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Association of targeted temperature management on progression to brain death after severe anoxic brain injury following cardiac arrest: an observational study

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ABSTRACT

Objective Targeted temperature management (TTM), through its physiological effects on intracranial pressure, may impede the progression to brain death (BD) in severe anoxic brain injury post-cardiac arrest (CA). We examined the potential association between the use of TTM and the occurrence of BD after CA.

Design Monocentric, retrospective study.

Setting Intensive care unit, Versailles Hospital, France.

Participants Comatose survivors of CA who died from BD or postanoxic encephalopathy (PAE) after 24 hours.

Main outcome measures PAE deaths corresponded to withdrawal of life-sustaining therapy (WLST) due to irreversible postanoxic coma or vegetative state according to prognostication guidelines. BD corresponded to the cessation of cerebral vascularisation secondary to intracranial hypertension. The diagnosis of BD was definite by clinical diagnosis of deep coma according to the Glasgow Coma Scale 3, loss of all brainstem reflexes and the demonstration of apnoea during a hypercapnia test. A cerebral omputed tomography (CT) scan or two isoelectric and unreactive electroencephalograms were used to confirm BD. To identify the independent association between TTM and BD, we conducted a multivariable logistic regression analysis.

Results Out of 256 patients included between 2005 and 2021, 54.3% received TTM for at least 24 hours, and 56 patients (21.9%) died from BD. In the multivariable analysis, TTM for 24 hours or more was not associated with a decrease in BD (Odds Ratio 1.08, 95% CI 0.51 to 2.32). Factors associated with BD included a total duration of no-flow plus low-flow exceeding 30 min, CA due to neurological causes or hanging and a high arterial partial pressure of carbon dioxide between days 1 and 2 after admission.

Conclusions This exploratory analysis of post-CA patients with severe anoxic brain injury did not find an association between TTM ≥24 hours and a reduction in BD. Further studies are needed to identify specific subgroups of post-CA patients for whom TTM may be especially futile or even harmful.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study addresses a unique aspect of targeted temperature management (TTM) by examining its potential futility in patients with severe anoxic brain injury post-cardiac arrest, a perspective underexplored in prior research.
⇒ The population is limited to patients with severe anoxic brain injury who ultimately died, allowing focused analysis of TTM's effects in this specific group.
⇒ The single-centre, retrospective design may limit generalisability and restrict the ability to establish causal relationships between TTM and brain death incidence.

INTRODUCTION

Despite improved practices, mortality after cardiac arrest (CA) remains very high, with an average hospital survival rate of only 30%. The primary cause of death in these patients is withdrawal of life-sustaining therapy (WLST) due to irreversible postanoxic encephalopathy (PAE).[1]

Targeted temperature management (TTM) has been widely debated in recent years as a potential neuroprotective treatment for CA patients.[2–4] TTM may reduce neuroinflammation secondary to ischaemia-reperfusion injury and prevent neuronal apoptosis. Additionally, TTM requires sedation, which can interfere with neurological examination and prognostication. Therefore, it is essential to identify scenarios where TTM may be ineffective or even futile.

TTM is also used in traumatic brain injury as a method to control intracranial hypertension.[2 3] In severe anoxic brain injury post-CA, progression to brain death (BD) occurs in approximately 10–12% of cases.[4] For these patients, TTM may reduce brain oedema and intracranial pressure, potentially preventing progression to BD without necessarily improving neurological outcomes. These patients pass away due to withdrawal of life-sustaining treatment (WLST).

In patients with very severe anoxic brain injuries post-CA, TTM might influence progression to BD, and consequently, the pool of potential organ donors. This study examines the potential association between TTM and progression to BD in this specific population.

METHODS

This single-centre, retrospective, observational cohort study was conducted using a prospectively collected dataset from Versailles hospital (NCT03594318). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Patient and public involvement

Patients were not involved in the research.

Study setting and intensive care unit management

The management protocol for patients admitted to the intensive care unit (ICU) after CA aligns with international guidelines. Before 2016, TTM was induced and maintained using ice packs at the groin and neck and a cold-air tunnel around the patient's body. After 2016, an automated temperature-controlled system, either the Criticool or Arctic Sun, was used. The system was set at 33°C for comatose patients after out-of-hospital CA (OHCA) with an initial shockable rhythm until 2013. From 2013 onwards, the target was 33°C for OHCA patients with a shockable rhythm and 36°C or fever control for other patients, maintained for 24 hours. Before 2016, rewarming was done gradually, in increments of 0.25–0.5°C, done passively and actively controlled thereafter.

During the first 72 hours in the ICU, treatments were adapted to maintain homeostasis, including glucose control, normocapnia using a pH-stat strategy, titration of inspired oxygen to maintain arterial saturation between 94–98% and mean arterial pressure (MAP) of 65–75 mm Hg. For patients who remained comatose 72 hours after return of spontaneous circulation (ROSC) and after sedation cessation, a multimodal prognostication protocol was applied to identify cases of irreversible PAE. This protocol has followed international guidelines since 2005.[5–8]

Study objective

Our objective was to investigate an independent negative association between TTM and BD in a population of post-CA patients with very severe anoxic brain injury.

Study population

All adults admitted to the ICU in a comatose state following an OHCA or an in-hospital CA, with sustained ROSC between January 2005 and June 2021, who ultimately died from BD or PAE were included. This restricted population represents patients with the most severe brain damage, where a positive outcome is unlikely and TTM could be potentially futile. We excluded patients whose CA occurred in the ICU, those who were not in a coma and patients who died within 24 hours. Additionally, patients who were discharged alive from the ICU and those who died from another cause than BD or PAE (such as refractory shock, recurrence of CA, refractory acute respiratory distress syndrome, WLST due to comorbidities and secondary shock) were not included.

Definitions

PAE is defined as cases where patients died following WLST due to irreversible neurological injury, in accordance with prognostication guidelines.[5–7] On the other hand, BD was defined by the cessation of cerebral blood flow due to intracranial hypertension, with diagnosis following French legal criteria. This includes clinical signs of deep coma (Glasgow Coma Scale score of 3), absence of all brainstem reflexes and apnoea demonstrated during a hypercapnia test, in which arterial partial pressure of carbon dioxide ($PaCO_2$) rises to ≥50 mm Hg (6.6 kPa) after 10 min of disconnection. Additional confirmatory tests, such as cerebral CT angiography or two 30 min isoelectric and unreactive electroencephalograms taken 4 hours apart, were also used to confirm BD.[9–11]

Data collection

Demographic characteristics and CA data were prospectively collected in an electronic database according to the Utstein style.[12] Information included age, gender, CA setting, initial rhythm, time from collapse to cardiopulmonary resuscitation (CPR) initiation (no-flow), time from CPR initiation to ROSC (low-flow), presence of a witness, number of defibrillations and administration of epinephrine. The final aetiology of CA was also reported, with patients classified into five groups (cardiac, respiratory, neurological, hanging or other causes) by two blinded authors (CH and MP) with a third author (SL) resolving any disagreements. This classification aimed to isolate CAs at higher risk of intracranial hypertension, such as neurological causes or hanging.

Additional in-ICU variables were collected, including postresuscitation shock, use of TTM and secondary brain insult parameters (eg, minimum and maximum serum sodium, temperature, MAP and PaCO2 between days 1 and 2 after admission, excluding PaCO2 from the apnoea test for BD diagnosis). Only TTM lasting ≥24 hours was considered complete. While Witten *et al* grouped BD and PAE together as neurological deaths, the authors opted to dichotomise these as PAE due to neurological WLST and BD.[1]

To further explore the association between TTM and BD, we recorded the depth and duration of TTM, date of death and presence of cerebral oedema on the CT scan from the first day of admission. Cerebral oedema was identified based on radiologist reports in patient records; CT scans were not reanalysed. Reports indicating loss of grey-white matter differentiation, brain swelling or cerebral oedema were classified as showing cerebral oedema.

Statistical analysis

Values are presented as medians with IQRs or as numbers with percentages, as appropriate. Univariate comparisons between patients who died from BD and those who died from PAE were conducted using the Mann-Whitney U test for continuous variables and the χ^2 or Fisher's exact test for categorical variables, as appropriate. To identify an independent association between TTM ≥24 hours and BD, we compared subjects with BD to those with PAE using univariate analysis followed by logistic regression.

Prior to the multivariable analysis, non-log-linear variables were transformed into dummy variables based on their median values. Non-collinear variables with p values <0.05 in the univariate analysis, TTM ≥24 hours and clinically relevant variables were considered for inclusion in the multivariable model. Associations between factors and BD are reported as ORs with 95% CIs. The Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve (C-statistic) were calculated for the final models. Missing data were rare and managed using complete case analysis. All tests were two-sided, and p values <0.05 were considered significant.

Finally, a sensitivity analysis was performed, excluding patients managed with TTM at 36°C to compare only TTM at 33°C versus no TTM. All analyses were conducted using R software V.4.0.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org; accessed 13 March 2021).

Data availability

The anonymised datasets used and/or analysed during the current study are available from the corresponding author on reasonable request with permission from the Centre Hospitalier de Versailles.

RESULTS

Figure 1 presents the patient flow chart. From January 2005 to June 2021, 918 patients were admitted following CA, of whom 662 were excluded: 76 had CA in the ICU, 40 were not comatose after ROSC, 148 died within the first 24 hours, 160 died from causes other than BD or PAE and 238 were discharged alive from the ICU. Ultimately, 256 patients were included in the study.

Patient features and outcomes

Among the 256 patients, 75% received TTM for ≥12 hours (60.7% in the BD group and 79.0% in the PAE group, p value =0.005) and 54.3% received TTM for ≥24 hours (44.6% in the BD group and 57.0% in the PAE group, p value =0.10). 56 patients (21.9%) died from BD, and 200 (78.1%) died from PAE, with a median (IQR) time to death of 4 days (2–5 days) and 7 days (5–9 days), respectively.

Table 1 shows the characteristics of patients according to their progression to BD or PAE. Patients who died from BD were younger (58 years vs 65 years, p value < 0.001) and had a lower frequency of witnessed CA (64.3% vs 81.5%, p value = 0.006) and initial shockable rhythm (16.1% vs 37.0%, p value = 0.003) compared to those who died from PAE. Median (IQR) no-flow plus low-flow duration was longer in the BD group (36 min (28–45 min) vs 30 min (20–37 min), p value= 0.001), and admission lactate levels were higher (6.4 mmol/L (4.8–9.4 mmol/L) vs 5.4 mmol/L (2.9–7.5 mmol/L), p value = 0.003).

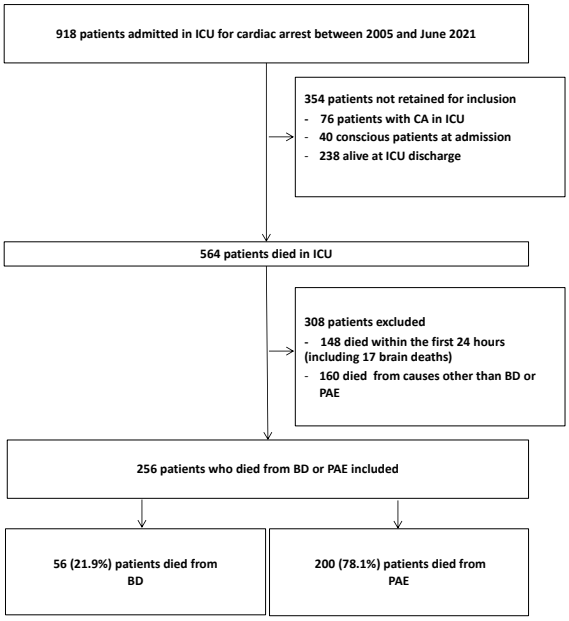

Figure 1 Study flow chart. BD, brain death; CA, cardiac arrest; ICU, intensive care unit; PAE, postanoxic encephalopathy.

The cause of CA differed significantly between the two groups, with more neurological causes and hangings in the BD group (p value <0.001). When the initial aetiological brain CT scan was performed, cerebral oedema was more frequent in the BD group (18/32 (56.3%) vs 18/88 (20.5%), p value <0.001). The CT scans were conducted at a median (IQR) of 3 hours[2–8 13–15] post-CA, with no significant difference between the groups.

Although TTM for ≥24 hours was used less frequently in the BD group compared with the PAE group (44.6% vs 57.0%), this difference was not statistically significant (p value =0.10). The BD group had higher maximal temperature, maximal PaCO2, maximal MAP and maximal serum sodium levels between days 1 and 2 after admission (see table 1).

Among the 22/56 (39%) patients who donated organs, 12/22 (55%) had cerebral CT angiography confirming cerebral vascular arrest and 10/22 (45%) had two electroencephalographies (EEG) confirming isoelectric EEG.

Factors independently associated with BD

TTM ≥24 hours was not significantly associated with BD in either univariate analysis (OR 0.61, 95% CI 0.35 to 1.10,

Table 1 Patient characteristics

N (%) or median (IQR)				
	Total (N=256)	**Brain death (N=56)**	**PAE (N=200)**	**P value**
Age, years	63 (53–75)	58 (45–65)	65 (55–76)	<0.001
Male	167 (65.2)	32 (57.1)	135 (67.5)	0.20
OHCA	214 (83.6)	50 (89.3)	164 (82.0)	0.20
Public place at CA	129 (50.4)	34 (60.7)	95 (47.5)	0.08
Arrest witnessed/monitored	199 (77.7)	36 (64.3)	163 (81.5)	0.006
Bystander CPR	64 (25.0)	13 (23.2)	51 (25.5)	0.70
Shockable first recorded rhythm	83 (32.4)	9 (16.1)	74 (37.0)	0.003
Total number of defibrillations before ROSC	0 (0–2.0)	0 (0–2.0)	0 (0–2.3)	0.053
Use of epinephrine	222 (86.7)	49 (87.5)	173 (86.5)	0.80
Total epinephrine dose before ROSC, mg	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.9–4.0)	0.50
Time from CA to CPR (no-flow), min	5 (0–11)	6 (2–15)	5 (0–10)	0.30
Time from CA to ROSC (low-flow), min	21 (15–30)	26 (20–36)	20 (15–30)	0.006
No-flow+low-flow, min (n=245)	30 (20–40)	36 (28–45)	30 (20–37)	0.001
Cerebral oedema on initial CT scan (n=120)	36/120 (30.0)	18/32 (56.3)	18/88 (20.5)	<0.001
Time to CT scan, hours after CA	3 (2–11)	3 (2–11)	3 (2–4)	0.4
Lactate concentration on ICU admission, mmol/L	5.7 (3.2–8.1)	6.4 (4.8–9.4)	5.4 (2.9–7.5)	0.003
Final identified cause of CA				<0.001
Cardiac	95 (37.1)	15 (26.8)	80 (40.0)	
Respiratory	62 (24.4)	11 (19.6)	51 (25.5)	
Neurological	17 (6.6)	11 (19.6)	6 (3.0)	
Hanging	22 (8.6)	9 (16.1)	13 (6.5)	
Other	60 (23.4)	10 (17.9)	50 (25.0)	
First temperature at admission, °C	36.2 (36.0–37.0)	36.0 (34.5–36.9)	36.3 (35.1–37.2)	0.11
TTM	213 (83.2)	38 (67.9)	175 (87.5)	<0.001
Time to TTM target, hours after CA	6 (3-7)	5 (3-10)	6 (3-9)	0.9
Duration of TTM, hours	26 (20–31)	25 (20–29)	26 (20–32)	0.40
TTM>12 hours	192 (75.0)	34 (60.7)	158 (79.0)	0.005
TTM≥24 hours	139 (54.3)	25 (44.6)	114 (57.0)	0.10
33°C	110/139 (79.1)	19/25 (76.0)	91/114 (79.8)	0.7
36°C	29/139 (20.9)	6/25 (24.0)	23/114 (20.2)	0.70
Body temperature between days 1 and 2 after admission, °C				
Minimal	33.0 (32.1–34.0)	33.0 (31.9–34.5)	33.0 (32.1–34.0)	0.70
Maximal	37.0 (36.4–37.9)	37.4 (36.7–38.0)	37.0 (36.4–37.8)	0.028
$PaCO_2$ between days 1 and 2 after admission, mm Hg				
Minimal	29.0 (26.0–32.0)	29.0 (26.5–35.0)	29.0 (26.0–33.0)	0.50
Maximal	45.0 (39.0–54.0)	50.0 (42.0–59.0)	44.0 (39.0–52.0)	0.009
Natraemia between days 1 and 2 after admission, mmol/L				
Minimal	137.0 (134.8–140.0)	138.0 (135.0–142.0)	137.0 (134.0–140.0)	0.078
Maximal	143.5 (139.0–146.0)	145.0 (141.0–148.0)	143.0 (139.0–144.0)	<0.001
MAP between days 1 and 2 after admission, mm Hg				
Minimal	59 (51–64)	57 (50–62)	59 (51–64)	0.30
Maximal	114 (102–128)	124 (106–141)	113 (101–125)	0.004
Post-resuscitation shock	188 (73.4)	42 (75.0)	146 (73.0)	0.80
Continued epinephrine use	100 (39.1)	26 (46.4)	74 (37.0)	0.20

Continued

Table 1 Continued

N (%) or median (IQR)	Total (N=256)	Brain death (N=56)	PAE (N=200)	P value
Renal replacement therapy	37 (14.5)	5 (8.9)	32 (16.0)	0.20
Time between admission and death, days*	6 (4–9)	4 (2–5)	7 (5–9)	<0.001

*Time between admission and death corresponds to the date of brain death diagnosis in BD patients.
CA, cardiac arrest; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; MAP, mean arterial pressure; OHCA, out-of-hospital cardiac arrest; $PaCO_2$, arterial partial pressure of carbon dioxide; PAE, postanoxic encephalopathy; ROSC, return of spontaneous circulation; TTM, targeted temperature management.

p value =0.14) or multivariate analysis (OR 1.08, 95% CI 0.51 to 2.32, p value =0.80; see table 2). The following factors were independently associated with an increase in BD: no-flow plus low-flow duration >30 min (OR 3.17, 95% CI 1.48 to 7.23, p value =0.004), CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49 to 17.90, p value<0.001) and a high $PaCO_2$ between days 1 and 2 after admission >45 mm Hg (6 kPa) (OR 3.92, 95% CI 1.82 to 9.00, p value<0.001). After exclusion of patients managed with TTM at 36°C, the association between TTM at 33°C and BD was still not statistically significant (OR 0.43, 95% CI 0.16 to 1.17, p value =0.093) (Electronic supplementary material (ESM)).

DISCUSSION

This retrospective analysis of 256 patients with severe anoxic brain injuries following CA revealed that 56 patients (21.9%) died from BD within a median of 4 days (IQR 2–5), while 200 patients (78.1%) died from PAE within 7 days. There was no association between TTM ≥24 hours and BD in multivariable analysis. Factors independently associated with an increased likelihood of BD included a CA duration of more than 30 min, a CA due to neurological causes or hanging and a maximum PaCO2 of over 45 mm Hg (6 kPa) between days 1 and 2 postadmission.

Table 2 Factors associated with brain death by multivariable analysis*

	OR (95% CI)	P value
TTM>24 hours	1.08 (0.51 to 2.32)	0.80
Shockable first recorded rhythm	0.43 (0.16 to 1.03)	0.068
No-flow+low-flow >30 min	3.17 (1.48 to 7.23)	0.004
Neurological cause of cardiac arrest or hanging	6.49 (2.49 to 17.90)	<0.001
Maximal $PaCO_2$ between days 1 and 2 after admission>45 mm Hg	3.92 (1.82 to 9.00)	<0.001
Maximal natraemia between days 1 and 2 after admission>143 mmol/L	1.93 (0.93 to 4.03)	0.077

*Variables included in the model selection process: TTM>24 hours, age>63 years, shockable first recorded rhythm, no-flow+low-flow >30 min, neurological cause of cardiac arrest or hanging, maximal MAP between days 1 and 2 after admission >114 mm Hg, maximal arterial carbon dioxide between days 1 and 2 after admission >45 mm Hg, maximal natraemia day 1>143 mmol/L. Goodness-of-fit Hosmer-Lemeshow test, p value=0.82; area under the receiver operating characteristics curve estimated by the C-statistic=0.81.
MAP, mean arterial pressure; $PaCO_2$, arterial partial pressure of carbon dioxide; TTM, targeted temperature management.

In recent years, TTM has generated significant debate as a potential neuroprotective intervention following CA.[16 17] Its effectiveness, however, remains uncertain, particularly in specific patient subsets.[18] Furthermore, TTM is not without risks, including cardiac complications, bleeding tendencies and electrolyte imbalances. Additionally, TTM can delay neurological assessments, as it necessitates sedation to manage patient tolerance to cooling.

Given these complexities, it is essential to carefully evaluate scenarios in which TTM may ultimately prove futile or even harmful.

During TTM, the reduction in cerebral blood flow—driven by a corresponding decrease in metabolic demand—contributes to lowering intracranial pressure by directly reducing the volume within the intravascular compartment. This effect is partially mediated by the physiological decrease in $PaCO_2$ that occurs with cooling.[19] As a result, TTM at 35–36°C remains a 'tier-three' recommendation for managing intracranial hypertension in international guidelines.[20] In post-CA patients, TTM may also reduce brain oedema and intracranial pressure, but this effect might not translate into meaningful clinical benefits in all patients. TTM could potentially be negatively associated with the progression to BD without improving neurological outcomes, possibly reducing the pool of potential organ donors from BD cases. More than 10% of post-CA deaths are due to BD, occurring at a mean delay of 3 days post-ROSC, and over 40% of brain-dead patients are potential organ donors.[4 21] As the number of patients on transplant waiting lists rises each year, with waiting times growing longer and reducing their chances, it is crucial to recognise that post-CA patients who progress to BD represent a valuable source of potential organ donors.

In our exploratory study, 139 patients (54.3%) received TTM for ≥24 hours. TTM ≥24 hours was not statistically

associated with a reduction in BD in multivariable analysis (OR 1.08, 95% CI 0.51 to 2.32, p value =0.80). Previous TTM studies have not provided specific information on BD as a cause of death in either treatment group.[16 22] In the HYPERION study, BD accounted for 10.4% and 12.6% of deaths in each group, respectively, though no statistical comparison was made.[17] One study examined risk factors for progression to BD after OHCA based on admission data to the ICU but found no significant association.[23] More recently, a French team developed a predictive score for BD post-OHCA using data from 1056 patients, with 15.2% patients progressing to BD, TTM was not associated with BD when compared with patients who died from other causes.[24 25] Compared with these studies, our work uniquely focuses on a homogeneous population of patients with severe anoxic brain injury, excluding those who were discharged alive or died early from other causes.

We identified three independent risk factors for BD in this selected population of patients with severe brain injury. A combined duration of no-flow and low-flow exceeding 30 min was associated with an increased risk of BD, likely due to the extent of the initial brain insult. Cour *et al* previously reported that a low-flow duration greater than 16 min is a risk factor for progression to BD.[24] CA due to neurological causes or hanging was also independently associated with BD, as documented in the literature.[24–26] Neurological causes can directly increase the volume of the parenchymal or cerebrospinal fluid compartments and may lead to impaired cerebral autoregulation, while hanging introduces cerebral hypoxia before CA. Unfortunately, a subgroup analysis of patients with neurological or hanging causes was not possible due to the small sample size.

Interestingly, a maximum $PaCO_2$ >45 mm Hg (6 kPa) between days 1 and 2 after admission was also associated with progression to BD. $PaCO_2$ plays a crucial role in managing secondary brain injury, as it is the primary regulator of cerebral blood flow.[15] A prospective, multicentre, randomised phase trial of 1700 post-CA patients found that therapeutic mild hypercapnia during the first 24 hours ($PaCO_2$ 50–55 mm Hg (6.6–7.3 kPa)) did not lead to better neurologic outcomes at 6 months than targeted normocapnia in comparison to normocapnia ($PaCO_2$ 35–45 mm Hg (4.6–6 kPa)). The numbers of patients with confirmed BD leading to organ donation were similar in the two groups.[26] Furthermore, a recent multicentre study indicates a U-shaped association between $PaCO_2$ and in-hospital mortality, with higher risk associated with $PaCO_2$ levels below 35 mm Hg (4.6 kPa) or above 55 mm Hg (7.3 kPa), though specific causes of death were not detailed.[27]

The authors acknowledge several limitations in this study, which should be viewed as an exploratory analysis rather than definitive evidence. First, the retrospective design of the outcome analysis limits the ability to establish causal relationships between TTM and BD. Second, the long study period may introduce variability due to changes in clinical practices, particularly following the publication of the TTM and HYPERION trials, which revised recommendations for post-CA TTM.[12 16] Although in the sensitivity analysis considered only patients managed with TTM 33°C excluding patients managed at TTM 36°C, a significant association between TTM and BD was not found. Third, this is a single-centre study, and the recruitment may have been biased because the rate of CA of neurological cause may have been lower due to the absence of a neurosurgery department in the hospital. However, the recruitment represents a vast geographical area of western Paris. Fourth, the population was restricted to patients who died from BD or PAE, which does not allow comparison of the population with the literature or to answer the question of the incidence of post-CA BD. But the authors wanted to explore the association in the most severely brain-injured CA patients. For this reason, patients who were discharged alive, as their neurological impairment was by definition less severe were not included, and currently, based on the literature, the neuroprotective effect of TTM in this patient population cannot be questioned. Fifth, the fact that the self-fulfilling prophecy limits the results of the study cannot be excluded. Indeed, patients judged to be more severe by the clinician may have been less likely to be put on TTM, which may have been considered futile. For this reason, we decided to exclude—from the outset—patients who died within 24 hours, among whom 17 died of BD. Moreover, we decided to define TTM use as TTM ≥24 hours to ensure consistency in exposure across the cohort. However, this may have minimised the potential effect of shorter durations of TTM on the primary outcome. In the same aspect, the fact that TTM 33°C and 36°C were used in the population could be a limitation.

CONCLUSION

In this exploratory analysis of a retrospective cohort of post-CA patients with severe anoxic brain injury, no association was found between TTM ≥24 hours and a reduction in progression to BD. These findings highlight the need for further research to better identify specific subgroups of post-CA patients in whom TTM may offer limited benefit or even potential harm. Such studies could contribute to refining treatment strategies and optimising patient care.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Name of the Ethics committee or Institutional Board: French Intensive Care Society and French health authorities' regulations (French Data Protection Authority). The reference/approval ID: CESRLF 20-41, #MR004_2209691. Participants gave informed consent before taking part: Data collection was approved by the Ethics Committee of the French Intensive Care Society which waived the requirement for written consent in accordance with French law on retrospective studies of anonymised data. The next of kin has given oral consent for the patient's participation in the data collection.

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