

FULL-LENGTH ORIGINAL RESEARCH

Transient shivering during Wada test provides insight into human thermoregulation

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SUMMARY

Purpose: Some patients with pharmacoresistant epilepsy undergoing the Wada test experience transient shivering. The purpose of this study was to investigate various clinical and radiographic characteristics of these individuals to delineate underlying mechanisms of this phenomenon.

Methods: A systematic review of prospectively collected information on patients undergoing the Wada test was performed. All demographic, clinical, and radiographic information was obtained and reviewed by the appropriate expert in the field; statistical analysis was performed to determine the predictors of transient shivering.

Results: A total of 120 consecutive carotid artery injections in 59 patients were included in the study. Shivering

was observed in 46% of the patients, and it was not significantly affected by gender, age, location of epileptogenic zone, brain lesion on magnetic resonance imaging (MRI), side of the first injection, duration of the hemiparesis, or excess slow wave activity on electroencephalography (EEG). However, shivering was more likely to follow sodium amobarbital injection if there was no filling of the posterior circulation on cerebral angiogram.

Discussion: Transient shivering during the Wada test is common. A transient but selective functional lesion of the anterior hypothalamus produced by the effects of sodium amobarbital may result in disinhibition of the posterior hypothalamus and other brainstem thermoregulatory centers, thereby inducing transient shivering.

KEY WORDS: Shivering, Thermoregulation, Wada test, Intracarotid amobarbital procedure, Epilepsy.

Resective epilepsy surgery is performed in patients with medically intractable localization-related epilepsy to control or eliminate their seizures (Engel et al., 2003). This involves surgical removal of the epileptogenic zone, and it frequently includes unilateral temporal lobe resection. Some patients undergo the intracarotid amobarbital procedure (IAP) or Wada test, performed by injecting sodium amobarbital into each internal carotid artery separately, thereby anesthetizing and creating a temporary functional lesion of the brain perfused by that circulation. We have observed transient shivering in some patients during the Wada test. The relationship of shivering in the context of this test has not been delineated. Therefore, in this study, we

attempt to attain further understanding regarding this clinical phenomenon.

In mammals, the hypothalamus is known to be critically involved in thermoregulation. Shivering is part of the thermoregulation process and is quickly activated if the organism is exposed to cold temperature. We also know that although the branches originating from the anterior circulation perfuse the anterior hypothalamus, the branches from the posterior circulation perfuse the posterior aspect of the hypothalamus (Haymaker, 1969). We hypothesize that the transient “functional lesion” of part of the hypothalamus induced by the sodium amobarbital injection is responsible for temporary shivering.

METHODS

The IAP is performed as part of the presurgical workup for patients with pharmacoresistant epilepsy to evaluate language dominance and functional memory reserve of the contralateral temporal lobe. At our institution, a team of a neuroradiologist, a neurologist, and a neuropsychologist performs the test. The neuroradiologist introduces a catheter

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into the proximal internal carotid artery (ICA) via the transfemoral route under fluoroscopic guidance. When the catheter is in place, contrast dye is injected and images are captured (Fig. 1). Baseline testing of language and motor functions is performed and instructions are provided to the patient. The language testing is performed by evaluating spontaneous speech, naming, and repetition, and asking the patient to follow simple and complex commands. Patients are asked to maintain their upper extremities outstretched in front of them and to count audibly. This is followed by slow manual push of a predetermined dose of sodium amobarbital over 60–90 s (usually 2 mg/kg, maximum 100 mg per side initially) followed by a 10-ml saline flush to ensure its delivery into the carotid circulation. This induces immediate contralateral hemiplegia and aphasia in the case of the dominant hemisphere. In case of inadequate effect, an additional dose of the drug is given in 10- to 20-mg increments until desired clinical effects are observed. The dose of sodium amobarbital ranges from 100–175 mg per side with an average dose of 110 mg. During IAP, the patient's electroencephalography (EEG) is monitored continuously to record the duration of the medication effects and to identify the occurrence of electrographic seizures that may alter the test results. Following the injection, language and motor function testing is performed repeatedly (every 30–90 s) until functions return to baseline. The encoding aspect of memory testing is performed immediately upon lateralized slowing on the EEG by presenting objects individually to the patient and asking him/her to identify them. The retrieval aspect of the memory testing is performed after the clinical and EEG effects of the drug clears completely, by presenting the objects previously shown along with twice as many foils in a random fashion. The subject is asked to iden-

tify each object and declare whether each object was seen before or not. A memory score is calculated by giving one point for each correct answer and subtracting 0.5 point for each wrong answer. Usually the side of proposed surgery is injected first, followed by injection of the other side after a 30-min interval.

During IAP, we observed that some of the patients develop transient, involuntary, fine motor movements of the entire body that resemble shivering due to sudden exposure to cold temperature or rigors. We (and invariably the patients) identified this phenomenon as shivering, and because it introduces electromyography (EMG) artifact in the EEG recording, we routinely document its onset and cessation. Therefore, it provides us a unique opportunity to study differences between groups of individuals who shiver and those who do not.

The study was performed by retrospective review of prospectively collected information from patient records. Consent was obtained from each subject for the procedure, but no separate consent for the research was obtained. The local institutional review board approved the study. The following variables were recorded: age, race, sex, side of seizure onset, antiepileptic medications at the time of Wada test, side of injection, dose of sodium amobarbital, time between the drug injection and the onset of shivering (lag time), duration of shivering, onset and duration of slowing on the EEG (as a surrogate for continued effects of sodium amobarbital on the brain), duration of hemiparesis, hemispheric dominance, and memory scores.

Normally the ICA perfuses the middle cerebral artery (MCA) and anterior cerebral artery (ACA) ipsilaterally. The neuroradiologist reviewed each angiogram in a blinded fashion and identified any significant perfusion of

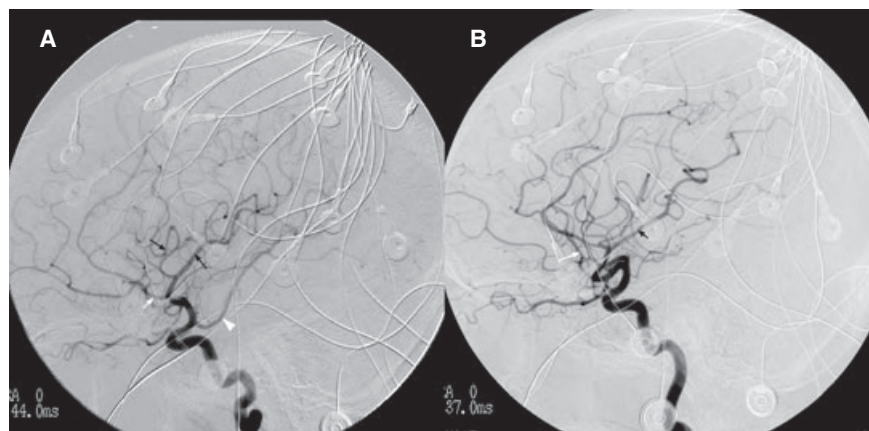


Figure 1.

Lateral projection views of (A) the left and (B) the right internal carotid artery angiograms in a patient undergoing intracarotid amobarbital procedure (IAP). Note opacification of the branches of the middle cerebral artery (black arrows) and the anterior cerebral artery (white arrows). On the left injection, an additional territory of the posterior cerebral artery is also filling via the internal carotid artery (arrow head). The patient exhibited transient shivering following injection of the drug into the right internal carotid artery only.

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additional territories, such as perfusion of the contralateral ACA through the anterior communicating artery (ACoM), or perfusion of the posterior cerebral artery (PCA) through either the posterior communicating artery (PCoM) or via fetal origin of the PCA (Fig. 1).

RESULTS

A total of 59 patients were included in the study that underwent Wada testing as part of the presurgical workup. Shivering was observed in 27 (46%) of 59 patients, and always followed injection of sodium amobarbital and not the initial injection of contrast material. The average age of the patients was 29 years (range 10–50 years) in the shivering group, and 21 years (range 9–67 years) in the nonshivering group. The shivering group consisted of 12 male and 15 female patients, whereas the nonshivering group comprised 17 male and 15 female patients. The average number of antiepileptic drugs used at the time of Wada testing was 1.89 (range 0–4) in the shivering group and 1.88 (range 0–4) in the nonshivering group. The cranial magnetic resonance imaging (MRI) showed an identifiable abnormality in 81% of the patients in both shivering (22 of 27), and nonshivering groups (26 of 32) (Table 1).

The number of subjects who shivered (46%) versus not (54%) did not differ significantly from an expected 50/50 ratio (binomial test; $z = -0.7$, n.s.), indicating that equal proportions of subjects would shiver, or not. There was no difference in mean age [t test; $t(56) = 0.49$, n.s.]. There was no difference in the proportions of female to male patients

who shivered or did not [χ^2 test; $\chi^2(1) = 0.44$, n.s.]. There was no difference in terms of number of AEDs patients were taking [t -test; $t(57) = 0.084$, n.s.], or abnormality found on MRI (binomial test, $z = -0.07$, n.s.).

Shivering occurred on injection of only one ICA in 21 patients, whereas 6 patients shivered following injection of both carotid arteries. In patients who shivered following injection of one side only, it followed left injection in 12 and right carotid in the rest of the patients. Of these patients, shivering was observed on injection of the language-dominant hemisphere in 11 and nondominant side in 9 patients, whereas one patient had bilateral representation of the language function. Similarly, shivering followed the first injection in 14 patients and second injection in 7 patients (Table 2). Of the total patients in the study, the left hemisphere was dominant for language function in 51 patients, whereas five patients were right hemisphere dominant and 3 exhibited bilateral language representation. The left side was injected first in 41 patients. Note that for hemispheric dominance, little can be said about the role it played, if any, as by luck of the draw, most patients in our sample were left dominant and had the left side injected first (69%), with too few (31%) having the right injected first.

These 59 patients had a total of 120 carotid injections of sodium amobarbital. Two patients had repeat left-sided injections due to unreliable memory function testing following the first injection. Both repeat injections were on the left side. One patient did not shiver with either injection. The other patient had shivering following the first injection, but not after the repeat injection. However, she received a smaller dose of sodium amobarbital for the repeat testing. The average dose of amobarbital in the shivering group was 112 mg, whereas in the nonshivering group it was 108 mg. There was no statistically significant difference in dose of sodium amobarbital given (t -test). In the patients who shivered on injection of one side only, three patients received different doses of the drug on injection of two sides. One had a higher dose on injection of the side that induced shivering, and two received a higher dose on the nonshivering side. Therefore, the dose of sodium amobarbital did not appear to be a factor for induction of shivering.

The average lag from the time of injection of sodium amobarbital to the onset of shivering was 107 s [standard deviation (SD) = 51], and to the onset of lateralized EEG

Table 1. Characteristics of shivering patients versus nonshivering during intracarotid amobarbital procedure (IAP)

	Shivering	Nonshivering
Number	27	32
Age, mean (range)	29 years (10–50)	21 years (9–67)
Gender		
Male	12	17
Female	15	15
Number of AEDs, mean (range)	1.89 (0–4)	1.88 (0–4)
Abnormality found on cranial MRI	81.50%	81.30%
Dose of sodium amobarbital, mean (range)	112 mg (100–175)	108 mg (100–160)
Language Dominance		
R side injection first		
Left	8	8
Right	0	0
Bilateral	1	1
L side injection first		
Left	15	20
Right	3	2
Bilateral	0	1

AED, antiepileptic drug; L, left; MRI, magnetic resonance imaging; R, right.

Table 2. Characteristics of 21 patients who exhibited shivering only on injection of one side during intracarotid amobarbital procedure (IAP)

Side of injection producing shivering	12 Left	9 Right	
Language dominance	11 Left	9 Right	1 Bilateral
Order of injection that produced shivering	14 First injection	7 s Injection	

slowing was 44 s (SD = 47). The average duration of the shivering was 235 s (SD = 131), and excess slow wave activity on EEG was 331 s (SD = 138). The time from administration of the drug to resolution of hemiparesis was 350 s (SD = 136), whereas the EEG returned to baseline at 366 s (SD = 102) and shivering stopped on average at 339 s (SD = 132). This suggests that the effects of the drug wore off in about 6 min, and shivering stopped roughly around the same time (Fig. 2). A correlation matrix with all variables was calculated to determine if there was a significant relationship between times when hemiparesis resolved, the EEG became lateralized, the EEG returned to baseline, onset of shivering, total time of shivering, and when shivering stopped. The only significant relationship was between resolution of hemiparesis and the EEG returning to baseline ($r = 0.40$, $p < 0.05$). No other correlation reached signi-

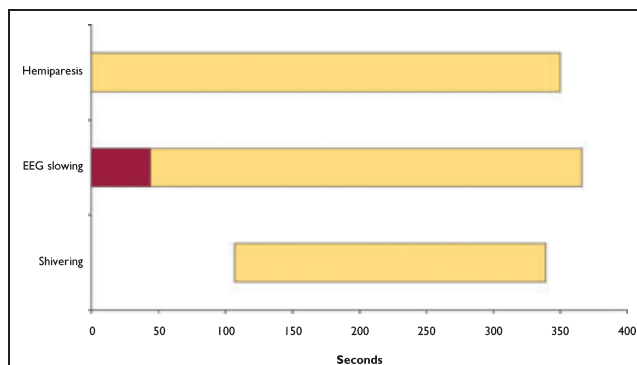


Figure 2.

Timeline of the various clinical and electrophysiologic changes during intracarotid amobarbital procedure (IAP).

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ficance, including the relations between resolution of hemiparesis and shivering ($r = -0.08$, $r = 0.26$, $r = 0.25$, respectively, n.s.), lateralization of EEG ($r = 0.13$, $r = -0.25$, $r = -0.18$, respectively, n.s.), and time EEG returned to baseline ($r = 0.12$, $r = -0.08$, $r = 0.02$, respectively, n.s.)

No electrographic seizure was recorded during the IAP in these individuals. Piloerection was part of seizure semiology in one patient who did not shiver. None of the patients reported feeling cold while or immediately following shivering.

Analysis of the carotid circulation perfusion showed filling of the contralateral ACA 29 of 120 trials, and shivering was noted in 13 of those trials. This effect was not significant [$\chi^2(1) = 0.02$, n.s.]. On the other hand, contralateral ACA filling was absent in 91 patients and shivering was noted in 42 of them (Fig. 3). The ipsilateral PCA did not fill on 76 trials; 43 subjects (57%) shivered, and 33 (43%) did not. The ipsilateral PCA territory filled on 44 of 120 trials, and shivering was noted on only 12 trials (27%); shivering was not present on 32 trials (73%). This effect was significant [$\chi^2(1) = 9.64$, $p < 0.01$]. Therefore, perfusion of the ipsilateral PCom and/or PCA was significantly and inversely associated with the occurrence of shivering; it inhibited shivering.

DISCUSSION

One of the evolutionary successes in the animal kingdom is the emergence of warm-blooded animals who maintain temperature within a narrow range despite fluctuations in environmental temperatures, keeping body function and metabolic rate at a relatively constant level. Body temperature is regulated almost entirely by feedback mechanisms in the nervous system. Several animal studies with either

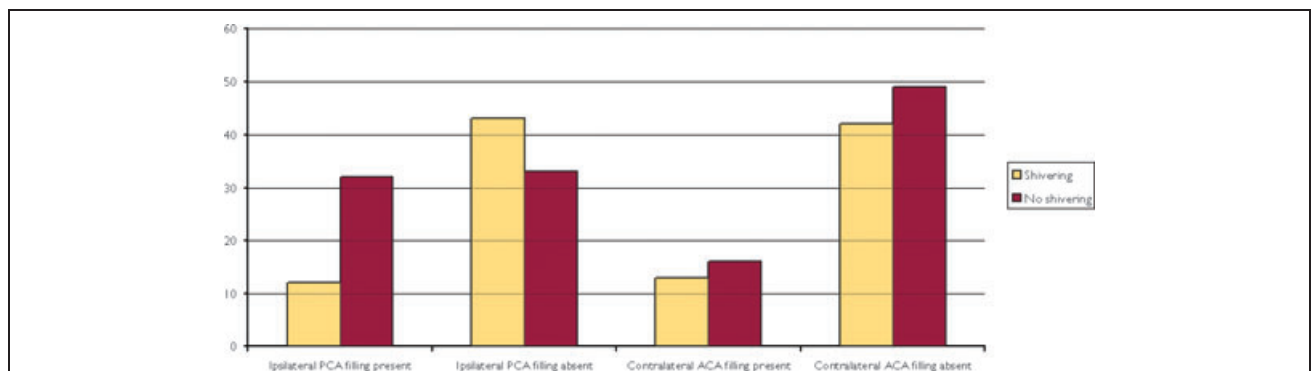


Figure 3.

Angiographic evidence of filling of additional territories [beyond ipsilateral anterior cerebral artery (ACA) and middle cerebral artery (MCA)] following contrast dye injection in the proximal internal carotid artery (ICA) during intracarotid amobarbital procedure (IAP), and its relationship to shivering following sodium amobarbital injection. The numbers on the y-axis represent true incidence of each occurrence (ICA, internal carotid artery; ACA, anterior cerebral artery; MCA, middle cerebral artery; PCA, posterior cerebral artery).

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lesion or thermal stimulation of various regions of the central nervous system suggest that temperature regulation is controlled by a hierarchy of neural structures, with the hypothalamus playing a critical role (Baldwin & Ingram, 1968; Banet et al., 1978; Boulant, 1981, 2000). Further study of patients with lesions affecting thermoregulation and *in vitro* studies of cellular and molecular mechanisms has expanded this understanding (Rudelli & Deck, 1979; Kelso et al., 1982; Hori et al., 1988; Kloos, 1995; Boulant, 1998; Martinez-Rodriguez et al., 2006; Alty & Ford, 2008).

Temperature regulation occurs through feed forward and feedback mechanisms (Huckaba et al., 1971; Morrison et al., 2008). For effective operation of this system, there are temperature detectors, mechanisms to integrate and respond to information, and an efferent pathway to modify body's heat production, conservation, and loss. The thermoreceptors or sensors are widespread over the entire body. The peripheral thermoreceptors are located in the skin and mucous membranes, as well as in the form of visceral and vascular thermoreceptors (Schepers & Ringkamp, 2009). The information sent from these receptors travels through the neuraxis and is modulated by the neurons in the spinal cord and the brainstem (Necker, 1975; Nakamura & Morrison, 2008). The central thermoreceptors are located primarily in the hypothalamus in the form of temperature sensitive neurons. The inputs from these sensors are summed in a comparator or integrator, which also receives input from an intrinsic reference signal or the set point. The integrator in turn is connected to the efferent response systems to generate both autonomic and behavioral responses (Satinoff, 1978; Mahmood & Zweifler, 2007). The anterior hypothalamus, especially the preoptic area (POA), is the main command center of thermoregulation. When the temperature of the POA increases, the skin over the entire body breaks out into a profuse sweat and skin blood vessels dilate, directing the body to lose heat. On the other hand, when the temperature drops below threshold, immediate reflex effects are invoked with shivering (with resultant increase in the rate of body heat production), and by inhibiting the process of sweating and skin vasoconstriction (to diminish loss of body heat) (Boulant, 2006; Romanovsky, 2007).

The POA contains large numbers of warm-sensitive (WS) neurons, cold-sensitive (CS) neurons, and temperature-insensitive neurons. The WS neurons function as temperature sensors or central integrators, as their activity is determined by their own temperature and by afferents from peripheral thermoreceptors. These WS neurons are spontaneously active, and they increase their firing rate with increase in body temperature. The CS neurons increase their firing rate when the body temperature drops (Szymusiak & Satinoff, 1982).

The posterior hypothalamus along with other brainstem structures mediates behavioral defenses and can be characterized as the effector arm of thermoregulation (Boulant, 2006; Romanovsky, 2007). Several parallel pathways

involving connections from POA to the dorsomedial nucleus of the hypothalamus (DMH), periaqueductal gray matter (PAG) of the midbrain, and raphe pallidus (RPa) of the medulla have been postulated to be involved in cold defense responses (Nagashima et al., 2000; Yoshida et al., 2005; Dimicco & Zaretsky, 2007; McAllen, 2007). The RPa is a key intermediary connecting the structures in the hypothalamus and upper brainstem to the final effector pathway of descending projections that activate sympathetic preganglionic neurons controlling skin vasoconstriction and nonshivering thermogenesis. Along with adjacent portions of the reticular formation, RPa also activates motor neurons that elicit shivering (Nagashima et al., 2000; McAllen, 2007; Nakamura & Morrison, 2007). According to a current model, the hypothalamic WS neurons tonically inhibit cold responsive neurons of the DMH and RPa. The DMH, both directly and via the caudal PAG, activates the RPa neurons, initiating cold defense responses (Nagashima et al., 2000; Yoshida et al., 2005; Benarroch, 2007; McAllen, 2007) (Figure 4). When the firing rate of WS neurons of POA is reduced (e.g., during cold exposure or selective lesion of the anterior hypothalamus), the effector arm is disinhibited. This in turn activates the descending pathways, inducing shivering by increasing the tone of the skeletal muscles throughout the body by facilitating the activity of the anterior horn motor neurons, and perhaps by enhancing feedback oscillation of the muscle spindle stretch reflex. During maximum shivering, body heat production can rise to 4–5 times normal.

The ICA bifurcates into the ACA and MCA after giving rise to the PCom. The ACA gives off the ACom that joins its counterpart from the contralateral side, and the PCom joins the PCA, completing the cerebral arterial circle (circle of Willis) (van Raamt et al., 2006). Normally, the PCA is a branch of the basilar artery, but in some individuals with a fetal-type posterior circulation (FTP), it originates from the ICA (van Raamt et al., 2006). In these individuals, the PCA territory is perfused via the anterior circulation (Fig. 1).

The arterial supply of the hypothalamus originates as perforating branches off the arterial circle, and can be divided into three groups: anterior, intermediate, and posterior. The anterior arterial group, arising from ACA and ICA, supplies the rostral part of the hypothalamus (the preoptic area and a part of the supraoptic region) (Dunker & Harris, 1976). The remainder of the hypothalamus receives blood from both the intermediate (arising from PCom) and posterior arterial groups (arising from PCA, PCom, and basilar artery) (Haymaker, 1969). The posterior hypothalamus is supplied by the branches of the posterior group (Haymaker, 1969; Marinkovic et al., 1989).

We believe that the shivering in our subjects is induced by the creation of a temporary and selective “functional lesion” of the anterior hypothalamus, with preserved function of the posterior hypothalamus. This is supported by our observation that patients are more likely to exhibit shivering

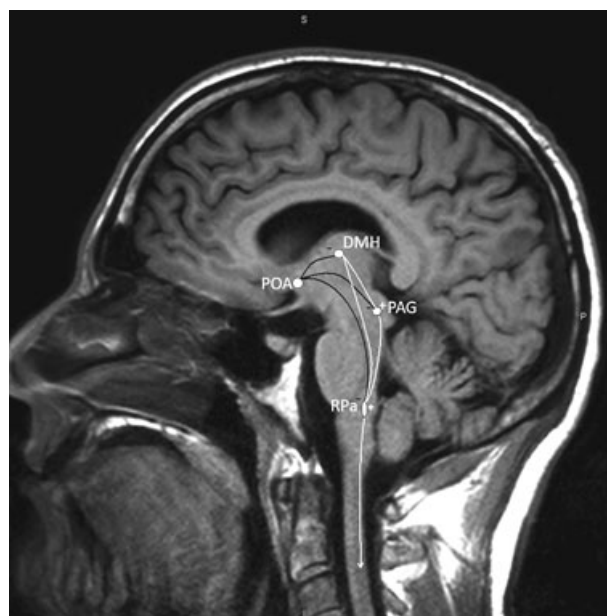


Figure 4.

Sagittal view of T₁-weighted magnetic resonance imaging (MRI) about 3 mm lateral to the midline passing through the hypothalamus (A, anterior; P, posterior; S, superior; I, inferior). Approximate locations of various thermoregulatory centers and their connections are shown with circles and lines superimposed on the MRI. The white lines represent excitatory and the black lines represent inhibitory influences. (POA, preoptic area; DMH, dorsal medial hypothalamus; PAG, periaqueductal gray matter; RPa, raphe pallidus.) The POA sends inhibitory input to the DMH, PAG, and RPa; whereas the DMH sends excitatory inputs to PAG and RPa, and PAG also sends excitatory connections to RPa. Under normal circumstances, warm-sensitive (WS) neurons of POA receive inputs from various thermoreceptors and they in turn send efferents to DMH, PAG, and RPa. During cold exposure, activity of the WS neurons is diminished and other areas are released from inhibitory control of POA. Activation of neurons in DMH, PAG, and finally RPa sends signals via descending spinal pathways to initiate cold defense responses to increase heat production (via shivering or nonshivering thermogenesis) and also to conserve heat loss (cutaneous vasoconstriction).

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following injection of sodium amobarbital if there is no perfusion of PCom or PCA during carotid injection. As mentioned earlier, the POA of the anterior hypothalamus (perfused by the branches of ACom and ACA) maintains an inhibitory influence over the DMH and PAG (perfused by the branches of PCA and PCom). Therefore, injection of sodium amobarbital into the ICA produces a “functional lesion” of only POA when there is no perfusion of the posterior circulation. This releases the posterior thermoregulatory areas from its tonic inhibitory influence of POA inducing shivering.

Alternatively, the cerebral cortex itself could be exerting inhibitory control over the shivering mechanisms, and the transient lesion of the cerebral cortex is responsible for the effect. However, we would like to discuss a case report where a brief period of shivering followed a retrobulbar block. They concluded this was due to spread of local anesthetic solution into the brainstem along the optic nerve, but consciousness of the patient was preserved making it unlikely (Lee & Kwon, 1988). Perhaps the effects were due to spread of the local anesthetic agent along the optic nerve to the floor of the third ventricle and adjacent anterior hypothalamus, producing a transient functional lesion of the anterior hypothalamus.

Another possibility is that shivering in our patients is due to the possibly cooler temperature of the solutions used for IAP cooling of the thermoregulatory centers. However, this is unlikely as the medication is diluted in normal saline at room temperature, and slow injection of the drug in the fast moving blood of the proximal ICA is unlikely to alter the blood temperature. In addition, larger volume injection of the contrast dye at room temperature failed to induce shivering.

Another interesting aspect of our study is the finding that shivering is more likely to occur following injection of one side. This raises a possibility that human thermoregulation is more lateralized. In animal experiments, no clear lateralization has been observed in responses to thermal changes. The data on human thermoregulation are limited, but interestingly, a human study investigating the cortical, thalamic, and hypothalamic responses to cooling and warming using positron emission tomography (PET) activation imaging of subjects observed more lateralized effects. The investigators noted importance of the right ventral hypothalamus with warming and deactivation of the region with cooling (Egan et al., 2005). It is intriguing to note that a different study observed that the epileptic auras of “cold shivers and/or goose bumps” were associated with seizures originating from the left temporal lobe (Stefan et al., 2002). Our study also showed a tendency toward left hemispheric injection to result in shivering; however, it failed to reach statistical significance.

In animal studies, it is shown that unilateral thermal manipulation causes shivering on both sides and information is not exchanged at the level of hypothalamus, but is caudal to it (Kanosue et al., 1994). We also observed that when shivering occurred, it occurred bilaterally, even though the hemiplegia was present in these individuals due to effects of the drug.

LIMITATIONS OF THE STUDY AND FUTURE DIRECTIONS

Our study is limited by its design. The data were reviewed retrospectively but collected prospectively,

except for review of the cerebral angiograms, although the images were reviewed in a blinded fashion. The second limitation is that the patients had medically intractable epilepsy, with most having structural or functional lesions affecting the temporal lobe. However, the side of the injection causing shivering and the side of seizure onset (presumably indicating the side of abnormal temporal lobe function) did not correlate and the total numbers of AEDs were similar in both groups. The third limitation is the assumption of perfusion of the parts of the hypothalamus by specific arterial branches. Hypothalamic perfusion pattern is highly variable, and angiograms can visualize only large blood vessels and not the small arteries perfusing the hypothalamus. On the other hand, our study indicates that similar methods of creating a reversible functional lesion can be utilized to study thermoregulation in humans or higher primates.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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