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ORIGINAL WORK

Minimizing Shivering During Targeted Normothermia: Comparison Between Novel Transnasal and Surface Temperature-Modulating Devices

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Abstract

Background: Shivering is a common adverse effect of achieving and maintaining normothermia in neurocritical care patients. We compared the burden of shivering and shivering-related interventions between a novel transnasal temperature-modulating device (tnTMD) and surface cooling temperature-modulating devices (sTMDs) during the first 24 h of targeted normothermia in mechanically ventilated febrile neurocritical care patients.

Methods: This is a case–control study controlling for factors that impact shiver burden: age, sex, body surface area. All patients underwent transnasal cooling (CoolStat, KeyTech, Inc.) as part of an ongoing multicenter clinical trial (NCT03360656). Patients undergoing treatment with sTMDs were selected from consecutively treated patients during the same time period. Data collected included the following: core body temperature (every 2 h), bedside shivering assessment scale (BSAS) score (every 2 h), and administration of antishivering medication for a BSAS score > 1. Time to normothermia (≤ 37.5 °C), as well as temperature burden > 37.5 °C (°C × h), were compared between groups using Student's *t*-test for mean differences. The proportion of patients requiring interventions, as well as the number of interventions per patient, was compared using the χ^2 test. Significance was determined based on a p value < 0.05.

Results: There were 10 tnTMD patients and 30 sTMD patients included in the analysis (mean age: 62 ± 4, 30% women, body surface area = 1.97 ± 0.25). There were no differences between groups in temperature at cooling initiation (tnTMD: 38.5 ± 0.2 °C vs. sTMD: 38.7 ± 0.5 °C, $p = 0.3$), time to ≤ 37.5 °C (tnTMD: 1.8 ± 1.5 h vs. sTMD: 2.9 ± 1.4 h, $p = 0.1$), or temperature burden > 37.5 (tnTMD: − 0.4 ± 1.13 °C × h vs. sTMD median [IQR]: − 0.57 ± 0.58 °C × h, $p = 0.67$). The number of tnTMD patients who received pharmacologic shivering interventions was lower than the number of controls (20 vs. 67%, $p = 0.01$). tnTMD patients also had fewer shivering interventions per patient (0 [range: 0–3] vs. 4 [range: 0–23], $p < 0.001$).

Conclusions: A transnasal cooling approach achieved similar time to normothermia and temperature burden with less shivering than surface cooling. This approach may be a feasible option to consider for mechanically ventilated febrile neurocritical care patients.

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Introduction

Given the evidence supporting the detrimental impact of fever on recovery from brain injury [1], targeted temperature management (TTM) with temperature-modulating devices has been widely adopted in clinical practice to achieve and maintain normothermia. Currently temperature-modulating devices achieve temperature control via conductive heat transfer with either surface, intravascular, or esophageal cooling [2–4]. However, all of these methods are associated with significant burden of shivering, which is associated with increases in systemic oxygen consumption [5, 6] and decline in brain tissue oxygenation [7]. To reduce shivering, pharmacological agents can be used; however, these can also negatively impact a patient's hospital course through prolonged mechanical ventilation, worsening neurological examination, and prolonged neurocritical care unit (NCCU) stay [8].

The CoolStat transnasal temperature-modulating device (tnTMD) is an investigational device that uses high-flow room temperature air delivered through the nose using a nasal mask to achieve normothermia via evaporative cooling. In a previous study, this tnTMD was shown to effectively induce normothermia in a cohort of intubated neurocritical care patients [9]. Interestingly, the associated burden of shivering and related sedation was minimal. However, the duration of normothermia was brief (8 h). We sought to investigate the cooling efficacy, impact on shiver burden, and pharmacological interventions for shivering using the tnTMD during the first 24-h period of induction and maintenance of normothermia as compared to traditional surface cooling temperature-modulating devices (sTMDs). We hypothesized that the tnTMD would effectively achieve and maintain normothermia with less shivering and fewer shivering interventions.

Methods

Case Selection

All case patients were selected from consecutive patients enrolled in a prospective multicenter clinical trial (NCT03360656). Adult patients admitted to the NCCU for subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), acute ischemic stroke, or seizures who experienced refractory fever (temperature $\geq$ 38.3 °C and remained $\geq$ 38.3 °C for 2 h after administration of acetaminophen) were prospectively identified between August 2019 and December 2021 to receive the tnTMD. Other inclusion criteria were intubation (endotracheal or tracheostomy with mechanical ventilation), planned stay in the NCCU > 24 h, and informed consent obtained from a legally authorized representative. Exclusion criteria included the following: (1) age < 18 or > 95, (2) intubation contraindicated, (3) coagulopathy (International Normalized Ratio (INR) > 1.5 or Partial Thomboplastin Time (PTT) > 45 s), (4) hemodynamic instability, (5) body mass index (BMI) $\leq$ 15 or $\geq$ 40, (6) history of cryoglobulinemia, (7) history of sickle cell disease, (8) history of serum cold agglutinin disease, (9) active/ongoing nosebleeds, (10) known/suspected pregnancy, (11) participation in another ongoing investigational study, (12) prisoners and/or patients with no legally authorized representative available, (13) airborne droplet disease isolation protocol, (14) immunocompromise, (15) thrombocytopenia (platelet count < 100,000), (16) nasal septal deviations, (17) chronic rhinosinusitis, (18) prior skull-based surgery, (19) penetrating cranial trauma, (20) recent nasal trauma or anterior base skull fracture, (21) presence of cardiac arrhythmias, (22) refractory hypoxemia, and (23) refractory hypercarbia.

Control Selection

Control patients admitted with SAH, ICH, or acute ischemic stroke who received at least 24 h of TTM with sTMDs in the NCCU between January 2019 and July 2021 were retrospectively selected, controlling for age, sex, and body surface area. These variables were selected because of their correlation with shivering during TTM [8, 10, 11]. Patients in the control group were febrile, refractory to acetaminophen, and received $\geq$ 24 h of surface cooling TTM with Arctic Sun 5000 (Medivance/Bard, Louisville, CO) or Gaymar (Gaymar Industries, Orchard Park, NY). All control patients selected for analysis met the same inclusion and exclusion criteria as patients undergoing normothermia with tnTMD. Patients cooled by an esophageal cooling device or more than one device were excluded.

Cooling with a tnTMD

For tnTMD patients, a continuous core temperature probe was placed, and a single-use double-nostril nasal mask was positioned over the patient's nose. The temperature probe was connected to the device, and the target temperature on the device was set to 36.5 °C. During cooling, the device circulated dry filtered room temperature air at a flow rate of 60 L/min through the patient's nose and directly out of their mouth. A few drops of isotonic saline were sprayed in the patient's nose a couple times a minute to minimize nasal desiccation. Mask fit was monitored throughout the cooling period by study staff and the clinical team. Normothermia was maintained for 24 h, after which tnTMD was discontinued and standard care for temperature control was continued.

Cooling with an sTMD

All patients undergoing normothermia with sTMD had a core temperature probe placed and connected to the bedside console to provide closed-loop feedback to a target temperature of 36.5 °C.

Shivering Management

Seven case patients and all 30 control patients received standing shivering prophylaxis with 30 mg of buspirone every 6–8 h as part of standard care for TTM. The three tnTMD case patients who did not receive buspirone were treated at an institution with different standard of care guidelines. For case patients and controls, the Bedside Shivering Assessment Scale (BSAS) score [6] was assessed every 2 h, and antishivering pharmacologic agents (meperidine, dexmedetomidine, fentanyl, propofol, magnesium sulfate, cisatracurium) were administered for shivering (BSAS score > 1) per study protocol (tnTMD patients) and institutional guidelines (sTMD patients).

Data Collection

Baseline demographic data and device-related complication data were collected for both the tnTMD and sTMD groups. Core temperature data and shivering data (BSAS scores) were collected every 2 h for both the sTMD and tnTMD groups. Core temperature data were collected by either bladder, esophageal, or superficial temporal probe. As has been previously reported, we considered any infusion initiation, dosage increase, or bolus of analgosedation a pharmacologic antishivering intervention [2, 8].

Statistical Analysis

Multiple controls who were matched for age, body surface area, and sex were selected per case patient (3:1 ratio), and a final sample of $n=10$ case patients and $n=30$ controls was used. The final sample of case patients ($n=10$) and controls ($n=30$) was assessed using a noncentrality parameter t-statistic using a power assumption of 80% ($\beta=0.2$) and significance of 5% ($\alpha=0.05$). This analysis demonstrated that adequate power was achieved with a total sample of 40 (10 case patients and 30 controls). The primary end point of cooling efficacy of the tnTMD was determined by time to achieve normothermia (≤ 37.5 °C) as well as temperature burden above 37.5 °C (°C × h) during the 24-h cooling period. A secondary end point of interest was the proportion and severity of shivering between the sTMD and tnTMD groups. This was determined by assessing the difference in shiver burden as determined by BSAS score > 0. These variables were compared between groups using Student's t-test for mean differences or the Mann–Whitney U-test for comparison of medians. The proportion of patients requiring interventions, as well as the number of interventions per patient, was compared using the χ^2 test. Significance was determined based on a p value < 0.05.

All data collection for retrospective analysis of participants undergoing sTMD was approved by the Institutional Review Board at the University of Maryland School of Medicine. Participants undergoing cooling with tnTMD were enrolled in a study that was approved at each site by the institutional review board and by the US Food and Drug Administration through an investigational device exemption and registered on ClinicalTrials.gov (NCT03360656).

Results

Demographics

Ten tnTMD patients and 30 sTMD matched controls who were cooled with Arctic Sun or Gaymar were included in the analysis. There were no differences between groups in baseline characteristics, including age, sex, body surface area, primary diagnosis of ICH or SAH, Glasgow coma scale at cooling initiation, and presence of intraventricular hemorrhage (Table 1). Neither group had device-related serious adverse events.

Temperature Measurements

There were no differences between groups in temperature at cooling initiation, time to ≤ 37.5 °C, or temperature burden > 37.5 °C (Table 2 and Fig. 1). All the sTMD patients achieved normothermia during the study period,

Table 1 Baseline characteristics

	tnTMD $n=10$	sTMD $n=30$	p Value
Age (years)	65 ± 19	62 ± 12	0.67
Women	3 (30%)	9 (30%)	1.00
BSA, m^2	1.99 ± 0.24	1.96 ± 0.26	0.71
BMI	27.5 ± 4.9	27.3 ± 5.3	0.88
GCS	8 (8–10)	7 (5–9)	0.07
Diagnosis			
Hemorrhagic stroke	5 (50%)	21 (37%)	0.25
Ischemic stroke	4 (40%)	9 (30%)	0.56
Seizures	1 (10%)	0 (0%)	0.04
IVH present	6 (60%)	17 (57%)	0.85
Temperature-modulating device			
Arctic Sun	–	23	n/a
Gaymar	–	7	

All continuous variables are shown as mean ± standard deviation. GCS is shown as median (interquartile range). All proportions are shown as number (percentage)

BSA body surface area, *BMI* body mass index, *GCS* Glasgow coma scale, *IVH* intraventricular hemorrhage, *n/a* not applicable, *sTMD* surface cooling temperature-modulating device, *tnTMD* transnasal temperature-modulating device

Table 2 Temperature and shivering data during cooling period

	tnTMD $n=10$	sTMD $n=30$	*p* Value
Temperature data			
Temperature at initiation (°C)	38.5 ± 0.2	38.7 ± 0.5	0.30
Time to 37.5 °C (h)	1.8 ± 1.5	2.9 ± 1.4	0.12
Temperature burden (°C × h)			
Above 37.5 °C	− 0.40 ± 1.13	− 0.57 ± 0.58	0.67
Above 38 °C	− 1.40 ± 1.13	− 1.59 ± 0.54	0.62
Shivering data			
BSAS score[a]	0 (0–2)	0 (0–3)	< 0.001
Shiver burden[b]			
BSAS 0	107 (96%)	254 (73%)	< 0.001
BSAS 1	1 (1%)	42 (12%)	
BSAS 2	3 (3%)	35 (10%)	
BSAS 3	0 (0%)	17 (5%)	
Patients receiving Intervention	2 (20%)	20 (67%)	0.01
Interventions per patient	0 (0–3)	4 (0–23)	< 0.001

All continuous data are shown as mean ± standard deviation. All categorical data are shown as *n* (%), and ordinal data are shown as median (range)

BSAS bedside shivering assessment scale, *sTMD* surface cooling temperature-modulating device, *tnTMD* transnasal temperature-modulating device

[a] The median (range) 24-h BSAS score for each group

[b] The percentage of time spent at each BSAS score during the cooling period. For the tnTMD cohort, this is out of 111 measurements (instead of 120) because of early discontinuation in two patients. For sTMD patients, this is out of 348 h (instead of 360) because of missing data in a retrospective chart review

and none had reported side effects related to the surface pads. One tnTMD patient did not achieve normothermia, and cooling was suspended at 4 h. Another tnTMD patient developed a pressure sore on the skin above their lip, and cooling was suspended at 20 h. All other tnTMD patients were cooled by the device for 24 h, and sTMD patients received cooling for at least 24 h.

Shivering Measurements

The number of tnTMD patients who received pharmacologic shivering interventions was significantly lower than the number of sTMD control patients (Table 2). tnTMD patients also had fewer shivering interventions per patient and lower BSAS scores. The proportion of time spent with a BSAS score > 0 was higher in the sTMD patients (28 vs. 4%; Fig. 2).

Discussion

The tnTMD tested in a multicenter single-arm study effectively achieved normothermia for 24 h in patients with a temperature burden no different from that of comparable patients undergoing sTMD. Moreover, the tnTMD patients had significantly less shivering and shivering-related intervention than sTMD patients.

Nasal cooling leverages the efficient physiologic process of conditioning large volumes of air through the nasal passages to extract heat from the body [12]. Experimental and clinical studies have shown this approach to be effective in rapidly reducing core [12] temperature. Magnetic Resonance (MR) thermography in patients undergoing nasal cooling have also shown reductions in brain temperature without significant regional differences [13]. Recent studies in cardiac arrest populations have used an intranasal cooling method using a

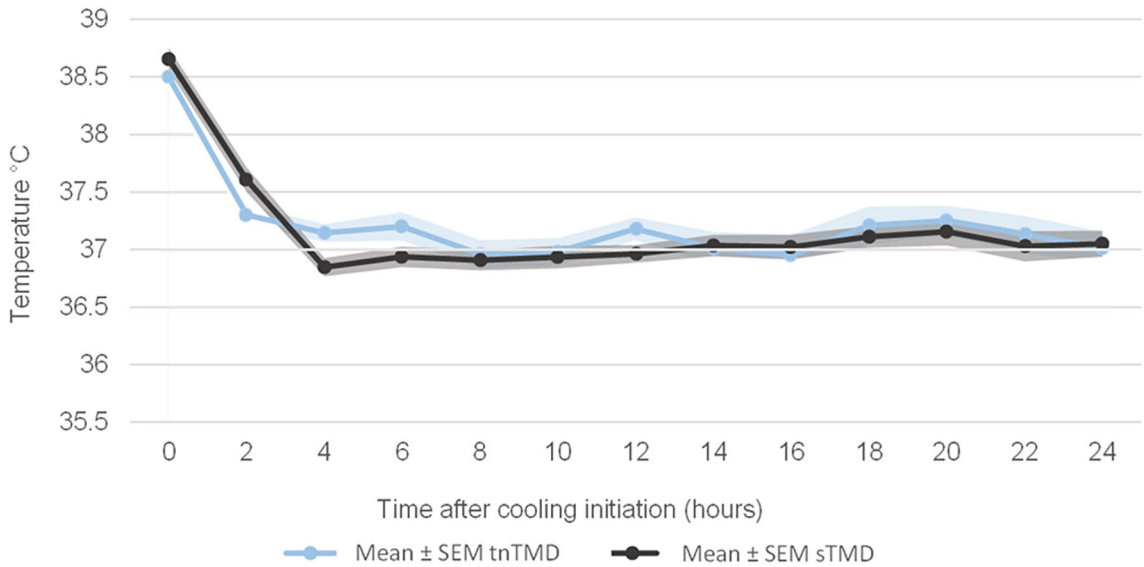

Fig. 1 Comparison of temperature curves between transnasal temperature-modulating device (tnTMD) and surface temperature-modulating device (sTMD). Temperature measurements for tnTMD and sTMD during study period

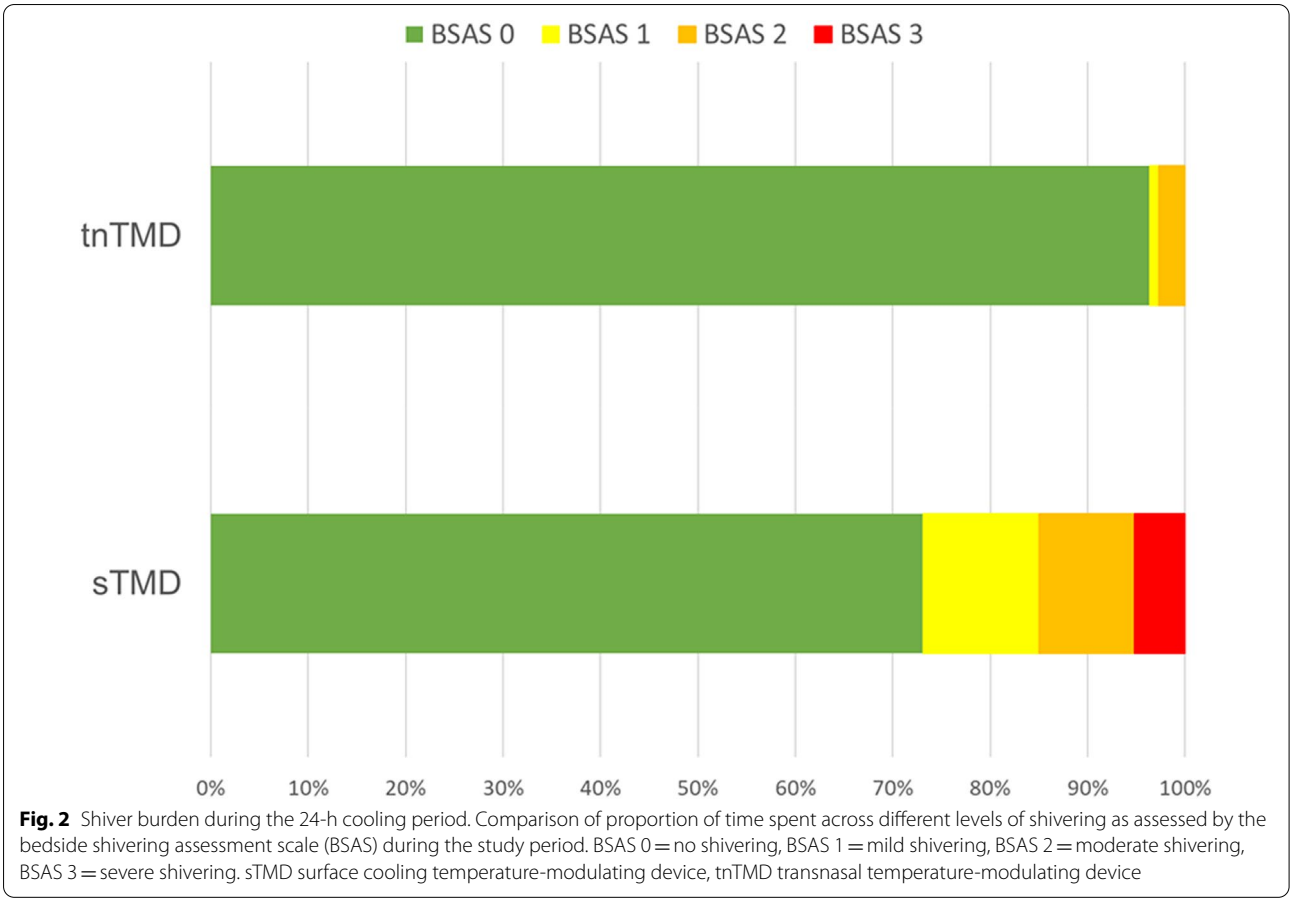

Fig. 2 Shiver burden during the 24-h cooling period. Comparison of proportion of time spent across different levels of shivering as assessed by the bedside shivering assessment scale (BSAS) during the study period. BSAS 0 = no shivering, BSAS 1 = mild shivering, BSAS 2 = moderate shivering, BSAS 3 = severe shivering. sTMD surface cooling temperature-modulating device, tnTMD transnasal temperature-modulating device

perfluorocarbon nasal spray along with high-flow oxygen to induce but not maintain target temperatures [14, 15]. By contrast, the transnasal cooling system tested in this study works with a current of dry air over inducing moisture of the nasal turbinates pulling energy out of the body to cool via an evaporative process. Moreover, as is shown in this study, this system has a feedback mechanism, allowing for both induction and maintenance of a targeted temperature. Given the rate of air flow through the upper respiratory tract, the cooling process can be rapid, as can be the return to normal temperatures with discontinuation. Clinical and experimental studies have demonstrated a rapid "wash out" of temperature reduction when devices were discontinued. This was observed during this study, with slight incremental increases in temperature occurring with air leaks, necessitating close, frequent monitoring by clinical and study staff. Rapid changes in core temperatures may have clinical implications should this device be used for hypothermia in conditions that may be impacted by rapid rewarming (e.g., cerebral edema, status epilepticus). Moreover, this technique may also have limitations related to patient size, as noted by the inability to achieve target temperature in a patient who had had a BMI 38.1. By contrast, all of the sTMD patients were able to achieve and maintain normothermia, regardless of BMI. Another potential concern was the potential pressure sore on the skin above the lip that limited the ability to complete the 24-h study in one patient. In this patient, the skin-related concerns resolved and did not pose any further concern. Though previous reports have noted skin injuries related to surface cooling [16], none were reported in the study period for sTMD patients.

This device is one of many that have been shown to achieve and maintain normothermia; however, unlike existing sTMDs, the burden of shivering appears to be significantly less. The reasons for this are not entirely clear but undoubtedly are related to the focal approach, which reduces the amount of surface area directly exposed to cold temperatures and blunts the shivering response to changes in core body temperature. Additionally, there may be a more direct impact on brain temperature, beneficially impacting hypothalamic regions that regulate the shivering response to changes in temperature. Given the significant impact of shivering and potential implications toward patient outcomes [6,

10, 17] during TTM, this novel device may be a feasible option to consider for mechanically ventilated febrile neurocritical care patients.

There are some limitations to this study. Control patients were selected from one institution, whereas tnTMD patients were treated at multiple institutions. This limits comparison because of differences in standards of care, but it may demonstrate the generalizability of the efficacy of cooling with the tnTMD. We also sought to determine whether cooling to normothermia with the tnTMD was possible and associated with less shivering than cooling with sTMDs. Because of this, control patients were matched on variables known to be associated with shivering, resulting in nonconsecutive controls and contributing to a possible selection bias. Additionally, we do not have outcome data for case patients or controls to determine whether there is a difference in clinical recovery for tnTMD versus sTMD patients. A fourth limitation is the small sample size. Though our power analysis indicates adequate sample size for our analyses, further analysis with more tnTMD recipients should be conducted to strengthen the findings from this study.

The CoolStat tnTMD is a novel cooling device that appears to be no different from sTMDs in achieving and maintaining normothermia in intubated brain-injured patients with refractory fever. Recipients of the tnTMD also experienced less burden of shivering, resulting in fewer pharmacologic interventions with analgosedation. Additional data examining advantages and disadvantages of this technique are required before proposing transnasal cooling as a viable option for attaining normothermia in a ventilated brain-injured population. Proposed new clinical trials are focusing on optimizing the efficiency of cooling while minimizing side effects with this technique.

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Author Contributions
SA contributed to concept, design, acquisition of data, and drafting of the manuscript. MA contributed to the acquisition of data and critical revision of the manuscript for intellectual content. LFT contributed to acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for intellectual content. HTripathi contributed to acquisition of data and analysis and interpretation of data. HTandri contributed to analysis and interpretation of data and critical revision of the manuscript for intellectual content. JJC contributed to analysis and interpretation of data and critical revision of the manuscript for intellectual content. HAC contributed to analysis and interpretation of data and critical revision of the manuscript for intellectual content. NB contributed to concept, design, analysis and interpretation of data, drafting of the manuscript, statistical analysis, obtaining funding, and administrative, technical, and material support supervision.

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Conflicts of Interest
The authors declare no conflicts of interest.

Ethical Approval/Infomed Consent
All data collection for retrospective analysis of participants undergoing sTMD was approved by the Institutional Review Board at the University of Maryland School of Medicine. Participants undergoing cooling with tnTMD were enrolled in a study that was approved at each site by the institutional review board and by the US Food and Drug Administration through an investigational device exemption and registered on ClinicalTrials.gov (NCT03360656).

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References

1. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008;39(11):3029–35.
2. Khan I, Haymore J, Barnaba B, et al. Esophageal cooling device versus other temperature modulation devices for therapeutic normothermia in subarachnoid and intracranial hemorrhage. Ther Hypothermia Temp Manag. 2018;8(1):53–8.
3. Diringer MN. Neurocritical care fever reduction trial G. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. Crit Care Med. 2004;32(2):559–64.
4. Mayer SA, Kowalski RG, Presciutti M, et al. Clinical trial of a novel surface cooling system for fever control in neurocritical care patients. Crit Care Med. 2004;32(12):2508–15.
5. Hata JS, Shelsky CR, Hindman BJ, Smith TC, Simmons JS, Todd MM. A prospective, observational clinical trial of fever reduction to reduce systemic oxygen consumption in the setting of acute brain injury. Neurocrit Care. 2008;9(1):37–44.
6. Badjatia N, Strongilis E, Gordon E, et al. Metabolic impact of shivering during therapeutic temperature modulation: the bedside shivering assessment scale. Stroke. 2008;39(12):3242–7.
7. Oddo M, Frangos S, Maloney-Wilensky E, Andrew Kofke W, Le Roux PD, Levine JM. Effect of shivering on brain tissue oxygenation during induced normothermia in patients with severe brain injury. Neurocrit Care. 2010;12(1):10–6.
8. Choi HA, Ko SB, Presciutti M, et al. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. Neurocrit Care. 2011;14(3):389–94.
9. Badjatia N, Gupta N, Sanchez S, et al. Safety and feasibility of a novel transnasal cooling device to induce normothermia in febrile cerebrovascular patients. Neurocrit Care. 2021;34(2):500–7.
10. Badjatia N, Kowalski RG, Schmidt JM, et al. Predictors and clinical implications of shivering during therapeutic normothermia. Neurocrit Care. 2007;6(3):186–91.

11. Lyden P, Ernstrom K, Cruz-Flores S, et al. Determinants of effective cooling during endovascular hypothermia. Neurocrit Care. 2012;16(3):413–20.
12. Chava R, Zviman M, Raghavan MS, et al. Rapid induction of therapeutic hypothermia using transnasal high flow dry air. Ther Hypothermia Temp Manag. 2017;7(1):50–6.
13. Covaciu L, Weis J, Bengtsson C, et al. Brain temperature in volunteers subjected to intranasal cooling. Intensiv Care Med. 2011;37(8):1277–84.
14. Nordberg P, Taccone FS, Truhlar A, et al. Effect of transnasal evaporative intra-arrest cooling on functional neurologic outcome in out-of-hospital cardiac arrest: the PRINCESS randomized clinical trial. JAMA. 2019;321(17):1677–85.
15. Taccone FS, Hollenberg J, Forsberg S, et al. Effect of intra-arrest trans-nasal evaporative cooling in out-of-hospital cardiac arrest: a pooled individual participant data analysis. Crit Care. 2021;25(1):198.
16. Jarrah S, Dziodzio J, Lord C, et al. Surface cooling after cardiac arrest: effectiveness, skin safety, and adverse events in routine clinical practice. Neurocrit Care. 2011;14(3):382–8.
17. Madden LK, Hill M, May TL, et al. The implementation of targeted temperature management: an evidence-based guideline from the neurocritical care society. Neurocrit Care. 2017;27(3):468–87.