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LESSONS FROM HISTORY

Induced Hypothermia to 4.2°C with Neurologically Intact Survival: A Forgotten Case Series

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The lowest recorded core temperature from which a person with accidental hypothermia has survived neurologically intact is 11.8°C in a 2-y-old boy. The lowest recorded temperature from which an adult has been resuscitated neurologically intact is 13.7°C in a 29-y-old woman. The lowest core temperature with survival from induced hypothermia has been quoted as 9°C. We discovered a case series (n=50) from 1961 in which 5 patients with core temperatures below 11.8°C survived neurologically intact. The lowest core temperature in this group was 4.2°C. The authors also presented cardiovascular and other physiologic data at various core temperatures. The patients in the case series showed a wide variation in individual physiological responses to hypothermia. It is not known whether survival from accidental hypothermia is possible with a core temperature below 11.8°C, but this case series suggests that the lower limit for successful resuscitation may be far lower. We advise against using core temperature alone to decide whether a hypothermic patient in cardiac arrest has a chance of survival.

Keywords: cardiopulmonary bypass, cardiac arrest, resuscitation, rewarming

Introduction

The lowest published core temperature from which a person with accidental hypothermia has been resuscitated with neurologically intact survival is 11.8°C in a 2-y-old boy who sustained an unwitnessed asystolic cardiac arrest.[1] He underwent cardiopulmonary resuscitation for 135 min before he was rewarmed with extracorporeal membrane oxygenation. The lowest published core temperature from which an adult has been resuscitated is 13.7°C.[2] The patient was a 29-y-old woman who fell into an ice-covered stream while ski touring. She made a full recovery and was neurocognitively intact after rewarming, although she took many years to recover from severe peripheral sensorimotor polyneuropathy.

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The lowest core temperature with neurologically intact survival from induced hypothermia has been widely quoted as 9°C.[3] The patient was a 51-y-old woman with terminal ovarian cancer who was cooled in an effort to treat the tumor. No surgical procedure was performed. She made a full recovery from cooling, but died 38 d later from complications of the malignancy. There was no evidence that hypothermia had an effect on the tumor.

There is a difference of several degrees between the lowest core temperature with survival in accidental and induced hypothermia. Induced hypothermia is not the same as accidental hypothermia. One difference is that cooling in accidental hypothermia proceeds from the body surface inward (centripetal), whereas induced hypothermia is produced by core cooling that spreads to the periphery (centrifugal). We do not know how this difference affects the chance of survival. It is not known whether survival in accidental hypothermia is possible at temperatures as low as those in induced hypothermia. Another difference is the duration of cold exposure. In accidental hypothermia, the

Table 1. Patients cooled with induced hypothermia below 11.8°C, the current lowest published core temperature in accidental hypothermia with neurologically intact survival[4]

Patient no.	*Age*	*Lowest temperature, °C*	*Results*
1	5 y	10.3	Satisfactory
2	11 y	11.0	Satisfactory
3	15 y	10.2	Satisfactory
4	2 mo	7.0	Died on table; cardiac failure
5	8 y	10.0	Satisfactory
6	4 y	9.5	Died on table; cardiac failure
7	39 y	4.2	Uneventful recovery. Gradual deterioration due to recurrence of brain tumor.
8	46 y	9.0	Did not awaken. Died 4 mo postoperatively.
9	52 y	6.0	Died on table. Impossible to control bleeding from vascular anomalies.

exposure to low ambient temperatures is much longer than with direct cooling of blood for surgery.

We have discovered a published, but forgotten, case series in which 1 patient survived neurologically intact after induced hypothermia with a core temperature of 4.2°C. This case was reported in 1961 in the paper "Physiologic reactions during profound hypothermia with cardioplegia," published in *Anesthesiology*.[4] The authors reported 50 cases in which patients were "subjected to profound hypothermia." There were 47 patients who underwent cardiovascular surgery for conditions such as tetralogy of Fallot and defects of the cardiac septum. Of the 47 patients who underwent cardiovascular surgery, 34 were 14 y of age or younger. Twenty-seven had satisfactory results. The remaining 3 patients were adults who underwent operations on the brain.

Nine patients were cooled to core temperatures below 11.8°C, the current lowest published core temperature with neurologically intact survival in accidental hypothermia (Table 1). Five of these patients had satisfactory results; the other 4 died during the operation or did not awaken. The patient with the lowest core temperature of 4.2°C died 4 months postoperatively of recurrence of brain tumors after an initial uneventful recovery. Six of the 9 patients underwent cardiovascular surgery (patients 1–6 in Table 1). Of these 6 patients, 5 were younger than 14 y. Two died of cardiac failure during surgery. The remaining 3 (patients 7–9 in Table 1) of the 9 patients underwent brain surgery. All were adults, and 2 died.

The authors presented data regarding heart rate at various temperatures and the threshold temperatures for ventricular fibrillation (VF) and other physiological effects. They also discussed the methods of measuring core temperature.

Case Report

A 39-y-old patient (patient 48 in the original case series; patient 7 in Table 1) underwent subtotal removal of a brain metastasis from a carcinoma of the lung. The patient was cooled using extracorporeal circulation and a heat exchanger.[5] The lungs were hyperventilated during the operation. The patient made an "uneventful recovery" after being rewarmed from a core temperature of 4.2°C, measured in the midesophagus.[4]

PHYSIOLOGIC OBSERVATIONS

The paper reported investigations at Duke University Medical Center in Durham, North Carolina. The rationale for inducing profound hypothermia, which the authors defined as below 22°C, was to reduce tissue metabolism to "near zero" to be able to reduce perfusion to a very low level or to stop it completely. Cardioplegia was induced by hypothermia. The authors developed a heat exchanger that could reduce esophageal temperature by $1°C \cdot min^{-1}$.[5] Esophageal and rectal temperatures, electroencephalogram (EEG), electrocardiogram, and arterial blood pressures were continuously monitored. The authors cautioned that physiologic reactions caused by profound hypothermia may have been modified by anesthesia, by effects of the operation, and by factors associated with extracorporeal circulation.

RESPIRATORY EFFECTS

Because ventilation was controlled, there were no data regarding respiratory activity. However, the authors reported that 2 patients with accidental hypothermia had presented to their hospital, 1 with a rectal temperature of 24°C who had regular shallow respirations at 6 $breaths \cdot min^{-1}$ and another with a rectal temperature of 21.6°C and a respiratory rate of 9 $breaths \cdot min^{-1}$.[4]

CARDIOVASCULAR EFFECT

With rapid induction of hypothermia, heart rate slowed progressively with cooling. VF occurred between 31 and 16.3°C (mean 25.1°C) in 13 patients who were not cooled enough to cause asystole and between 29 and 18°C (mean 23.2°C) in 16 patients who went on to have asystole.

Asystole occurred between 27 and 10.8°C (mean 18.5°C) in the 16 patients who were in VF and between 27 and 13°C (mean 18.6°C) in 8 patients who developed asystole without having had VF.

During rewarming, effective cardiac activity resumed spontaneously without VF in 10 patients between 17 and 30°C (mean 23.1°C). In 8 patients in whom effective cardiac activity resumed spontaneously after a period of VF, VF began between 13.9 and 24.5°C (mean 17.3°C) and effective cardiac activity resumed between 18.8 and 28.9°C (mean 25.1°C). In 19 patients, electrical defibrillation was necessary to restore a perfusing rhythm. In these patients, VF occurred between 13.9 and 28°C (mean 20.8°C) in 14 patients with a known temperature at which VF occurred. In all 19 patients who required defibrillation, effective cardiac activity was restored between 14.5 and 33°C (mean 28.8°C). Defibrillation was most easily accomplished at esophageal temperatures above 29°C.

CENTRAL NERVOUS SYSTEM EFFECTS

Observations of central nervous system (CNS) effects in patients with induced hypothermia were limited to electroencephalography because the patients were anesthetized. Below 32°C, maintenance of anesthesia required "minimal concentrations of anesthetic drugs."[4] The EEG was minimally affected during cooling until the esophageal temperature reached the low 20s. Electroencephalographic activity ceased, as indicated by flattening of the EEG, between 20 and 14°C.

SITES OF TEMPERATURE MEASUREMENT AND TEMPERATURE GRADIENTS

Rapid core cooling by extracorporeal circulation caused large temperature gradients among different parts of the body. There were different patterns, depending on the cannulation sites. The authors stated, "Rectal temperature measurements, in general, are unreliable."[4] They concluded that esophageal temperatures were the most accurate, although they were not identical to the temperatures of the brain and the heart.

COMPLICATIONS

Of the 50 patients who underwent surgery using profound hypothermia (<21.3°C) with cardioplegia, 27 recovered. Of the 23 who died, 3 patients initially recovered but died within months, most likely from their primary conditions. Seven patients died during their operations; 5 patients never recovered consciousness and subsequently died, and 7 patients woke after their operations but died within 17 d. One patient, whose state of consciousness was not reported, died 16 d after operation. Of the 30 patients who woke and did not die within 17 d of the operation, no evidence of cerebral injury was reported.

Discussion

The discovery of a case series describing uneventful recovery from induced hypothermia with very low core temperature as low as 4.2°C raises the question of the limits of human survival from hypothermia.[4] The study has far more value than just the case report of the patient who survived neurologically intact from a core temperature of 4.2°C. The study also contains careful observations of physiology in profoundly hypothermic patients, including cardiovascular effects, CNS effects, and the core temperatures necessary to produce asystole. There are also observations concerning induction of and recovery from VF with cooling and rewarming, including temperatures at which defibrillation was successful.[4]

We are now aware of 6 cases of neurologically intact survival from core temperatures below 11.8°C after induced hypothermia, 5 from this case series[3] and 1 case of survival from a core temperature of 9°C.[3] For almost 2 decades, the lowest published core temperature with survival in accidental hypothermia was 13.7°C.[2] There were also published cases of full recovery from a core temperature of 13.8°C after submersion in a 7-y-old girl[6] and from 14.2°C in a 31-mo-old girl after cold exposure.[7]

LIMITATIONS

Pulmonary artery temperature is considered to be the "gold standard" for measurement of core temperature. Esophageal temperature generally provides the best approximation for the temperature of the heart as measured by pulmonary artery temperature.[8] In some special circumstances, such as abdominal surgery without induced hypothermia, bladder temperature may provide a closer approximation of pulmonary artery temperature than esophageal temperature.[9] As observed in the case series, there are spatial variations in temperature that depend on the site at which cooling takes place.[4] A more recent study investigated temporal and spatial dispersion of body temperature during deep hypothermia in patients undergoing heart valve replacement. This study was complicated by the use of ice packs around the head to cool the brain in addition to cooling using cardiopulmonary bypass.[10] The authors concluded that temperatures should be measured as close as possible to "the site of interest." We will never know the brain temperatures of these patients with profound hypothermia.

In addition to uncertainty regarding the accuracy of esophageal temperature measurements, there are other potential problems in using data from induced hypothermia as a proxy for accidental hypothermia. The effects of anesthesia in profound hypothermia on the cardiovascular system and on the CNS are unknown.

We also do not know the time course of core temperatures in the reported cases. It is likely that longer durations of cooling have more pronounced physiologic effects.

Another limitation of the study is the lack of formal assessment of neurologic outcomes. Without the results of neurocognitive testing, we have assumed that the patients who made a satisfactory or uneventful recovery were reasonably neurologically intact.

One characteristic of human physiology that stands out in a wide range of studies is extreme individual variability in response to various stimuli, including cooling and rewarming. The data in this case series are consistent with this principle. There was wide variability in the temperatures at which VF occurred during cooling and rewarming and at which asystole was induced. Whether VF occurred during cooling and rewarming and whether VF resolved spontaneously or required defibrillation during rewarming were also variable among individuals. These findings emphasize that no one should be considered dead until warm and dead.

Conclusions

Neurologically intact survival from a core temperature of 4.2°C has been reported in induced hypothermia. In addition to the well-known case of induced hypothermia to 9°C, there are now 5 additional cases of survival from core temperatures in induced hypothermia below 11.8°C, which is the lowest reported core temperature with survival in accidental hypothermia. There is wide variation in individual physiologic responses to hypothermia. It is not known whether survival from accidental hypothermia is possible with a core temperature below 11.8°C, but this case series suggests that the lower limit for successful resuscitation may be far lower. We advise against using core temperature to decide whether a hypothermic patient in cardiac arrest has a chance of survival.

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