlled disruption of cortical functions in experimental animals, and in this report, the authors describe their experience using a device to achieve this same objective in patients undergoing neurosurgery. The cooling probe consists of a stainless steel chamber with thermocouples and electroencephalography (EEG) recording contacts. Active cooling is achieved by infusing chilled saline into the chamber when the cooling probe is positioned on the pial surface. Experiments were performed in 18 patients. Temperature gradient measurements indicate that the entire thickness of gray matter under the probe is cooled to temperatures that disrupt local synaptic activity. Statistically significant changes in spontaneous and stimulus-evoked EEG activity were consistently observed during cooling, providing clear evidence of reversible disruption of physiological functions. Preliminary findings during functional mapping of the Broca area demonstrated qualitative differences between the temporary neurological deficits induced by cooling and those caused by electrical stimulation. These findings indicate the safety and utility of the cooling probe as a neurosurgical research tool. Additional rigorously designed studies should be undertaken to correlate the effects of cooling, electrical stimulation, and focal lesioning.

KEY WORDS • functional mapping • brain cooling probe • synapse • temperature

NEUROSURGEONS routinely examine human brain functions by using invasive functional mapping methods. By observing the effects of temporary disruption of local brain activity, it is possible to infer what neurological functions are mediated by that brain region and predict what deficits might result if that region were resected or lesioned.

Although a variety of invasive methods have been used in humans and experimental animals to cause localized reversible brain dysfunction, electrical stimulation mapping is the only approach that is used routinely to create a functional map of the human cerebral cortex.[10,13] In this report we describe our experience using localized cortical cooling, a mapping method that has theoretical advantages over traditional methods of electrical stimulation.

Materials and Methods

We designed and tested a variety of devices (cooling probes) with the common design features described in Fig. 1. A localized region of the brain surface is cooled using a stainless-steel cooling probe chamber. The device is actively cooled to a temperature close to, but not below, 0˚C by infusing chilled saline into the chamber. The experimenter manually controls the rate of cold saline flow and continuously monitors temperatures within the chamber by referring to thermocouple readings. Bipolar EEG contacts embedded in the undersurface of the chamber record field potentials from the brain surface. In addition to the thermocouple that is positioned within the cooling chamber, one cooling probe variant has a penetrating thermocouple that enables investigators to obtain measurements of tissue temperature within the underlying brain. Invasive testing with the cooling probe and penetrating thermocouple was only performed in a portion of the anterior temporal lobe cortex, which had been scheduled for removal independent of the functional testing that was performed. The specific cooling probe dimensions depicted in Fig. 1 apply to the device used to disrupt motor speech functions, as described later in this paper.

Cooling probes were carefully tested to address all relevant patient safety issues before use in the operating room. Bench-top experiments were conducted to confirm the functional integrity of the electronic elements within the probe and to ensure that the desired chamber temperatures could be reached and maintained in a well-controlled fashion. As part of the preclinical review process, the University Hospital Biomedical Engineering Department analyzed the device and deemed it safe for the intended use. In accor-

Abbreviation used in this paper: EEG = electroencephalography.

dance with federal regulations, all devices and experiments were reviewed and approved by the University of Iowa Institutional Review Board as well as by review panels of the National Institutes of Health. In reaching this decision, the review boards considered the preclinical engineering testing data described earlier as well as data from a large number of previously published experimental cooling studies in animals and published experiences with cortical and subcortical cooling in patients undergoing neurosurgery.[1–5,7–9,11,12,14–19] These cumulative data provide strong evidence of the clinical safety of cooling localized regions of cerebral cortex to the temperatures targeted in the current study.

All human experiments were performed in patient volunteers who were scheduled to undergo surgery for medically intractable epilepsy. Three types of cooling probe experiments were conducted. One set of experiments was directed at examining the thermal gradients that are created under the cooling probe during active cooling. In these experiments, the cooling probe was positioned on the cerebral cortex of the anterolateral temporal lobe before it was resected. Temperature readings were obtained at varying depths of the cortex immediately under the cooling probe. Continuous simultaneous measurements were made of temperatures within the chamber and in the underlying brain parenchyma (OMEGA Engineering, Inc., Stamford, CT).

A second set of experiments was conducted to examine the effects of cooling on spontaneous and stimulus-evoked local EEG activity. Continuous bipolar recordings were obtained from the surface EEG contacts embedded in the cooling chamber as the brain was cooled and then rewarmed. Electroencephalography signals were amplified 5000 times (BAK Electronics, Germantown, MD), digitized at 500 or 1000 Hz (DataWave Technologies, Longmont, CO), and saved on the hard drive of a Windows-based personal computer. Data were analyzed offline by using appropriate software (MATLAB; MathWorks, Inc., Natick, MA). The power spectra of the EGG recordings were derived using discrete Fourier transform on 1024 data points (2.048 seconds at 500 Hz and 1.024 seconds at 1000 Hz). Power spectra were obtained for 60 consecutive periods containing 1024 data points each, which represented the baseline, cooling, and rewarming stages of the experiment. Power spectra were grouped into five bands (θ 4–8 Hz, α 8–12 Hz, β 12–30 Hz, low γ 30–55 Hz, high γ 65–95 Hz). The statistical significance of the difference in power spectra between the baseline and cooling stages was tested by performing a paired t-test for each patient for each EEG band. Probability values were corrected by applying the Bonferroni method for multiple comparisons. The mean changes in power spectra across all patients were obtained.

Evoked potential activity was studied using electrical stimulation tract-tracing methods in five patients. Using this method, electrical impulses are delivered at one brain site and evoked potentials are recorded from a distant brain region that is functionally connected to the brain site being electrically stimulated.[6,16,20,21] In the current experiments, the evoked potentials were recorded from the Broca area while electrical stimuli were delivered to the Wernicke area. Evoked potential waveforms were examined for evidence of cooling-induced changes. Responses to electrical stimuli were averaged over 50 presentations. Latency periods of the first negative peak and the first positive peak were measured twice in each patient during the baseline, cooling, and rewarming stages. Latency data were pooled across patients and the differences among the baseline, cooling, and rewarming stages of the experiments were analyzed statistically by using the Wilcoxon signed-rank test.

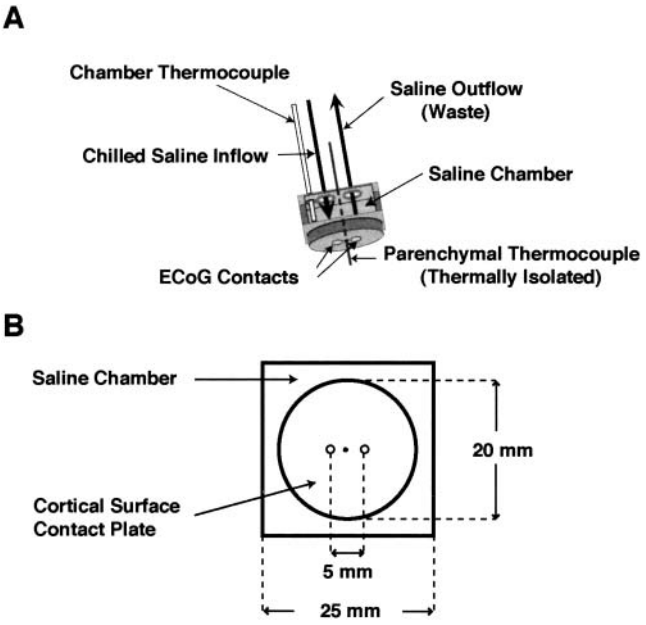

FIG. 1. A: Schematic depiction of the cooling probe design. The chamber is cooled by chilled saline, which is contained within a standard clinical intravenous infusion bag. The saline is infused through the inflow tube and discharged through the outflow tube. The temperature within the chamber is continuously monitored via the chamber thermocouple, and the flow rate of the saline is adjusted manually up to 150 ml/minute according to the monitored temperature. Electrocorticography (ECoG) contacts are embedded in the undersurface of the cooling chamber. The parenchymal thermocouple shown in the figure is only present in cooling probes that are used in experiments involving brain regions that will be resected. In those cases, the parenchymal thermocouple is advanced through the brain tissue to obtain temperature recordings at different levels of the cerebral cortex (see Fig. 2). B: Illustration showing the dimensions of the cooling probe as viewed from below. A 20-mm-diameter contact plate has a pair of 2-mm-diameter silver electrode contacts at its center, which are spaced 5 mm apart.

The third set of experiments are preliminary in nature and represent our initial observations when cooling is used to cause temporary dysfunction in eloquent areas of the cerebral cortex. To date, these experiments have been confined to cooling sites in the lateral frontal lobe that are involved in motor speech production, as determined by the results of electrical stimulation functional mapping. Qualitative observations were recorded to compare the effects of electrical stimulation with those of cooling at these brain sites.

Results

Cooling experiments were performed in 18 patients. In all cases it was possible to cool the chamber temperature to between 0 and 3˚C. Tissue temperature gradients below the pial surface changed markedly as a function of distance from the brain surface (Fig. 2). Detailed studies in experimental animals indicate that cortical synaptic activity begins to be disrupted at tissue temperatures below 20˚C.[18]

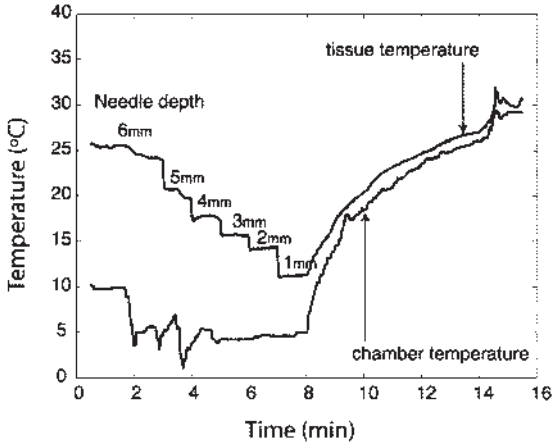

FIG. 2. Graph showing data from a cooling probe experiment performed on a portion of the anterior temporal lobe, which was subsequently resected. The lower trace depicts temperatures within the cooling chamber during active cooling followed by rewarming. Brain tissue temperatures at various depths of the cerebral cortex under the cooling probe are shown in the upper trace. Depth temperature recordings were first obtained 6 mm below the cortical surface and then the temperature recording device was sequentially elevated to 1 mm below the brain surface. These data demonstrate that the effects of cooling are highly localized. Heat dissipation from blood flow limits the distribution of surface cooling effects.

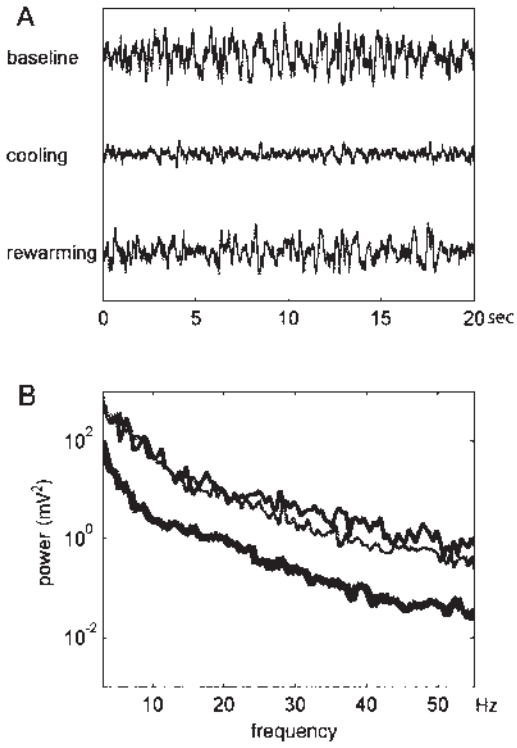

FIG. 3. Graphs displaying data showing the effects of cooling on local spontaneous EEG activity. A: Representative EEG tracings obtained before cooling, during active cooling, and during rewarming as recorded from the cooling probe. B: Results of the Fourier transform power spectrum analysis showing statistically significant cooling-induced changes that reverse with rewarming ($p < 0.05$, Wilcoxon rank-sum test). The *upper line* represents the baseline stage, the *lower line* the cooling stage, and the *center line* the rewarming stage of the experiment.

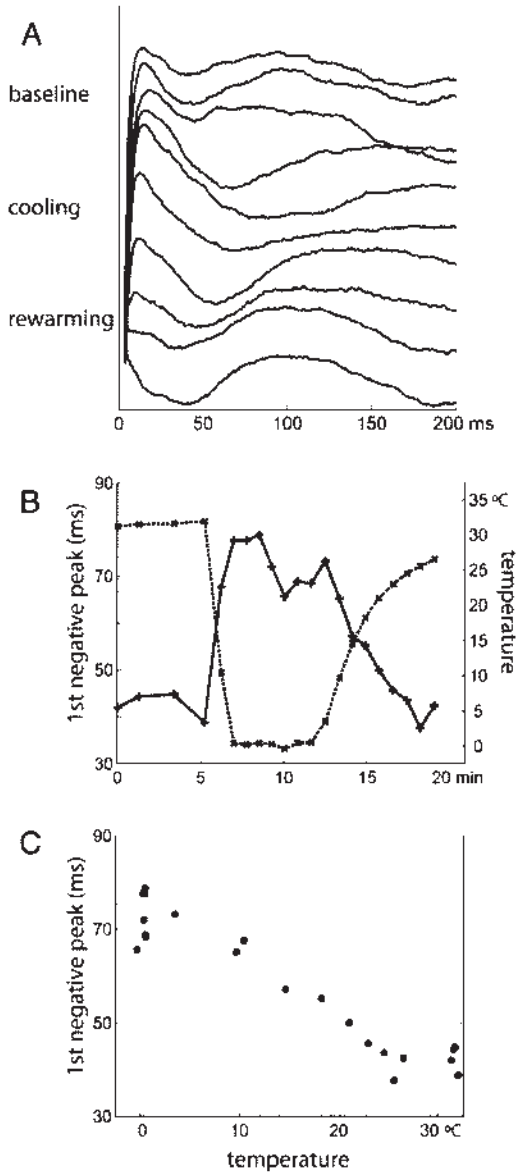

FIG. 4. Graphs depicting the effects of cooling on electrical stimulation–evoked field potentials. Electrical stimuli were delivered to the posterior superior temporal gyrus and responses were recorded with the cooling probe positioned on the inferior frontal gyrus. A: Representative averaged evoked potentials recorded from the cooling probe before, during, and after active cooling. Changes in the morphological structure of the waveform were noted throughout the course of the experiment. B: Cooling causes statistically significant changes in the peak latency period of the first negative component of the evoked potential, which returns to baseline on rewarming ($p < 0.05$, Wilcoxon signed-rank test). C: Scatterplot demonstrating the correlation between chamber temperature and the peak latency period of the first negative component of the evoked field potential ($r = -0.952$, $p < 0.0001$).

Our data indicate that temperatures below this threshold are achieved throughout the gray matter directly below the cooling probe (< 4 mm thickness). The steep temperature gradients caused by the heat-sink effect of blood flow are such that tissue temperatures at brain sites farther than 6 mm from the probe surface do not reach this threshold.

TABLE 1

*Mean changes in power spectra compared with baseline**

Power Spectrum Band (Hz)	Change in EEG Power From Baseline Stage (dB)	
	Cooling Stage	Rewarming Stage
θ (4–8)	−7.06 ± 1.16	−0.46 ± 1.64
α (8–12)	−5.06 ± 2.80	0.16 ± 1.58
β (12–30)	−3.37 ± 2.01	0.91 ± 1.41
low γ (30–55)	−4.33 ± 2.50	0.26 ± 1.31
high γ (65–95)	−6.24 ± 1.91	−0.01 ± 1.70

* Values are expressed as the means ± standard deviations.

TABLE 2

*Mean latency periods of the first negative and first positive peaks of evoked potentials recorded at different stages of the cooling procedure**

Stage	Latency Period (msec)	
	1st Negative Peak	1st Positive Peak
baseline	22.9 ± 12.8	45.4 ± 27.2
cooling	33.9 ± 27.6†	76.6 ± 65.7‡
rewarming	24.6 ± 12.1	50.4 ± 29.7

* Values are expressed as the means ± standard deviations obtained in five patients who underwent the cooling procedure.
† $p < 0.05$.
‡ $p < 0.01$.

Local cooling caused significant changes in spontaneous and stimulus-evoked EEG activity (Figs. 3 and 4). We analyzed temperature-related changes in spontaneous EEG activity in five patients. The average EEG power of the θ, α, β, low γ, and high γ bands decreased 7.06 ± 1.16, 5.06 ± 2.8, 3.37 ± 2.01, 4.33 ± 2.5, and 6.24 ± 1.91 dB, respectively (Table 1). In all patients, the power of the θ and high γ bands decreased significantly, and in four patients, the power of the α, β, and low γ bands significantly decreased as well. In all five patients the rewarming procedure reversed the EEG power spectrum back to baseline. The EEG power spectrum did not display significant changes at adjacent noncooled cortices in all three patients in whom local cortical EEG signals adjacent to the cooling probe were recorded.

The amplitude of stimulus-evoked field potentials was reversibly attenuated during active cooling, and the latency periods of the first negative peak and the first positive peak of averaged electrically evoked potentials were delayed significantly from 22.9 ± 12.8 msec to 33.9 ± 27.6 msec ($p < 0.05$) and from 45.4 ± 27.2 msec to 76.6 ± 65.7 msec ($p < 0.01$), respectively (Table 2). Figure 4A demonstrates a representative example in which both negative and positive peak latency periods changed as a function of chamber temperature. Correlation coefficients between the temperature in the cooling probe and the latency periods of the first negative peak (Fig. 4B and C) and the first positive peak (data not shown) were −0.952 and −0.947, respectively; both correlations are highly significant ($p < 0.001$).

Critical sites of language in the left frontal lobe were cooled in two patients. These sites were initially identified using a hand-held stimulator as patients performed a verbal counting task. When electrical stimuli were delivered to the critical site of language at an intensity below the after-discharge threshold, both patients demonstrated complete speech arrest. The cooling probe was then positioned over the physiologically identified site. Electrical stimulation was repeated and this time it delivered the stimuli through EEG contacts incorporated within the cooling probe. Speech arrest was again observed, confirming that the cooling probe was properly positioned over the frontal lobe language site.

When the temperature of the cooling probe chamber had been decreased and maintained within a range of 1 to 3˚C, both patients demonstrated qualitatively similar speech dysfunction during the verbal counting task. Both patients generated audible numbers in the correct sequences; however, the rate of speech was diminished and the time interval between each spoken number became less regular. The patients' vocalizations seemed to require more effort and were prolonged. Following rewarming, both patients performed the counting task in a normal fashion.

No adverse effects were observed with focal cooling. Physiological measures returned to baseline and the cooling-induced speech dysfunction resolved rapidly when active cooling was discontinued. With the exception of experiments involving the use of a penetrating thermocouple, the cortical surface under the cooling probe appeared normal at the completion of each experiment.

Discussion

In this report we describe an experimental device that safely allows neurosurgeons to cool localized regions of cerebral cortex so that local synaptic activity can be reversibly disrupted. For longer than a century methods of electrical stimulation have been used to cause localized disruption of cortical activity during neurosurgical procedures.[10,13] This is an efficient and effective mapping method, but it does have a number of limitations. Seizures can be evoked even when electrical stimulation strengths are maintained below the after-discharge threshold. Additionally, the rigorous interpretation of the effects of local electrical stimulation on neurological functions is difficult. Electrical stimuli delivered to one brain site are conducted to distant brain sites, thus causing disruption in a distributed neural network.[6,16,20,21] Local and distant effects cannot be disambiguated, thus making it difficult to infer precisely what neurological functions are mediated exclusively by the brain site being stimulated.

To cause reversible cortical dysfunction in a more controlled and interpretable manner, neuroscientists have made extensive use of local cooling methods in experimental animals.[1,2,5,9,12] When cortical tissue is cooled to temperatures between 0 and 20˚C, local synaptic activity is disrupted without causing permanent injury to brain tissue or affecting the function of axons passing through the region being cooled. Cooling is highly localized, as reflected in the steep thermal gradients caused by the heat-transfer effects of cortical blood flow. The safe, reversible nature of focal brain cooling is reflected in the results of extensive studies in experimental animals, which showed restoration of physiological responses and the absence of histological changes after temporary cooling to temperatures above 0˚C.[1,2,5,9,12,14,18,19]

Although thermocouple-regulated focal cortical cool-

ing has not been previously reported for the purpose of functionally mapping the human cerebral cortex, brain cooling has been used in other neurosurgical settings. Penetrating cooling devices have been used extensively in conjunction with ablative subcortical stereotactic cryosurgical procedures.[3,4,15] Focal intraoperative cooling of the exposed hippocampus has been performed for the purpose of evaluating the risk of amnesia associated with hippocampal resection.[8] Additionally, cold saline has been safely and effectively applied to exposed cerebral cortex to block seizure activity during neurosurgical procedures.[7,11,17]

In the current report we describe a simple and safe device designed to cool a localized region of the human cerebral cortex. Engineering safety tests were performed and approval was obtained from the Institutional Review Board before the study commenced. The experimental results demonstrate the ability of the device to decrease tissue temperatures throughout the underlying gray matter to levels that are known to cause disruption of synaptic activity in experimental animals. The fact that spontaneous and stimulus-evoked field potential activities were reversibly disrupted during active cooling provides clear evidence that comparable cooling-induced physiological effects occur in the human cerebral cortex.

Although the current results demonstrate the utility and safety of this device as a research tool, it is premature to reach conclusions regarding its clinical usefulness. Preliminary results of functional mapping indicate that electrical stimulation and local cooling cause qualitatively different types of temporary neurological dysfunction. Additional, carefully controlled experimental studies are required before firm conclusions can be reached regarding the relative functional effects of electrical stimulation and cortical cooling. It will be even more challenging to determine how these effects correlate with those caused by a lesion. The results of our study may assist other neurosurgical investigators who share this research interest.

Acknowledgments

We thank our patient volunteers for making this generous scientific contribution.

Disclaimer

The authors have no investment or financial interest in the subject under discussion or the materials used in this study.

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Manuscript received February 21, 2003.
Accepted in final form May 14, 2003.
This research was supported by National Institutes of Health Grant Nos. R01 DC04290 (M.A.H.) and F32 DC00417 (H.E.B.).
Address reprint requests to: Matthew A. Howard III, M.D., Department of Neurosurgery, University of Iowa Health Care, 200 Hawkins Drive, Iowa City, Iowa 52242. email: matthew-howard@uiowa.edu.