Cerebral protection: Antegrade cerebral perfusion in the modern era. Does temperature matter?

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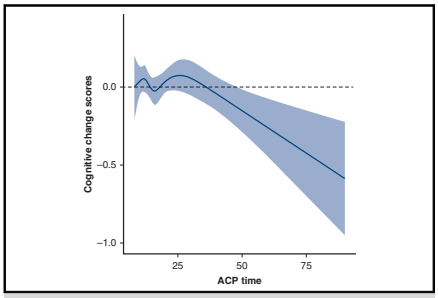
Despite the growth of endovascular approaches,[1] open replacement remains the most common technique for repairing the aortic arch.[2] The primary challenge of open aortic arch surgery is the requirement for hypothermic circulatory arrest (HCA) to provide a bloodless field, but which also places tissue beds at risk for ischemic insult. Although all end organs are at risk for ischemia during HCA, the brain is particularly at risk due to its high metabolic demand and reliance on aerobic energy production.[3] For this reason, neuroprotection is of paramount concern when performing aortic arch surgery and, in the modern era, most commonly relies on the technique of antegrade cerebral perfusion (ACP) to provide continued regional flow to the brain during the period of HCA.[4-6]



Global cognitive decline occurs after 35 minutes of HCA + ACP with domain-specific deficits even earlier.

CENTRAL MESSAGE

The optimal temperature for HCA is unclear. Available RCT data suggest noninferiority of low-moderate versus deep hypothermia for preservation of global cognitive function, but further work is needed.

OPTIMAL TEMPERATURE FOR HCA REMAINS UNCLEAR

Although the use of ACP has emerged as the predominant neuroprotective adjunct worldwide during HCA,[4-6] the optimal temperature for HCA has remained unclear.[7] During systemic cooling, concomitant reduction in brain temperature results in progressive slowing of cerebral electrical activity by electroencephalography (EEG) (Table 1) until electrocerebral inactivity (ECI) is reached, and ECI represents the point of maximal suppression of the cerebral metabolic rate of oxygen consumption.[8] However, data from our institution in 396 patients undergoing thoracic aortic operation with HCA found that cooling to a nasopharyngeal (NP) temperature of 12.7 °C was required to achieve ECI in >95% of patients (Figure 1),[8] a temperature well below that utilized even in centers routinely employing deep (<20.0 °C) hypothermia.[2] In addition, data from another study from our institution examining EEG findings in patients undergoing hemiarch replacement with moderate HCA (median NP temperature 25.7 °C at onset of HCA) found that 66% of patients still demonstrated a continuous EEG pattern at this temperature, with only 34% demonstrating evidence for partial cerebral metabolic suppression in the form of a burst suppression pattern, and no patients reaching ECI at these warmer temperatures. Furthermore, 45% of patients demonstrated a transient, abrupt loss of electrocerebral activity after onset of HCA and before institution of ACP suggestive of transient cerebral ischemia (Figure E1).[9] As such, these data suggest that the systemic, and therefore brain, temperature at the onset of HCA may have important implications for neurologic outcomes following aortic arch surgery with HCA.

EVIDENCE BASE GUIDING BEST PRACTICES FOR HCA

Despite this supposition, until recently there existed only retrospective, nonrandomized data comparing outcomes for deep versus moderate hypothermia strategies during arch surgery with HCA.[7] Furthermore, these prior studies generally reported only short-term clinical outcomes, such as

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TABLE 1. Electroencephalography changes during cooling and rewarming[3]

Nasopharyngeal temperature (°C)	Duration (min)	Changes in electroencephalography
Cooling		
>29.6 ± 3		Continuous
29.6 ± 3	7.9 ± 3	Lateralized and generalized periodic discharges
24.4 ± 4	12.7 ± 6	Burst suppression
17.8 ± 4	27.5 ± 10	Electrocerebral inactivity
Rewarming		
<21.2 ± 5		Electrocerebral inactivity
21.2 ± 5	19.0 ± 9	Burst suppression
30.1 ± 5	47.1 ± 26	Continuous

Values are presented as mean ± SD.

mortality or stroke, as comparator variables[10] and have not utilized higher-level evidence, including brain imaging and comprehensive neurocognitive assessments, which are more sensitive indicators of neurologic injury[11] and postoperative cognitive dysfunction.[12] However, with the recent publication of the CoGnitive Effects Of Body Temperature During HypothermIc Circulatory ArrEst (GOT ICE) multicenter, prospective, randomized, controlled trial of patients undergoing aortic arch surgery comparing deep versus moderate systemic HCA strategies utilizing comprehensive end points, including clinical outcomes, neurocognitive function, and anatomic and functional imaging data,[13] higher quality evidence is now available to help guide best practices with regards to arch surgery.

The trial randomized adult patients undergoing elective aortic arch surgery (hemiarch and total arch) via median sternotomy with HCA and ACP to 1 of 3 treatment groups: deep (Group DP) (≤20.0 °C), low-moderate (Group LM): (20.1-24.0 °C), and high-moderate (Group HM): (24.1-28.0 °C), all in conjunction with cold unilateral ACP (ACP target flow rate 5-15 cc/kg/minute with an inflow temperature 12-14 °C to a target right radial arterial line pressure of 50-70 mm Hg). These ACP parameters were based upon prior work in the early 2000s demonstrating that cold (10-15 °C) temperatures were superior to warmer (20-25 °C) temperatures[14] and that perfusion pressures of 50 to 70 mm Hg were superior to 90 mm Hg[15] with regard to neurological function. Temperature was monitored at the NP and bladder with NP temperatures at onset of HCA utilized for treatment group assignments in accordance with prior consensus guidelines recommending NP temperature as the preferred site for core temperature measurement during cardiopulmonary bypass.[16] The temperature ranges in the trial were in accordance with the previously described hypothermia categories utilized in a large comparative effectiveness analysis from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database[2] and which have now been adopted as a consensus hypothermia classification in the 2023 European Association for Cardio-Thoracic Surgery (EACTS)/STS Aortic Disease Clinical Practice Guidelines[17] (Figure E2).

HCA TEMPERATURE AND COGNITIVE OUTCOMES

The primary outcome of the GOT ICE trial was the change in global cognitive index (⊿GCI) from preoperative baseline to 4 weeks postsurgery, comparing DP to LM and HM hypothermia. The GCI represents the mean of 5

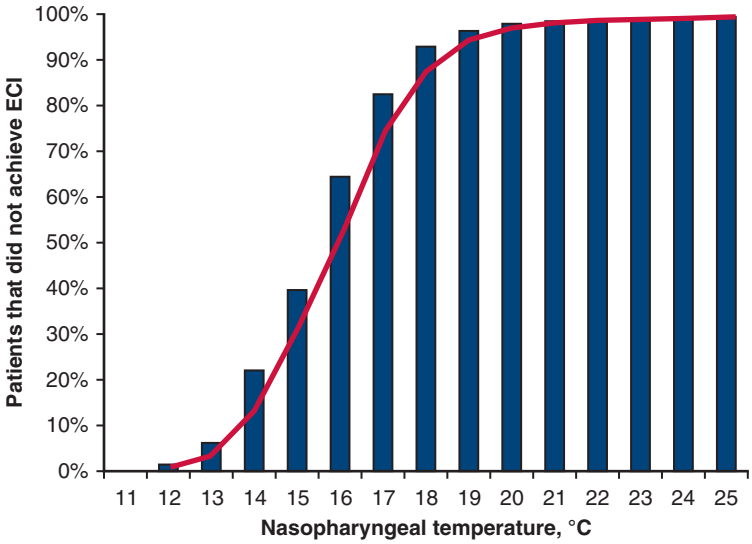

FIGURE 1. Nasopharyngeal (*NP*) temperature required to achieve electrocerebral inactivity (*ECI*) in a study of 396 patients undergoing thoracic aortic operation with hypothermic circulatory arrest found that cooling to a NP temperature of 12.7 °C was required to achieve ECI in >95% of patients. Reproduced with permission from reference.[8]

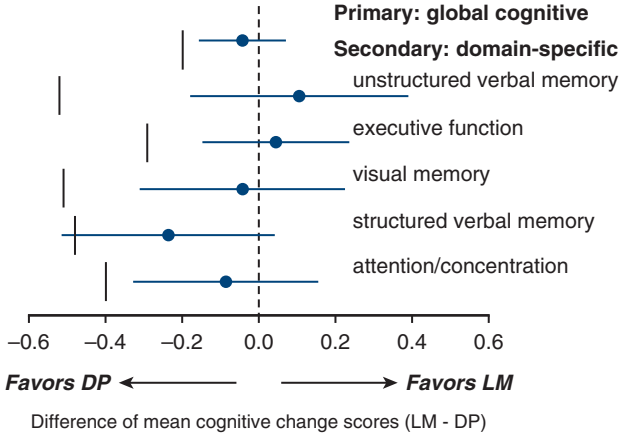

FIGURE 2. Comparison of global cognitive index and domain-specific cognitive change scores from preoperative baseline to 4-weeks postsurgery for deep (*DP*) versus low-moderate (*LM*) hypothermia groups in the Cognitive Effects of Body Temperature During Hypothermic Circulatory Arrest trial. There was no significant difference in global cognitive function, although structured verbal memory was significantly better preserved in the DP group. The *blue vertical lines* indicate the noninferiority margin. Similar findings were seen when comparing DP versus high-moderate hypothermia (reproduced with permission from reference[13]).

cognitive domain factor scores (structured verbal memory, executive function, visual memory, unstructured verbal memory, and attention-concentration), which were derived from a battery of 14 cognitive tests administered at baseline and 4 weeks postsurgery in accordance with the consensus statement on assessment of neurobehavioral outcomes after cardiac surgery.[18] A negative ΔGCI indicates cognitive decline, whereas a positive ΔGCI indicates cognitive improvement. Although ΔGCI was numerically highest in the DP group and lowest in the HM group, the differences were not statistically significant. However, when the domain-specific cognitive change scores were analyzed individually, structured verbal memory was statistically significantly better preserved in the DP group compared with the LM or DP groups (Figure 2).[13]

With regard to structural and functional magnetic resonance imaging data, no significant between-group differences were seen in changes in intracranial volumes, cortical thickness, or resting-state functional connectivity (RSFC) from presurgical baseline to 4 weeks postoperatively. However, when data from all 3 hypothermia groups were combined, patients undergoing HCA, regardless of temperature, demonstrated a significant reduction in cerebral gray matter volume, cortical thickness, and regional brain RSFC at 4 weeks postoperatively. Furthermore, cortical thickness loss in the right prostriate/posterior cingulate gyrus was significantly associated with a postoperative reduction in the structured verbal memory cognitive domain (Figure 3, *A* and *B*), whereas RSFC reduction between the posterior cingulate and left and right middle and superior frontal gyrus regions were significantly associated with a postoperative reduction in the attention-concentration cognitive domain[13] (Figure 3, *C* and *D*).

HCA TEMPERATURE AND SYSTEMIC OUTCOMES

Previous data from retrospective, nonrandomized studies have suggested increased rates of surgical mortality, renal dysfunction, coagulopathy and bleeding, and decreased patient-reported quality of life with the use of deep versus moderate hypothermia.[2,6,19] However, in the GOT ICE trial, no differences were observed in any major clinical outcome, including similar rates of mortality, stroke, prolonged ventilation, and renal failure, as well as a battery of 10 different quality of life scores, between the 3 hypothermia groups.[13]

The lack of difference in renal failure rates merits further discussion given that the recent EACTS/STS clinical practice guidelines[17] suggest that the use of NP temperature, as recommended in the aforementioned 2013 consensus document on the topic[16] and utilized in the GOT ICE trial,[13] may not adequately reflect core temperature. However, the GOT ICE findings are consistent with results from a prior study from our institution[20] examining the association between HCA temperature and postoperative acute kidney injury (AKI) in 759 patients undergoing proximal aortic surgery with HCA and analyzing AKI rates using both minimum NP and bladder temperatures. The study found the incidence of AKI did not differ between hypothermia groups, classified using the same temperature groupings as in the GOT ICE trial, whether analyzed using minimum NP or bladder temperature (Figure E3) and suggesting that moderate HCA does not confer an increased risk of renal injury.[20]

Finally, patients in the GOT ICE trial randomized to deep hypothermia did have a statistically significantly higher volume of blood products transfused than those in the LM or HM groups, although this did not translate into a higher rate of re-exploration for bleeding, prolonged ventilation, or postoperative infection.[13] These findings are likewise similar to a prior propensity score-matched study of 571 patients undergoing hemiarch replacement at our institution with either deep or moderate hypothermia, which found slightly increased perioperative blood loss and plasma transfusion requirement in the DP group, but no difference in rates of reoperation for bleeding or postoperative mortality or major morbidity.[21] As such, it is likely that deep hypothermia leads to a slight increase in perioperative coagulopathy rates, although the difference appears to be small and likely not clinically significant.

IS THERE A SAFE DURATION OF HCA?

It has long been held that the safe duration of HCA for the brain is at least 25 to 30 minutes at deep hypothermia and likely longer with the use of adjunctive ACP.[7] However, this claim is based primarily on clinical outcomes research

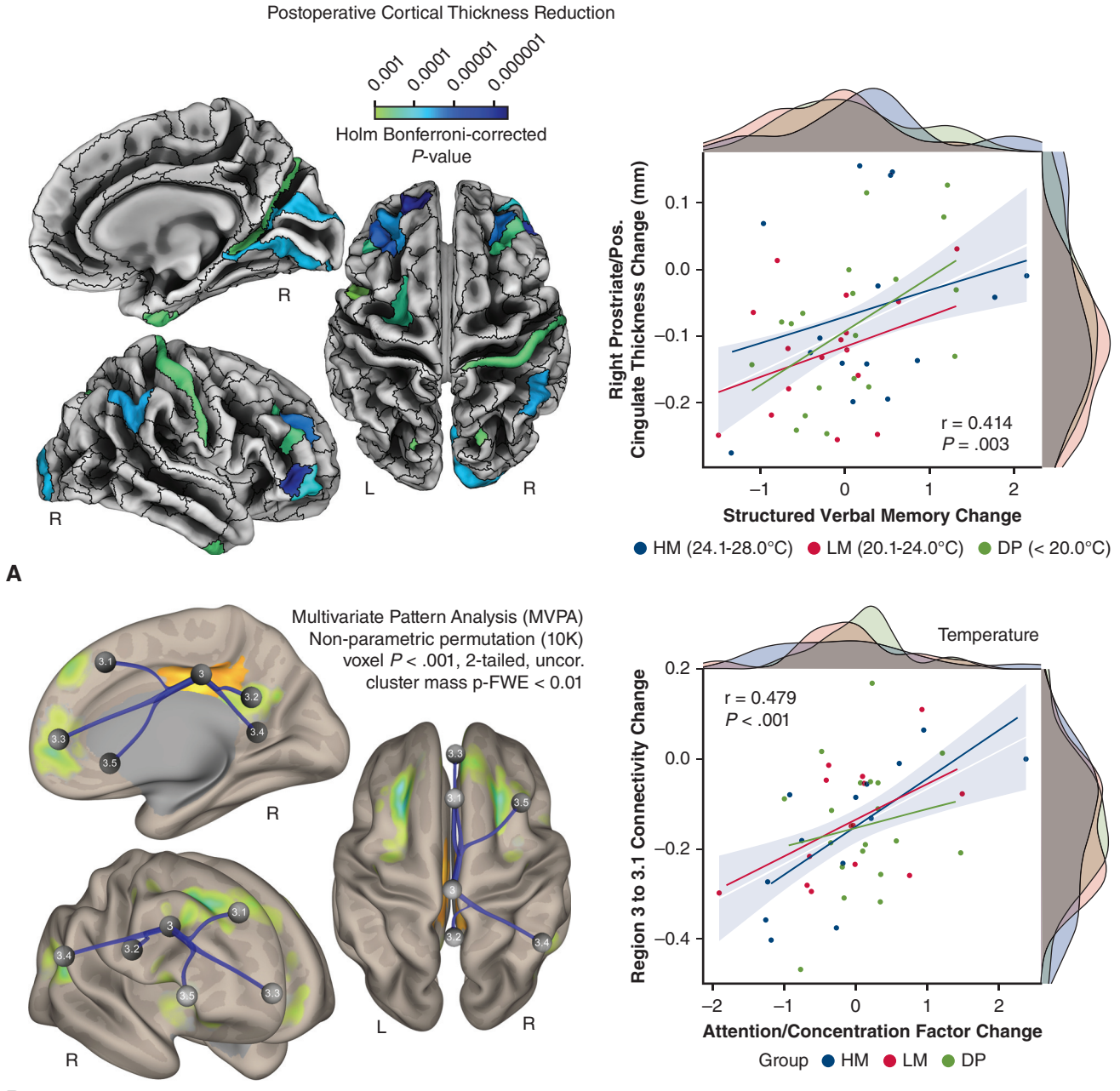

FIGURE 3. Postoperative cortical thickness and functional connectivity magnetic resonance imaging findings and their cognitive change associations. A, Brain regions demonstrating significant postoperative cortical thickness reduction in all hypothermic circulatory arrest (*HCA*) groups combined. B, Postoperative cortical thickness loss in the right prostriate/posterior cingulate gyrus was significantly associated with a postoperative reduction in the structed verbal memory cognitive domain. C, Default mode network-associated brain regions demonstrating significant postoperative reduction in resting-state functional connectivity (*RSFC*) in all HCA groups combined. D, RSFC reduction between the posterior cingulate and left and right middle and superior frontal gyrus regions were significantly associated with a postoperative reduction in the attention-concentration cognitive domain (reproduced with permission from reference[13]).

and has not been systematically investigated using more sensitive brain imaging and neurocognitive assessments as were utilized in the GOT ICE trial.[13] When analyzed in terms of global cognitive function, as was assessed by the primary outcome of the GOT ICE trial, namely the ΔGCI from baseline to 4 weeks postsurgery, previously unpublished data from the trial demonstrates cognitive change score to remain relatively unchanged until ACP time exceeds 35 minutes (Figure 4). However, when analyzed using a domain-specific indicator of cognitive

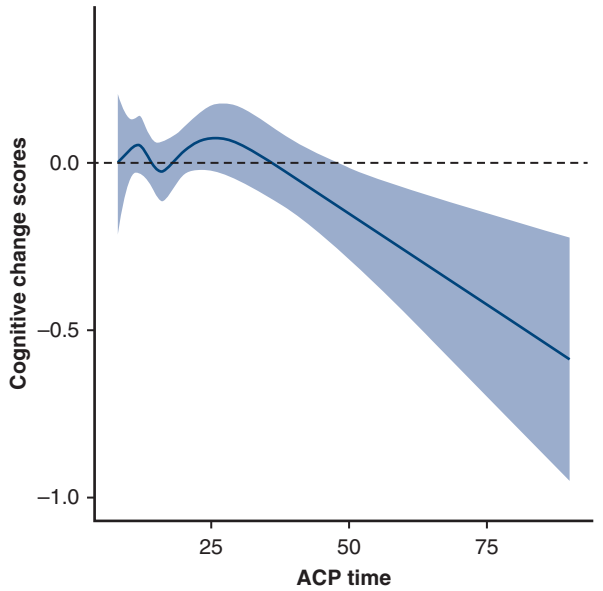

FIGURE 4. Decline in global cognition, as assessed by change in global cognitive index, with increasing antegrade cerebral perfusion (*ACP*) time. Shaded area represents 95% CI. The threshold for global cognitive decline was approximately 35 minutes of ACP.

decline, namely the dichotomous cognitive deficit, which is defined as a factor score decline by ≥1 SD in at least 1 of the 5 cognitive domains making up the *Δ*GCI, recently presented data from a substudy of the GOT ICE trial[22] demonstrates evidence for cognitive decline in ∼40% of patients, independent of systemic hypothermia temperature, following even short (<20 minutes) periods of HCA. Further, HCA duration was inversely associated with frontal lobe functional magnetic resonance imaging connectivity, suggesting this brain region may be preferentially sensitive to HCA. As such, surgeons should be aware that even short durations of HCA may not provide complete neuroprotection following aortic arch surgery.

CONCLUSIONS

The recently published EACTS/STS clinical practice guidelines[17] recommend the use of ACP along with high-moderate (24.1-28.0 °C) hypothermia for HCA during arch replacement, whereas the 2022 American College of Cardiology/American Heart Association guidelines do not make a recommendation, citing a lack of definitive evidence supporting 1 technique over another.[23] Our current practice, based on the results of the GOT ICE trial showing noninferiority for low-moderate (20.1-24.0 °C) versus deep (≤20.0 °C) hypothermia with regard to global cognitive and clinical outcomes, is to use low-moderate hypothermia for hemiarch repair and either deep or low-moderate hypothermia for total arch repair depending on the anticipated complexity of the arch portion of the case as well as the need for concomitant proximal (eg, root or valve) procedures; we continue to use NP temperature to guide cooling in accordance with the 2013 consensus guidelines[16] and have had excellent outcomes in both the primary[8,9,20,21,24] and redo[25] settings with this approach. Regardless, the better preservation of the structured verbal memory domain of cognitive function with deep hypothermia[13] merits further investigation. Further, the need for HCA in any particular case should be carefully considered given the observed detrimental effects of HCA, regardless of temperature, on brain volumes and function,[13] as well as the fact that even short durations of HCA may not provide complete neuroprotection.[22] Finally, more investigation is needed to better understand the mechanisms underlying these observed adverse effects of HCA on cognition and brain function to further continued improvements in the safety of aortic arch surgery.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: aortic arch surgery, hypothermic circulatory arrest, temperature, cerebral protection, outcomes, cognition

FIGURE E1. Example of electroencephalography (*EEG*) activity before and after onset of hypothermic circulatory arrest (*HCA*) with the establishment of antegrade cerebral perfusion (*ACP*) at high-moderate hypothermia. A, EEG immediately before HCA (nasopharyngeal temperature 26.6 °C) shows a burst suppression pattern. B, EEG immediately after HCA onset demonstrates abrupt loss of electrocerebral activity. C, EEG after ACP begun shows return of burst suppression pattern (reproduced with permission from reference[9]).

TABLE 6 Writing Committee 2023 Consensus on Hypothermia Classification in Aortic Surgery

Category	Core Temperature (Rectal/Bladder)
Deep hypothermia	≤20°C
Low-moderate hypothermia	20.1-24°C
High-moderate hypothermia	24.1-28°C
Mild hypothermia	>28°C

FIGURE E2. European Association for Cardio-Thoracic Surgery/Society of Thoracic Surgeons 2023 Consensus on Hypothermia Classification in Aortic Surgery (reproduced with permission from reference[17]) based on original description by Englum and colleagues[2] in 2017.

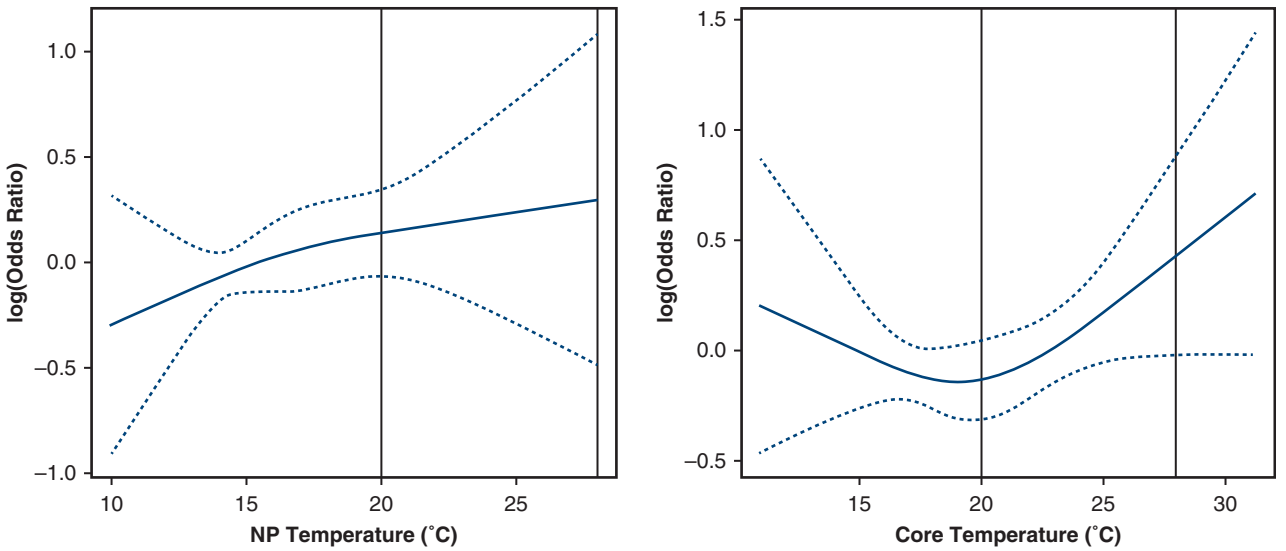

FIGURE E3. Odds ratio of acute kidney injury (*AKI*) by lowest nasopharyngeal (*left*) or bladder (*right*) temperature. There was no significant association between AKI rates and lowest intraoperative temperature, regardless of site of measurement. Reproduced with permission from reference.[20]