Temperature Considerations in the Determination of Death by Neurologic Criteria

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Determination of death by neurologic criteria is predicated on the accurate clinical evaluation for the permanent loss for the capacity of consciousness and brainstem function. One of the prerequisites for the determination of death by neurologic criteria is the elimination of any confounders of death by neurologic criteria. Hypothermia is simultaneously a potential consequence of death by neurologic criteria, due to loss of autoregulation, and a potential direct and indirect confounder to the determination of death by neurologic criteria. Hypothermia reduces brain metabolism and may exacerbate pharmacological confounding by alterations of pharmacokinetics of medications during hypothermia.

These issues require attention by clinicians considering performance of an evaluation for determination of death by neurologic criteria. In this chapter, we review the physiology, pharmacokinetics, and clinical issues relevant to temperature considerations in the determination of death by neurologic criteria, focusing on hypothermia. We also provide recommendations on managing temperature/hypothermia to facilitate determination of death by neurologic criteria.

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1 Alterations in the Regulation of Body Temperature After Death by Neurologic Criteria

The normal range of human core temperature is 36.4–37.5 °C. Heat is produced by metabolic activity, either basal and voluntary activity or though shivering and non-shivering thermogenesis, and is lost primarily through radiation and evaporation from the skin and respiratory tract [1]. Core body temperature is maintained in the physiological range by a variety of heat-generation and heat-conservation mechanisms. These mechanisms, however, can be overwhelmed under extreme environmental conditions or through application of therapeutic cooling (e.g. induced hypothermia) [1].

Thermogenesis may be lost after death by neurologic criteria. Because non-shivering and shivering thermogenesis are governed by the anterior and posterior hypothalamus, respectively, loss of these homeostatic functions after death by neurologic criteria may lead to disturbances in temperature with the onset of poikilothermia. This may be manifest clinically by hypothermia resulting from heat loss into the ambient environment without compensatory thermogenesis. The potential loss of thermoregulatory function after death by neurologic criteria requires clinicians to vigilantly monitor for hypothermia, which may confound the determination of death by neurologic criteria and may impact organ function in patients who will donate organs after death by neurologic criteria.

2 Relationship Between Temperature, Brain Metabolism, and Function

The human brain is metabolically highly active, and although it comprises only a few percent of human body mass, it accounts for one-quarter of the body's total glucose utilization and one-fifth of oxygen utilization at resting state [2]. This high metabolic rate also produces a considerable amount of heat, and activity-related heat generation is sufficient to generate regional variations of brain temperature corresponding to local metabolic activity [2]. The excess heat produced by the brain is cleared in the normal state by perfusing blood, leading to a venous-to-arterial temperature gradient [3]. Excess heat may also be removed through direct conduction to the cerebrospinal fluid and skull.

In addition to the brain producing heat through metabolic activity, almost all cerebral processes are passively affected by temperature. Oxygen consumption and energy expenditure decrease approximately 7% with every centigrade degree decrease in brain temperature, down to approximately 25 °C at which point cerebrovascular autoregulation is thought to fail [1]. The function of individual neurons and global cognitive function are sensitive to temperature fluctuations, as demonstrated in both in vitro and animal experiments [4, 5]. Over a range of physiological temperatures, in vitro experiments show neuron discharge rates decrease as temperature

drops, with this decrease becoming more dramatic once temperature drops below physiological temperatures. This phenomenon of temperature-metabolism coupling is used therapeutically in the application of targeted temperature management (TTM), induced hypothermia, and fever avoidance after acute brain injuries to try to limit secondary brain injury. In the context of an ischemic insult, this reduction in metabolism may also be neuroprotective, with multiple published cases of remarkable survival and neurological recovery after accidental severe hypothermia and prolonged circulatory arrest [6].

In the context of death by neurologic criteria, brain temperature falls because of cessation of brain metabolic activity as well and the loss of hemostatic and autoregulatory functions. This drop in temperature has been observed clinically, and the reversal of the normal positive brain temperature-core temperature gradient can occur, reflecting a lack of metabolic activity and cerebral perfusion [7]. One study found that brain and trunk temperature run parallel in time in patients who were unconscious but alive, but dissociated with loss of brain function: core body temperature fell over 6–12 h with a significantly greater decrease in brain temperature—such that the brain was the coldest part of the body, 2–4 °C lower than core body temperature [8].

3 Clinical Implication of Temperature on Determination of Death by Neurologic Criteria

Brain temperature, specifically hypothermia, may influence the determination of death by neurologic criteria in several ways. The key underlying requirement for determination of death by neurologic criteria is that there must be an established neurologic diagnosis with a sufficient severity to lead to the complete and irreversible loss of all brain function, and exclusion of conditions that either confound the clinical evaluation or mimic death by neurologic criteria. Hypothermia may confound determination of death by neurologic criteria either directly (by a reduction in brain metabolism) or indirectly through altered pharmacokinetics of drugs and medications (particularly sedative/hypnotic medications), leading to plasma accumulation and subsequent confounding of the determination.

3.1 Direct Confounding of Determination of Death by Neurologic Criteria by Hypothermia

Although the depression of cerebral metabolism and function by hypothermia is well-established from physiologic experiments and animal studies, there are no data to indicate a threshold temperature that precludes confounding of the clinical determination for death by neurologic criteria. Most of the published literature on the impact of temperature on the neurologic evaluation is in the context of therapeutic

hypothermia or TTM after circulatory-respiratory arrest. It is difficult to draw inferences from these data because the application of therapeutic hypothermia is usually associated with concurrent administration of other sedative medications which may also confound the determination of death by neurologic criteria.

There are some informative neurophysiologic data demonstrating that electroencephalographic silence occurs only at very low temperatures (below 20 °C) [9]. One neurophysiology study of 109 patients with hypothermic circulatory-respiratory arrest during surgery found that the mean core temperature when electroencephalographic silence appeared was 20.6 °C, with the highest nasopharyngeal temperature associated with electroencephalographic silence in their cohort being 27.2 °C. Likewise, the mean core temperatures associated with disappearance of the N20-P22 and N13 complexes on somatosensory evoked potentials were 24.7 °C and 20.1 °C respectively [9]. It should be noted that these patients also received induction of anesthesia with midazolam, fentanyl, and isoflurane, which may have further suppressed cortical function and raised the temperature threshold for electrophysiological silence. Another study found that the cortically generated component of somatosensory evoked potentials (N19) was consistently recordable at core temperatures above 26 °C, and disappeared after decreasing the temperature down to 20 °C [10]. These same authors studied brainstem auditory evoked potentials during induced hypothermia for cardiac surgery and found that the components were present in all patients at temperatures above 23 °C and absent below 20 °C [11].

These indirect data would suggest that decreased brain temperature by itself is unlikely to mimic death by neurologic criteria in the healthy brain except at very low temperatures (less than 30 °C). It is possible, however, that mild to moderate hypothermia sufficiently depresses the function of an injured brain below the threshold for clinical detection. Cognitive dysfunction has been observed with temperature exposure and mild fluctuations in core body temperature [12, 13].

The rate of rewarming from hypothermia is also an important consideration because rapid rewarming can exacerbate supply–demand mismatch and induce metabolic crisis and thus confound the clinical exam by inducing transient ischemic brain dysfunction. Animal and pediatric studies have demonstrated reversible impairment of pressure autoregulation after rewarming [14], and a transient mismatch between cerebral metabolic oxygen demand and supply [15]. One pediatric study of children undergoing cardiac procedures with profound hypothermia found that jugular bulb desaturation during rewarming correlated with rate of temperature rise, with lower saturations and higher arterio-venous saturation extraction associated with rapid warming [16]. The threshold rate of rewarming to avoid these phenomena is not known, and likely is dependent on the underlying brain injury, depth of hypothermia, and hemodynamic parameters. Suggested rates for rewarming after hypothermia or TTM after circulatory-respiratory arrest are often conservative, with rates of 0.15–0.5 °C/h [17, 18]. Care should be taken to warm slowly from moderate and severe hypothermia, or an adequate period of observation has passed to ensure transient energy debt or ischemia from rewarming is not present and confounding the evaluation.

3.2 Impact of Temperature on Drug Pharmacokinetics

Hypothermia has an important effect on the pharmacokinetics of medications which may confound the determination of death by neurologic criteria. Hypothermia may impact all or some of the enteral absorption, distribution, and elimination of medications. The rate of absorption of enteral medications, particularly for drugs reliant on active transport, is delayed and decreased with decreasing temperature. The volume of distribution (Vd) of drugs is affected by both the state of physiology and the physicochemical properties of the drug; hypothermia may increase or decrease Vd through complex and interdependent mechanisms including altered tissue perfusion, depressed organ function and disturbances in acid–base status and drug–protein binding [19]. Finally, drug clearance is the most significantly altered; impairment in renal and hepatic clearance can lead to increases in plasma levels of drug or active metabolites [19]. Studies have found that mild to moderate hypothermia has a significant impact on the pharmacokinetics of cytochrome P450-metabolized drugs with a decrease in systemic clearance between 7–22% for every degree below 37 °C, and an increase in serum concentrations that can persist for days post-rewarming [20, 21]. This was also true for common sedative agents, including midazolam [22]. This delayed clearance has been implicated in cases where there have been "reversible" findings consistent with death by neurologic criteria or a false positive determination of death by neurologic criteria related to confounded clinical examinations [23, 24].

4 Determination of Death by Neurologic Criteria After Therapeutic Hypothermia or Targeted Temperature Management

One particularly challenging situation is the determination of death by neurologic criteria in a patient who appears to have lost all brainstem reflexes following circulatory-respiratory arrest but is being treated with TTM. TTM, usually targeting mild hypothermia, became the standard of care in survivors of circulatory-respiratory arrest following the publication of studies demonstrating improved outcomes in patients who were cooled after out-of-hospital arrest with both shockable [25, 26] and unshockable [27] initial cardiac rhythms. Although subsequent studies have demonstrated the equivalency of targeting mild hypothermia and 36 °C [28, 29], cooling post-arrest remains a common practice. Unfortunately, despite best medical care, mortality following circulatory-respiratory arrest is high and many of these deaths are determined by neurologic criteria. In one study comparing treatment with controlled hypothermia and normothermia, over 10% of all deaths were determined by neurologic criteria, and over 40% of all patients who were rewarmed early at the discretion of their treating physician did so because of suspected death by neurologic criteria [27].

Determination of death by neurologic criteria following circulatory-respiratory arrest and TTM is challenging due to the multiple potential confounders of the evaluation. Firstly, if cooling to moderate hypothermia is administered, brainstem reflexes may be temporarily depressed or absent due to the impact of hypothermia on brain metabolism and function. Secondly, the administration of sedatives and opioids, which may confound the determination for death by neurologic criteria, is common during TTM. Most studies implementing a temperature target of 32 °C administered sedative and opioid infusions in all patients for some period of time [25–29], and many studies also administered sedation to all patients treated with targeted normothermia for some period to prevent or treat shivering [27, 28]. The choice of sedative regimen is also important, as some regimens may shorten the time to awakening in comatose survivors of circulatory-respiratory arrest treated with TTM [30]. Since the abolition of brainstem reflexes has been documented with sedatives [31] and neuromuscular blockade agents [32] respectively, clinicians must exercise caution to ensure that these potential confounders have not accumulated during the period of hypothermia as a result of the temperature-related disturbances in pharmacokinetics and pharmacodynamics. One study found that sedative medications were commonly used in proximity of neurological assessment in comatose survivors of arrest, thus potentially confounding accurate neuroprognostication [33].

5 Existing Guidance on Temperature Considerations for the Clinical Evaluation of Death by Neurologic Criteria

Despite these issues, only 78% of international standards on determination of death by neurologic criteria address temperature considerations [34]. There is considerable variability in the recommend minimum core temperature, ranging from 32 °C to 36 °C, and some standards merely specify that the patient be normothermic, or not be hypothermic. Further, standards do not routinely stipulate that clearance of drugs may be prolonged after hypothermia due to increased accumulation when the core temperature was low. There is no standard waiting period or delay from TTM or rewarming before determination of death by neurologic criteria [35–39]. Although eight standards specifically address determination of death by neurologic criteria after hypothermia, only two clearly indicate how long clinicians should delay the determination in this setting; Australia/New Zealand advise waiting 24 h and Poland advises waiting at least 24 h [34].

The variability across standards is problematic from the point of view of construct validity for the determination of death by neurologic criteria. Standards should be consistent across jurisdictions, so determination of death is the same everywhere.

6 Ancillary Testing and Core Body Temperature

While the clinical evaluation for death by neurologic criteria can be impacted by temperature, there is less concern about this with the use of ancillary testing to provide support for the determination. Most ancillary testing modalities evaluate for

absence of brain circulation. Given the neuroprotective effects of hypothermia, it is necessary to consider the potential impact of temperature, particularly severe hypothermia, on both the diagnostic accuracy of ancillary testing and the assumptions in a patient who is hypothermic.

There are no human studies evaluating the receiver operating characteristics of any modern ancillary testing modalities for the determination of death by neurologic criteria during hypothermia. Cerebral blood flow may fluctuate during hypothermia and rewarming because of metabolic-flow coupling, but there are no reports of temperature-related reversal of absence of brain circulation demonstrated on ancillary testing. There are reassuring data from animal studies that show cerebral blood flow may decrease with hypothermia, but is preserved even at very low temperatures. One study demonstrated persistent brain circulation in the microvasculature of rats during severe hypothermia, even at temperatures below 18 °C [40]. Another study in pigs found that brain circulation decreased with cooling, but persisted despite suppression of metabolic activity even at temperatures as low as 8 °C [41]. These data are helpful because they support the idea that absence of brain circulation cannot be reversibly induced by hypothermia.

7 Our Recommendations on Considerations Pertaining to Temperature Management in the Determination of Death by Neurologic Criteria

Temperature may have a significant impact on the clinical determination of death by neurologic criteria. The effects may be direct through hypothermia related depression of brain metabolism and function, or indirect through the accumulation of confounding drugs from hypothermia-related changes in pharmacokinetics. These effects may also be additive such that mild hypothermia and a sub-therapeutic level of sedative may together effectively abolish clinical responses, so elimination of all possible confounders and restoration of normothermia is recommended. Given the importance and implications of death determination, we recommend a cautious and conservative approach to determination of death by neurologic criteria in the context of accidental hypothermia or recent application of TTM.

Given the potential for the evaluation for coma and absence of brainstem function to be impacted by hypothermia, patients suspected to be dead by neurologic criteria should not be hypothermic at the time of the determination. Firstly, patients with a clinical evaluation suggestive of death by neurologic criteria and a brain injury consistent in extent and severity to cause death should be warmed to normothermia using external warming, fluid warmers, heated ventilator circuits and automated temperature regulation devices as required. In jurisdictions where multiple independent evaluations are required, physicians should be aware that loss of thermoregulation due to loss of brain function may result in significant changes in body temperature between evaluations as patients become poikilothermic and verify the patient's temperature prior to each evaluation. We recommend a minimum body temperature of 36 °C prior to performing the clinical evaluation for determination of death by neurologic criteria. This reflects the aforementioned theoretical

potential for incremental confoundment at lower temperatures, the fact that the risks of warming to normothermia (36 °C) are few, and is consistent with the recent recommendation of the World Brain Death Project [36].

After normothermia has been established, a thorough review of all potentially confounding medications should occur. Caution should be exercised to ensure adequate time for drug clearance prior to clinical evaluation for determination of death by neurologic criteria, given the likelihood of pharmacological confounding from either medication administered during hypothermia or accumulation related to changes in drug pharmacokinetics after cooling. Careful attention should be paid to the timing of administration in relation to the timing and duration of hypothermia. If there is no concern regarding confounding of the clinical exam, determination of death by neurologic criteria can proceed as per accepted standards. If any confounding medications have been administered, the clinician has two options: delay the determination to allow clearance of accumulated drugs, or perform the clinical evaluation and an ancillary study to evaluate for absence of brain circulation. It is extremely difficult to estimate the required delay to ensure elimination of accumulated drug during hypothermia, due to the complex and competing changes in pharmacokinetics related to temperature for different drugs. Indeed, this issue has come into play in high-profile published cases of reversible or false positive determinations of death by neurologic criteria [23, 24]. Accordingly, we recommend extreme caution and a conservative approach in this regard, with prolonged delay of the determination when possible and use of ancillary testing to support the clinical evaluation when necessary.

8 Conclusion

In summary, variations in temperature outside of the normal range, particularly hypothermia, have important effects on brain function, metabolism, and physiology and may confound the determination of death by neurologic criteria. This effect may be exacerbated by loss of thermoregulation when brain function is lost leading to poikilothermia and a decrease in core temperature in response to ambient heat loss. Careful attention to restoration of normal core body temperature and to the accumulation and clearance of potentially confounding medications are required to ensure that determination of death by neurologic criteria is accurate. Special attention is warranted in patients who are treated with therapeutic hypothermia due to the ubiquitous administration of confounding medications and the potential for their delayed clearance. Finally, if there is concern that pharmacological confounders cannot be excluded after hypothermia, ancillary testing should be performed to support the clinical evaluation for determination of death by neurologic criteria.

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