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Association between targeted temperature management and reduction of brain death in severe anoxic brain injured patients post cardiac arrest

Marine Paul, MD [1,2], Charles Hickel, MD[1], Gilles Troché, MD[1], Virginie Laurent, MD[1], Olivier Richard, MD[3], Sybille Merceron, MD[1], and Stéphane Legriel, MD, PhD[1,2,4]

[1] Intensive Care Unit, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France

[2] AfterROSC Study Group, Paris, France

[3] SAMU 78, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France 4

[4] University Paris-Saclay, UVSQ, INSERM, CESP, Villejuif, France

Correspondent

Marine Paul, MD

Intensive Care Department, Centre Hospitalier de Versailles - Site André Mignot, 177 Rue de Versailles, 78150 Le Chesnay, France

mpaul@ght78sud.fr

Twitter: @Marine_PAUL

ORCID: 0000-0002-0717-9555

What is already known on this topic ? Targeted temperature management could theoretically limit the evolution to brain death after cardiac arrest decreasing intracranial pressure.

What is our hypothesis? Some patients with very severe anoxic brain injuries may have been at risk of progressing towards brain death, but the application of therapeutic hypothermia could have prevented this progression, potentially reducing the pool of potential organ donors post cardiac arrest.

What this study adds ? In this study, targeted temperature management during 24 h after CA was not associated with evolution to brain death (BD). But BD was associated with longer no-flow plus low-flow time, a neurological injury or hanging as the cause of CA, and high $PaCO_2$ between days 1 and 2 after admission.

How this study might affect research, practice or policy? Further studies are warranted to find subgroups of post-CA patients for whom TTM is especially beneficial or futile.

Abstract

Background : Targeted temperature management (TTM) has recently been challenged after cardiac arrest (CA). It is imperative to question situations where TTM might prove ineffective or even futile. Our hypothesis posits that some patients with very severe anoxic brain injuries may have been at risk of progressing towards brain death (BD), but the application of TTM could have prevented this progression, potentially reducing the pool of potential organ donors. We investigated whether there was a negative association between the use of TTM and BD after CA.

Methods: Monocentric and retrospective study including comatose survivors after CA who died from BD or post-anoxic encephalopathy (PAE) after 24 hours. To identify the independent association between the TTM and BD , we performed a multivariable logistic regression analysis.

Results: Of 256 patients included between 2005 and 2021, 75% of patients received a TTM ≥12 hours, 54,3 % a TTM ≥24 hours and 56 (21.9%) died from BD. In multivariable analysis, TTM ≥24 hours was not associated with decrease of BD (OR 1.08, 95% CI 0.51–2.32] in a multivariate analysis taking into account factors associated with BD occurrence. Factors associated with BD were total duration of no-flow plus low-flow >30 minutes, CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49–17.90, $p < 0.001$) and a high arterial partial pressure of carbon dioxide ($PaCO_2$) between days 1 and 2 after admission >45 mmHg (6 kPa) (OR 3.92, 95% CI 1.82–9.00, $p < 0.001$).

Conclusion : In our selected population of severe brain damage patients post CA, TTM was not associated with less BD. Further studies are warranted to find subgroups of post-CA patients for whom TTM is especially futile limiting the passage to brain death.

Key words: cardiac arrest, brain death, targeted temperature management, post anoxic encephalopathy, organ donor.

Introduction

Despite improved practices, mortality after cardiac arrest (CA) remains very high, with an average hospital survival rate of only 30%.[1] Withdrawal of life-sustaining therapy (WLST) for irreversible post-anoxic encephalopathy (PAE) is the primary reason for death after CA.[2]

Targeted temperature management (TTM) has long been considered the only neuroprotective treatment proven to improve neurological outcomes until recently being challenged in comatose survivors after CA [3]. One of the key pathways through which TTM may confer neuroprotection in post cardiac arrest patients is by reducing intracranial pressure and brain edema, maintaining cerebral perfusion and preventing secondary brain injury. [4–6] Identification of subgroups of patients who are better candidates for TTM based on pathophysiology is the new objective.

It is crucial to question the scenarios where TTM might be ineffective or even futile. In cases of severe anoxic brain injury, patients may progress to a state of brain death. Indeed 10% of CA patients died after brain death[7]. Through its mechanisms of action, TTM may prevent or delay the irreversible anoxic neurological damage that leads to brain death in these post CA patients. In this context, it is legitimate to inquire whether the early implementation of TTM in patients with significant cerebral anoxia could potentially prevent this progression towards brain death without necessarily improving neurological outcomes. These patients may subsequently pass away due to Withdrawal of Life-Sustaining Treatment (WLST). Our hypothesis posits that some patients with very severe anoxic brain injuries may have been at risk of progressing towards brain death, but the application of therapeutic hypothermia could have prevented this progression, potentially reducing the pool of potential organ donors from BD. The objective of the study was to evaluate whether there is a negative association between TTM and BD after CA.

Methods

Patient and public involvement

This single-center, retrospective, observational cohort study was conducted using a prospectively collected dataset from Versailles hospital (NCT03594318). Data collection was approved by the Ethics Committee of the French Intensive Care Society (#CESRLF 20-41) which waived the requirement for written consent in accordance with French law on retrospective studies of anonymized data. The study was conducted according to French health authorities' regulations (French Data Protection Authority #MR004_2209691). The study is reported according to the STROBE statement.

Study Setting and ICU Management

The management protocol for patients admitted to our ICU after CA is in accordance with international guidelines. Before 2016, TTM was induced then maintained by ice packs at the groin and neck and a cold-air tunnel around the patient's body. After, the cooling system was automated temperature controlled with the Criticool ® or Articsun ® device. The targeted temperature was 33°C for patients in coma after an out-of-hospital cardiac arrest (OHCA) and initial shockable rhythm until 2013; after 2013, it was 33°C for patients with OHCA with initial shockable rhythm and 36°C or fever control for other patients during 24 hours. Rewarming was progressive in 0.25–0.5°C increments, passively before 2016 and actively controlled after. During the first 72 hours of ICU stay, treatments were adapted to maintain homeostasis with glucose control, normocapnia with pH stat strategy, inspired fraction of O_2 titrated for arterial saturation of 94–98%, and mean arterial pressure (MAP) 65–75 mmHg. Among patients who were still comatose 72 hours after return of spontaneous circulation (ROSC) and after sedation discontinuation, a multimodal prognostication protocol was used to identify patients with irreversible PAE. This protocol was consistent with international guidelines since 2005[8–11].

Study Objective

Our objective was to search for an independent negative association between TTM and BD in a population of very severe brain damaged patients post CA.

Study Population

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

Definitions

PAE deaths corresponded to WLST due to irreversible post-anoxic coma or vegetative state according to prognostication guidelines[8–10]. BD corresponded to the cessation of cerebral vascularization secondary to intra-cranial hypertension. The diagnosis of BD was based on the French definition: clinical diagnosis of deep coma (Glasgow Coma Scale 3), loss of all brainstem reflexes, and the demonstration of apnea during a hypercapnia test with a rise in arterial partial pressure of carbon dioxide ($PaCO_2$) after a 10-minute disconnection from a base value to ≥50 mmHg (6.6 kPa). Ancillary tests (e.g., cerebral CT angiograph or two isoelectric and unreactive electroencephalograms of 30 minutes duration, 4 hours apart) were used to confirm BD.[12]

Data Collection

Demographic characteristics and data related to CA were prospectively collected in an electronic database according to the Utstein style[13], including age, gender, setting of CA, initial rhythm, time from collapse to cardiopulmonary resuscitation (CPR) initiation (no-flow) and from CPR initiation to ROSC (low-flow), presence of a witness on scene, number of

defibrillations, and administration of epinephrine. The final etiology of CA was also reported, with classification of patients into five groups (cardiac, respiratory, neurological, hanging, or other cause) by two authors (C.H. and M.P.) who were blinded from each other, and a third (S.L.) in case of disagreement. This classification is intended to isolate cardiac arrests at higher risk of intracranial hypertension such as neurological causes or hanging. In-ICU variables were also collected: post-resuscitation shock, use of TTM, secondary brain insult parameters (e.g., minimal and maximal serum sodium, temperature, MAP, and $PaCO_2$ between days 1 and 2 after admission, excluding the $PaCO_2$ after the apnea test for BD diagnosis). Only a TTM ≥24 hours was considered complete. While Witten et al. described cause of death into five categories, pooling BD and PAE in the same group of neurological death, we choose to dichotomize PAE with neurological withdrawal of life-sustaining therapy and BD[2]. To further investigate the association of TTM with BD we recorded: depth and duration of TTM, date of death, and cerebral oedema on the CT scan during the first day of admission. Cerebral oedema was collected from the report of radiologist in the medical record of each patient and CT were not reanalyzed. When reports mentioned a loss of gray-white matter differentiation or a brain swelling or a cerebral oedema we considered a presence of cerebral oedema.

Statistical Analysis

Values are presented as medians and interquartile ranges (IQRs) or numbers and percentages, as appropriate. Univariate comparisons between patients who died from BD or PAE were performed using the Mann–Whitney U test for continuous variables and the Chi-square or Fisher's exact tests for categorical variables, as appropriate. To identify independent association between TTM≥ 24 and BD, we compared subjects with BD and subject with PAE using univariate analysis then logistic regression. Before performing the multivariable analysis, non-log-linear variables were transformed into dummy variables according to their median value. Non-collinear variables that yielded *p* values < 0.05 by univariate analysis, TTM≥ 24 and variables deemed clinically relevant were considered for the multivariable model. Associations of factors with BD are reported as odds ratios (OR) with their associated 95% confidence intervals (CI). The Hosmer-Lemeshow goodness-of-fit test and area under the

receiver operating characteristics curve estimated by the C-statistic were computed on the final models. Missing data were uncommon and were handled using case complete analysis. All tests were two sided and *p* values < 0.05 were considered significant. Finally, we performed a sensitive analysis after exclusion of patients managed with TTM 36°C to assess only TTM 33°C vs no TTM. All analyses were performed using R program version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org; accessed March 13, 2021).

Data Availability

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

Results

Figure 1 is the patient flow chart. From January 2005 to June 2021, 918 patients were admitted for CA, among whom 662 were excluded :76 patients CA occurred in the ICU, 40 were not comatose after ROSC, 148 died early within the first 24 hours, 160 died of another cause than BD or PAE and 238 discharged alive from the ICU. Ultimately, 256 patients were retained in the study.

Patient Features and Outcomes

Among the 256 patients, 75% of patients received a TTM ≥12 hours (60,7% in BD group and 79,0% in PAE group, P=0,005) and 54,3 % a TTM ≥24 hours (44,6% in BD group and 57 % in PAE group, P=0,10). Fifty-six patients (21.9%) died from BD and 200 (78.1%) from PAE within a median (IQR) time of 4 (2–5) and 7 (5–9) days, respectively. The characteristics of patients studied according to their progression to BD or PAE are shown in Table 1. Patients who died from BD were younger (58 vs 65 years, $p < 0.001$) and less frequently had witnessed CA (64.3% vs 81.5%, $p = 0.006$) and initial shockable rhythm (16.1% vs 37.0%, $p = 0.003$) than patients who died from PAE. Median (IQR) no-flow plus low-flow was longer in the BD group (36 [28–45] vs 30 [20–37] minutes, $p = 0.001$) and admission lactate was higher (6.4

[4.8–9.4] vs 5.4 [2.9–7.5] mmol/L, p = 0.003). The cause of CA varied significantly between the two groups, with more neurological causes and hangings in patients who died from BD (p < 0.001). When the initial etiologic brain CT scan was performed, cerebral edema was more frequent in the BD group (18/32 (56.3%) vs 18/88 (20.5%), p < 0.001). The CT scan was performed at a median (IQR) of 3 hours [2-11] after cardiac arrest with no difference between groups. TTM ≥24 hours was used somewhat less frequently in the BD vs PAE group (44.6% vs 57.0%), but this was not statistically significant (p = 0.10). The BD group had higher maximal temperature, maximal $PaCO_2$, maximal MAP, and maximal serum sodium between days 1 and 2 after admission (Table 1). Among 22/56 (39%) patients who gave organ, 12/22 (55%) patients had a cerebral CT angiograph confirming cerebral vascular arrest and 10/22 (45%) patients had 2 EEG confirming isoelectric EEG.

Factors Independently associated with BD

TTM ≥24 hours was not significantly associated with BD (OR 1.08, 95% CI 0.51–2.32, p = 0.80; Table 2). The following factors were independently associated with an increase in BD: no-flow plus low-flow duration >30 minutes (OR 3.17, 95% CI 1.48–7.23, p = 0.004), CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49–17.90, p < 0.001) and a high $PaCO_2$ between days 1 and 2 after admission >45 mmHg (6 kPa) (OR 3.92, 95% CI 1.82–9.00, p < 0.001). After exclusion of patients managed with TTM 36°C, the association between TTM 33 and BD was still not statistically significant (OR 0,43, 95% CI 0.16–1.17, p=0.093) (ESM).

Discussion

In this retrospective analysis of 256 patients with severe anoxic cerebral injuries post CA, 56 patients (21.9%) died of BD within a median (IQR) time of 4 (2–5) days and 200 (78.1%) died from PAE in 7 (5–9) days. Whereas TTM ≥24 hours was not significantly associated with BD, duration of no-flow plus low-flow >30 minutes, CA due to neurological cause or hanging, and highest $PaCO_2$ >45 mmHg (6 kPa) between days 1 and 2 after admission were independently associated with increased likelihood of BD.

TTM has sparked debates in recent years as a potential neuroprotective intervention post CA. [14,15] Its effectiveness remains to be determined, especially in a subset of patients. Additionally, TTM is not without cardiac, hemorrhagic, and hydroelectrolytic risks, and it can also delay neurological assessment. Indeed, TTM requires the administration of sedation to tolerate cooling, a debate treatment in 2024 as it is the primary confounding factor in the neurological assessment post-cardiac arrest, which is a cornerstone of post-resuscitation care. Given these complexities, it is imperative to scrutinize situations where TTM may prove futile.

During TTM, the decrease in cerebral blood flow, following the decrease in metabolic consumption, contributes to the decrease in intracranial pressure by direct reduction of the volume of the intravascular compartment. This effect is mediated in particular by the physiological decrease in $PaCO_2$ following the decrease in temperature. [16] Therefore, TTM at 35–36°C remains one of the treatments for intracranial hypertension, as a “tier-three” option in international recommendations.[17] Based on physiology, we hypothesize that certain patients with extremely severe anoxic brain injuries might have been prone to advancing towards brain death (BD). [18] However, the implementation of TTM could have hindered this progression without enhancing neurological outcomes, thereby delaying neurological assessment and potentially diminishing the pool of potential organ donors from BD. This is, in our opinion, a relevant question, as the main cause of post-CA death is neurological and BD represents 10–12% of CA deaths.[1,2]. WLST patients post CA could potentially become organ donors through the Maastricht III procedure, although this form of donation is less common than donation after BD.

In our study, 139 patients (54.3%) had a complete TTM ≥24 hours. TTM ≥24 hours was not statistically associated with a reduction in BD in multivariable analysis (OR 1.08, 95% CI 0.51–2.32, p = 0.80). In TTM studies, the authors did not provide any information on death from BD in either group.[14,19] In the HYPERION study, BD accounted for 10.4% and 12.6% of deaths in each group, respectively, without any statistical comparison.[15] A study looked at the risk factors for progression to BD after OHCA based on data at admission to the ICU, without succeeding in demonstrating a significant association. Among 246 patients included,

71 (29%) had TTM, with less TTM in the BD group (17%) compared to 32% in the Cerebral Performance Category 3-4-5 group without BD, although this difference was not significant.[20] More recently, a French team reported a predictive score for BD post-OHCA based on 1,056 patients, among whom 83.4% received TTM and 161(15.2%) evolved towards BD. TTM was not associated with BD compared with patients who died from another cause.[21,22] The selection of the population did not seem ideal in order to answer the question of the role of TTM in the evolution to BD. In our study, the exclusion of patients who were discharged alive from the ICU and those who died of a cause other than BD or PAE could help us to target the population of interest (i.e., those with severe anoxic brain damage), for whom TTM may have an effect. In addition, the exclusion of patients who died early made the population more homogeneous with respect to TTM exposure.

We highlight three independent risk factors for BD in this selected population of severe brain damaged patients. Duration of no-flow plus low-flow >30 minutes was associated with increased risk of BD, related to the extent of the initial brain insult. Cour et al. reported a low-flow duration >16 minutes as a risk factor for progression toward BD.[22] CA from neurological cause and hanging was independently associated with BD, as has been reported in literature.[21–23] Neurological causes will directly increase the volume of the parenchymal or cerebrospinal fluid compartment and may be associated with a loss of cerebral autoregulation. Hanging will also add cerebral hypoxia before CA. Unfortunately, subgroup analysis of neurological or hanging causes could not be performed due to the small numbers of patients. Interestingly, maximal $PaCO_2$ >45 mmHg (6 kPa) during between days 1 and 2 after admission was also associated with progression to BD. $PaCO_2$ is one of the pillars in the control of secondary brain injury by being the main regulator of cerebral blood flow.[4] In the literature, the occurrence of hypocapnia or hypercapnia within 24 hours after CA is associated with an unfavorable neurological prognosis with an OR >2.[24] Results from a prospective, multicenter, randomized phase II trial of 86 post-CA patients showed that therapeutic mild hypercapnia during the first 24 hours ($PaCO_2$ 50–55 mmHg (6.6- 7.3 kPa)) attenuated neuron-specific

enolase release compared with normocapnia ($PaCO_2$ 35–45 mmHg (4.6-6 kPa)). There was no significant difference in mortality or neurological outcome at 6 months. The authors reported no cases of intracranial hyper pressure and no cases of cerebral edema. No details were given regarding TTM.[25] Finally, in a recent multicenter study, it seems that $PaCO_2$ has a U-shaped association with in-hospital mortality with a risk for $PaCO_2$ <35 (4.6) and >55 mmHg (7.3 kPa), without any data on the causes of death.[26] We can assume that, in some post-CA patients, the cerebral protection mechanisms would be exceeded and hypoxic lesions were already too advanced. Patients in the BD group more often had a cerebral edema on their admission CT (56.3% vs 20.5%, $p < 0.001$). This early edema may reflect a more injured blood-brain barrier after CA, worsened by an altered cerebral autoregulation.[27–29] The initial cerebral oedema could be aggravated by a high $PaCO_2$ which could favor the evolution towards BD. This evolution could be slowed down in patients undergoing TTM, but the outcome would still be unfavorable with a secondary PAE in this population.

We acknowledge some limitations. The first limitation of our study is the retrospective nature of the outcome analysis strategy. Second, the study period may reflect variations in practice, particularly after the publication of the TTM and HYPERION trials, which modified the recommendations on post-CA TTM.[14,15] Although in our sensitivity analysis considering only patients managed with TTM 33°C excluding patients managed at TTM 36, we still did not find a significant association between TTM and BD. Thirdly, this is a single-center 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 neurosurgery in the hospital. However, our recruitment represents a vast geographic area of western Paris. Fourthly, the population was restricted to patients who died from BD or PAE, which does not allow us to compare our population with the literature nor to answer the question of the incidence of post-CA BD. But we wanted to test our hypothesis on the most severely brain injured CA patients. For this reason, we did not include patients who were discharged alive, as their neurological impairment was by definition less severe, and currently, based on the literature, we cannot question the neuroprotective

effect of TTM in this patient population. Fifthly, it cannot be excluded that self-fulfilling prophecy limits the results of the study. 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 with TTM ≥24 hours, we also potentially minimize the effect of TTM on the primary outcome. In the same aspect, the fact that we used TTM 33 and 36°C in the population could be a limitation.

Conclusion

In our selected population of severe brain damage patients post CA with unfavorable neurological issue, TTM was not associated with less BD. Further studies are warranted to find subgroups of post-CA patients for whom TTM is especially futile limiting the passage to brain death in patients who will not wake up anyway.

Glossary

BD = brain death; **CA** = cardiac arrest; **CI** = confidence interval; **CPR** = cardiopulmonary resuscitation; **ICU** = intensive care unit; **IQR** = interquartile range; **MAP** = mean arterial pressure; **OHCA** = out-of-hospital cardiac arrest; **OR** = odds ratio; **$PaCO_2$** = arterial partial pressure of carbon dioxide; **PAE** = post-anoxic encephalopathy; **ROSC** = return of spontaneous circulation; **TTM** = targeted temperature management; **WLST**= Withdrawal of life-sustaining therapy.

Declarations

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Conflict of interest statement:

None of the authors has any conflicts of interest to declare.

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Author contributions

Marine Paul and Charles Hickel wrote the first draft of the paper. All authors approved the final version of the manuscript.

MP: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

CH: Major role in the acquisition of data, Drafting/revision of the manuscript for content, including medical writing for content;

GT: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

VL: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

OR: Major role in the acquisition of data

SM: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

SL: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

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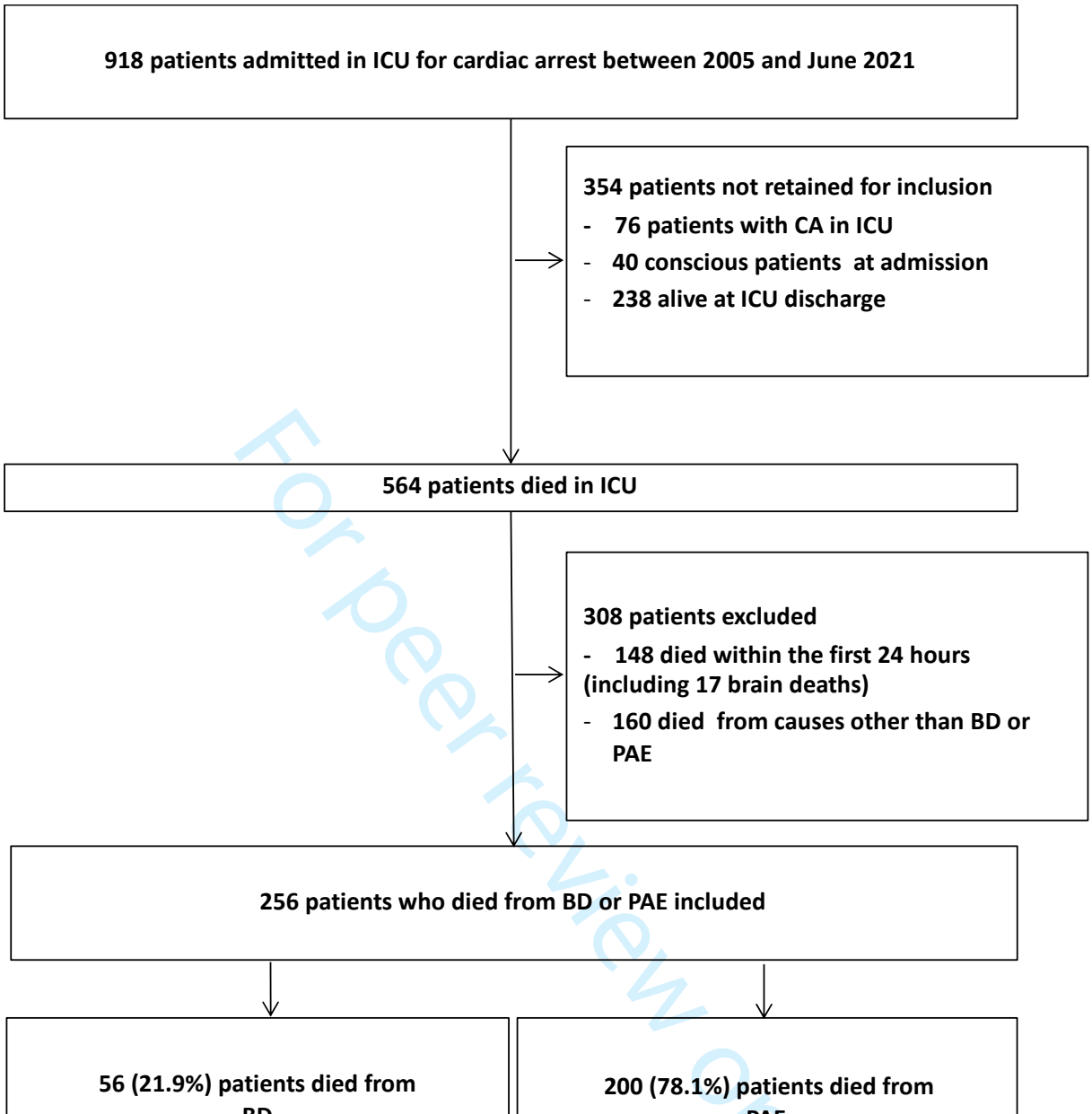
Figure and table legend

Figure 1 Study flow chart



Abbreviations: BD = brain death; CA = cardiac arrest; ICU = intensive care unit; PAE = post-anoxic encephalopathy.

Table 1 Patient Characteristics

N (%) or Median (interquartile range)	Total (N = 256)	Brain death (N = 56)	PAE (N = 200)	*p* value
Age, y	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 edema 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, mmHg				
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
Natremia 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, mmHg				
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
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

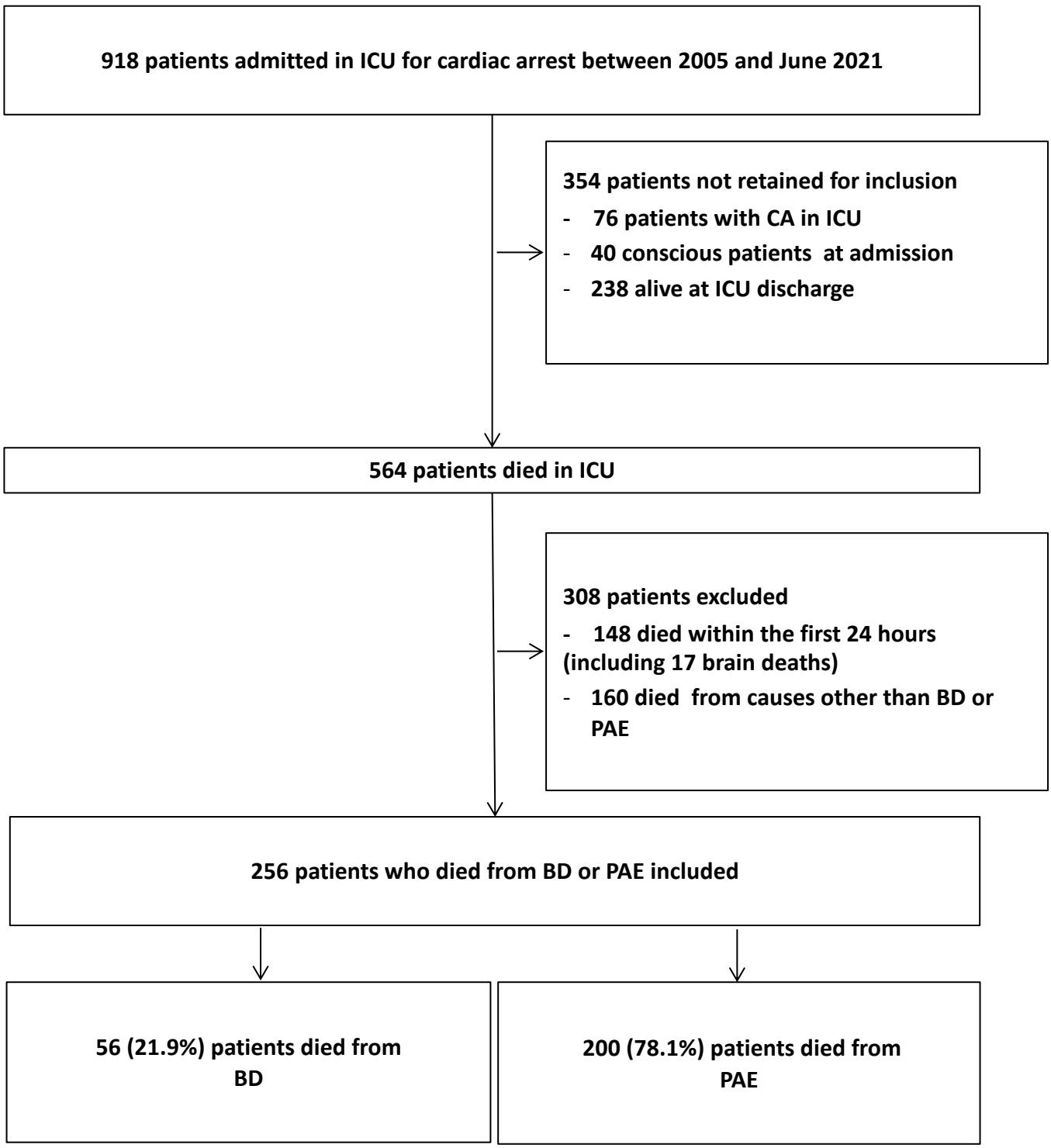
Abbreviations: CA = cardiac arrest; CPR = cardiopulmonary resuscitation; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial pressure; OHCA = out-of-hospital cardiac arrest; $PaCO_2$ = arterial partial pressure of carbon dioxide; PAE = post-anoxic encephalopathy; ROSC = return of spontaneous circulation; TTM = targeted temperature management.

Table 2 Factors associated with brain death by multivariable analysis[a]

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

Abbreviations: CI = confidence interval; TTM = targeted temperature management; MAP: mean arterial pressure; OR = odds ratio; $PaCO_2$ = arterial partial pressure of carbon dioxide.

[a]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 mmHg, maximal arterial carbon dioxide between days 1 and 2 after admission >45 mmHg, maximal natremia day 1 >143 mmol/L. Goodness-of-fit Hosmer-Lemeshow test, $p = 0.82$; area under the receiver operating characteristics curve estimated by the C-statistic = 0.81.



Electronic supplementary material

Association of targeted temperature management with brain death post cardiac arrest

ESM 1: Neurological prognostication and criteria for WLST

After the initial period of TTM and rewarming, neurological outcome was assessed daily for each patient by ICU physicians until death or ICU discharge. In patients who were still comatose 72 hours after ROSC and after sedation discontinuation, a multimodal prognostication protocol was used, consistent with international guidelines since 2007. Glasgow coma scale, pupillary and corneal reflexes are assessed and an EEG is performed to rule out status epilepticus and assess prognostic tools. Pupillary reflex and corneal reflexes are reported every 3 hours by nurse and 12 hours by physicians. Clinical or electrical status epilepticus was defined as refractory when it did not improve after treatment with 2 lines of major antiepileptic drugs (among phenytoin, phosphenytoin, valproate, phenobarbital, levetiracetam). N20 potentials on SSEP were also tested in a standardized way resulting from the averaging of cortical electrographic responses generated after repetitive electrical stimulations of the median nerve, transmitted to the contralateral post-central gyrus, and represented by a negative deflection on the recording, about 20 ms after the stimulation. We collected information about bilaterally absence N20 component on SSEPs with presence of P14 responses, by the external technicians and interpreted by the external neurophysiologist. Finally neuron-specific enolase (NSE) was dosed in serum at Day 3 post CA with a threshold of 80 ng/mL. When major predictors of poor outcome were not present (i.e., patients with N20 potentials and cranial reflexes preserved, motor GCS more than 2), decisions to withhold or withdraw life-support therapies were systematically delayed in order to search for a confounding factor (sepsis, remaining sedative drug effect, intercurrent disease process, other neurological disease). After this additional delay, an ethic meeting is held to incorporate all prognostic variables in the decision. This decision could be either to withhold or withdraw life-support therapies. WLST was always decided after a collegial decision. All deaths associated with end-of-life decisions occurred during the ICU stay.

ESM 2:Factors associated with brain death by multivariate analysis: initial complete model

	Multivariate analysis	
	OR (95%CI)	***P* value**
TTM >24h	1.07 (0.50-2.32)	0.9
Age > 63 years	0.70 (0.32-1.53)	0.4
Shockable first recorded rhythm	0.42 (0.15-1.05)	0.074
No-flow + low-flow >30 min	**3.06 (1.42-7.00)**	**0.006**
Neurological cause of cardiac arrest or hanging	**5.18 (1.89-15.1)**	**0.002**
Maximal MAP between day 1-2 > 114 mmHg	1.49 (0.70-3.17)	0.3
Maximal arterial carbon dioxide between day 1-2 > 45mmHg	**3.81 (1.76-8.81)**	**0.001**
Maximal natremia day 1-2 > 143 mmol/L	1.96(0.94-4.14)	0.075

CPR: cardio pulmonary resuscitation; ROSC: return of spontaneous circulation; TTM: targeted temperature management; MAP: mean arterial pressure
Goodness-of-fit Hosmer-Lemeshow test, P=0.82; area under the receiver operating characteristics curve estimated by the C-statistic, 0.82.

ESM 3: Factors associated with brain death by multivariable analysis in a sub group of patients receiving TTM 33° vs no TTM (after exclusion of patients receiving TTM 36°)

	OR (95% CI)	p value
TTM 33° >24 hours	0,43 (0.16–1.17)	0.093
Shockable first recorded rhythm	0.48 (0.17–1.24)	0.14
No-flow + low-flow >30 minutes	**2.54 (1.11–6.18)**	**0.031**
Neurological cause of cardiac arrest or hanging	**5.64 (2.06–16.40)**	**<0.001**
Maximal PaCO2 between days 1 and 2 after admission >45 mmHg	**3.65 (1.58–9.16)**	**0.004**

Abbreviations: CI = confidence interval; TTM = targeted temperature management; MAP: mean arterial pressure; OR = odds ratio; PaCO2 = arterial partial pressure of carbon dioxide.
aVariables included in the model selection process: TTM 33°>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 mmHg, maximal arterial carbon dioxide between days 1 and 2 after admission >45 mmHg, maximal natremia day 1 >143 mmol/L.

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Impact of Targeted Temperature Management on Progression to Brain Death after Severe Anoxic Brain Injury Following Cardiac Arrest: An Observational Study.

Marine Paul, MD [1,2], Charles Hickel, MD[1], Gilles Troché, MD[1], Virginie Laurent, MD[1], Olivier Richard, MD[3], Sybille Merceron, MD[1], and Stéphane Legriel, MD, PhD[1,2,4]

[1] Intensive Care Unit, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France

[2] AfterROSC Study Group, Paris, France

[3] SAMU 78, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France 4

[4] University Paris-Saclay, UVSQ, INSERM, CESP, Villejuif, France

Correspondent

Marine Paul, MD

Intensive Care Department, Centre Hospitalier de Versailles - Site André Mignot, 177 Rue de Versailles, 78150 Le Chesnay, France

mpaul@ght78sud.fr

Twitter: @Marine_PAUL

ORCID: 0000-0002-0717-9555

Abstract

Objective : This study explores whether TTM in severe anoxic brain injury post-cardiac arrest might be futile. We hypothesized that TTM could, through its physiological effects on intracranial pressure, impede the progression to BD potentially impacting organ donation opportunities, without improving neurological outcomes. We investigated whether there is a negative association between the use of TTM and the occurrence of BD after CA.

Design : Monocentric, retrospective study.

Setting: ICU, Versailles Hospital, France.

Participants : Comatose survivors of CA who died from BD or post-anoxic encephalopathy (PAE) after 24 hours.

Main outcome measures : PAE deaths corresponded to WLST due to irreversible post-anoxic coma or vegetative state according to prognostication guidelines. BD corresponded to the cessation of cerebral vascularization secondary to intra-cranial hypertension. The diagnosis of BD was definite by clinical diagnosis of deep coma Glasgow Coma Scale 3, loss of all brainstem reflexes, and the demonstration of apnea during a hypercapnia test. Cerebral 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 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 (OR 1.08, 95% CI 0.51–2.32). Factors associated with BD included a total duration of no-flow plus low-flow exceeding 30 minutes, CA due to neurological causes or hanging and a high arterial partial pressure of carbon dioxide (PaCO2) 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.

Key words: cardiac arrest, brain death, targeted temperature management, post-anoxic encephalopathy, organ donor.

Strengths and limitations of this study

- This study addresses a unique aspect of 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-center, retrospective design may limit generalizability and restricts 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%.[1] Withdrawal of life-sustaining therapy (WLST) for irreversible post-anoxic encephalopathy (PAE) is the primary reason for death after CA.[2]

Targeted Temperature Management (TTM) has been debated in recent years as a potential neuroprotective treatment in CA patients [3,4]. TTM may reduce neuroinflammation secondary to ischemia-reperfusion injury and prevent neuronal apoptosis . Additionally, TTM requires sedation, which can interfere with neurological examination and neuro prognostication. It is crucial to identify situations where TTM might be ineffective or even futile.

TTM is also used in traumatic brain injury as a method to control intracranial hypertension [5,6]. In cases of severe anoxic brain injury post-cardiac arrest, patients may progress to brain death in 10–12% of cases [7]. For patients with severe brain anoxia at risk of progressing towards brain death, TTM may reduce brain edema and intracranial pressure, thus preventing progression to brain death without necessarily improving neurological outcomes, these patients pass away due to Withdrawal of Life-Sustaining Treatment (WLST).

We hypothesize that in patients with very severe anoxic brain injuries post-cardiac arrest, TTM could potentially prevent progression to brain death, thereby reducing the pool of

potential organ donors. The objective of the study was to evaluate whether there is a negative association between TTM and BD after CA.

Methods

This single-center, retrospective, observational cohort study was conducted using a prospectively collected dataset from Versailles hospital (NCT03594318). Data collection was approved by the Ethics Committee of the French Intensive Care Society (#CESRLF 20-41) which waived the requirement for written consent in accordance with French law on retrospective studies of anonymized data. The study is reported according to the STROBE statement.

Patient and public involvement

Patients were not involved in the research.

Study Setting and ICU Management

The management protocol for patients admitted to our 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 Artic Sun®, was used. was set at 33°C for comatose patients after out-of-hospital cardiac arrest (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. Rewarming was gradual, in increments of 0.25–0.5°C, done passively before 2016 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 mmHg. 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[8–11].

Study Objective

Our objective was to investigate an independent negative association between TTM and BD in a population of post-cardiac arrest 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

Death from persistent PAE occurred in patients who underwent neurological WLST following prognostication of poor long-term outcomes, based on established guidelines. [8–10]. was defined as 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 apnea demonstrated during a hypercapnia test, in which arterial partial pressure of carbon dioxide ($PaCO_2$) rises to ≥50 mmHg (6.6 kPa) after 10 minutes of disconnection. Additional confirmatory tests, such as cerebral CT angiography or two 30-minute isoelectric and unreactive electroencephalograms taken 4 hours apart, were also used to confirm BD.[12–14]

Data Collection

Demographic characteristics and CA data were prospectively collected in an electronic database according to the Utstein style[15]. 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 (C.H. and M.P.) with a third author (S.L.) 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 post-resuscitation shock, use of TTM, and secondary brain insult parameters (e.g., minimum and maximum serum sodium, temperature, MAP, and PaCO2 between days 1 and 2 after admission, excluding PaCO2 from the apnea test for BD diagnosis). Only TTM lasting ≥24 hours was considered complete. While Witten et al. grouped BD and PAE together as neurological deaths, we opted to dichotomise these as PAE due to neurological WLST and BD [2].

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 interquartile ranges (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 Chi-square 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 odds ratios (OR) with 95% confidence intervals (CI). 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, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org; accessed March 13, 2021).

Data Availability

The anonymized datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and 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 cardiac arrest (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=0.005) and 54.3% received TTM for ≥24 hours (44.6% in the BD group

and 57.0% in the PAE group, p=0.10). Fifty-six 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) and 7 days (5–9), respectively.

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

Table 1 Patient Characteristics

N (%) or Median (interquartile range)	**Total (N = 256)**	**Brain death (N = 56)**	**PAE (N = 200)**	***p* value**
Age, y	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
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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 edema 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, mmHg				
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
Natremia 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, mmHg				
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
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

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

The cause of CA differed significantly between the two groups, with more neurological causes and hangings in the BD group ($p < 0.001$). 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%), $p < 0.001$). The CT scans were conducted at a median (IQR) of 3 hours [2–11] post-cardiac arrest, with no significant difference between the groups.

Although TTM for ≥24 hours was used less frequently in the BD group compared to the PAE group (44.6% vs 57.0%), this difference was not statistically significant ($p = 0.10$). 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 EEGs confirming isoelectric EEG.

Factors Independently associated with BD

TTM ≥24 hours was not significantly associated with brain death (BD) in either univariate analysis (OR 0.61, 95% CI 0.35–1.10, p = 0.14) or multivariate analysis (OR 1.08, 95% CI 0.51–2.32, p = 0.80; see Table 2). The following factors were independently associated with an increase in BD: no-flow plus low-flow duration >30 minutes (OR 3.17, 95% CI 1.48–7.23, *p* = 0.004), CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49–17.90, *p* < 0.001) and a high $PaCO_2$ between days 1 and 2 after admission >45 mmHg (6 kPa) (OR 3.92, 95% CI 1.82–9.00, *p* < 0.001). After exclusion of patients managed with TTM 36°C, the association between TTM 33 and BD was still not statistically significant (OR 0,43, 95% CI 0.16–1.17, p=0.093) (ESM).

Table 2 Factors associated with brain death by multivariable analysis[a]

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

Abbreviations: CI = confidence interval; TTM = targeted temperature management; MAP: mean arterial pressure; OR = odds ratio; $PaCO_2$ = arterial partial pressure of carbon dioxide.

[a]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 mmHg, maximal arterial carbon dioxide between days 1 and 2 after admission >45 mmHg, maximal natremia day 1 >143 mmol/L. Goodness-of-fit Hosmer-Lemeshow test, *p* = 0.82; area under the receiver operating characteristics curve estimated by the C-statistic = 0.81.

Discussion

In this retrospective analysis of 256 patients with severe anoxic brain injuries following cardiac arrest, 56 patients (21.9%) died from BD within a median of 4 days (IQR 2–5), while 200 (78.1%) died from PAE within 7 days. There was no association between TTM and BD. These findings do not support our initial hypothesis that TTM could reduce intracranial hypertension and subsequently lower the incidence of brain death in severe anoxic brain injury. Factors independently associated with an increased likelihood of BD included a cardiac arrest duration of more than 30 minutes, a CA due to neurological causes or hanging, and a maximum PaCO2 of over 45 mmHg (6 kPa) between days 1 and 2 post-admission.

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. Sedation itself remains a contentious treatment in 2024, as it is the primary confounding factor in post-cardiac arrest neurological assessments—a crucial component of post-resuscitation care. 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] Based on these physiological mechanisms, we hypothesize that in certain patients with extremely severe anoxic brain injuries, TTM could potentially impede the progression to BD without improving neurological outcomes, possibly reducing the pool of potential organ donors from BD cases. More than 10% of post-cardiac arrest deaths are due to brain death, occurring at a mean delay of 3 days post-ROSC, and over 40% of brain-dead patients are potential organ donors.[7,21] 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-cardiac arrest patients who progress to brain death represent a valuable source of potential organ donors. Patients undergoing WLST post-cardiac arrest could potentially become organ donors through the Maastricht III procedure, although this type of donation is less common than donation after BD.

In our 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 0.51–2.32, p = 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. Of the 246 patients included, 71 (29%) received TTM, with a lower TTM rate in the BD group (17%) compared to 32% in the Cerebral Performance Category 3-4-5 group without BD; however, this difference was not statistically significant.[23] More recently, a French team developed a predictive score for BD post-OHCA using data from 1,056 patients, 83.4% of whom received TTM, with 161 (15.2%) progressing to BD. [24,25] In this analysis, TTM was not associated with BD when compared to patients who died from other causes. Notably, the population selection in these studies may not ideally address the role of TTM in BD progression. In our study, we excluded patients discharged alive from the ICU and those who died from causes other than BD or PAE, allowing us to focus on patients with severe anoxic brain injury for whom TTM might have an impact. Additionally, excluding patients who died early created a more homogeneous population with respect to TTM exposure.

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 minutes 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 minutes is a risk factor for progression to BD .[25] 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 mmHg (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.[5] Literature suggests that both hypocapnia and hypercapnia within the first 24 hours post-CA are associated with poor neurological outcomes, with an odds ratio (OR) greater than 2. [27] A prospective, multicenter, randomized phase of 1700 post-CA patients found that therapeutic mild hypercapnia during the first 24 hours ($PaCO_2$ 50–55 mmHg (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 mmHg (4.6–6 kPa)). The numbers of patients with confirmed brain death leading to organ donation (Table S8) were similar in the two groups.[28] Neurofilament concentration did not differ in a post hoc analysis of the COMACARE trial, which compared two different targets of $PaCO_2$.[29] Furthermore, a recent multicenter study indicates a U-shaped association between $PaCO_2$ and in-hospital mortality, with higher risk associated with $PaCO_2$ levels below 35 mmHg (4.6 kPa) or above 55 mmHg (7.3 kPa), though specific causes of death were not detailed.[30] We can hypothesize that in some post-CA patients, cerebral protective mechanisms may become overwhelmed, with hypoxic damage already too advanced. Patients in the BD group more frequently presented with cerebral edema on admission CT (56.3% vs. 20.5%, $p < 0.001$). This early edema may reflect a more severely compromised blood-brain barrier post-CA, exacerbated by disrupted cerebral autoregulation.[31–33] Initial cerebral edema could be further aggravated by elevated $PaCO_2$, potentially accelerating progression toward BD. In patients undergoing TTM, this progression may be slowed, but the outcome remains poor, often resulting in secondary PAE.

We acknowledge several limitations in our study, which should be viewed as an exploratory analysis rather than definitive evidence. First, the retrospective design of the outcome analysis limits our ability to establish causal relationships between TTM and brain death. 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. [16,17] Although in our sensitivity analysis considering only patients managed with TTM 33°C excluding patients managed at TTM 36, we still did not find a

significant association between TTM and BD. Thirdly, this is a single-center 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 neurosurgery in the hospital. However, our recruitment represents a vast geographic area of western Paris. Fourthly, the population was restricted to patients who died from BD or PAE, which does not allow us to compare our population with the literature nor to answer the question of the incidence of post-CA BD. But we wanted to test our hypothesis on the most severely brain injured CA patients. For this reason, we did not include patients who were discharged alive, as their neurological impairment was by definition less severe, and currently, based on the literature, we cannot question the neuroprotective effect of TTM in this patient population. Fifthly, it cannot be excluded that self-fulfilling prophecy limits the results of the study. 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 with TTM ≥24 hours, we also potentially minimize the effect of TTM on the primary outcome. In the same aspect, the fact that we used TTM 33 and 36°C in the population could be a limitation.

Conclusion

This exploratory analysis of a retrospective cohort 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 and could help refine treatment approaches.

Glossary

BD = brain death; **CA** = cardiac arrest; **CI** = confidence interval; **CPR** = cardiopulmonary resuscitation; **ICU** = intensive care unit; **IQR** = interquartile range; **MAP** = mean arterial pressure; **OHCA** = out-of-hospital cardiac arrest; **OR** = odds ratio; **$PaCO_2$** = arterial partial pressure of carbon dioxide; **PAE** = post-anoxic encephalopathy; **ROSC** = return of spontaneous circulation; **TTM** = targeted temperature management; **WLST**= Withdrawal of life-sustaining therapy.

Declarations

Contributors

Study conception and design: MP, CH, SL

Data collection : MP, CH, SL

Analysis and interpretation of results: MP , SL

Draft manuscript preparation: CH MP

All authors reviewed the results and approved the final version of the manuscript.

Marine PAUL (MP) serves as guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patients were not involved in the research.

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Author contributions

Marine Paul and Charles Hickel wrote the first draft of the paper. All authors approved the final version of the manuscript.

MP: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

CH: Major role in the acquisition of data, Drafting/revision of the manuscript for content, including medical writing for content;

GT: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

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OR: Major role in the acquisition of data

SM: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

SL: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

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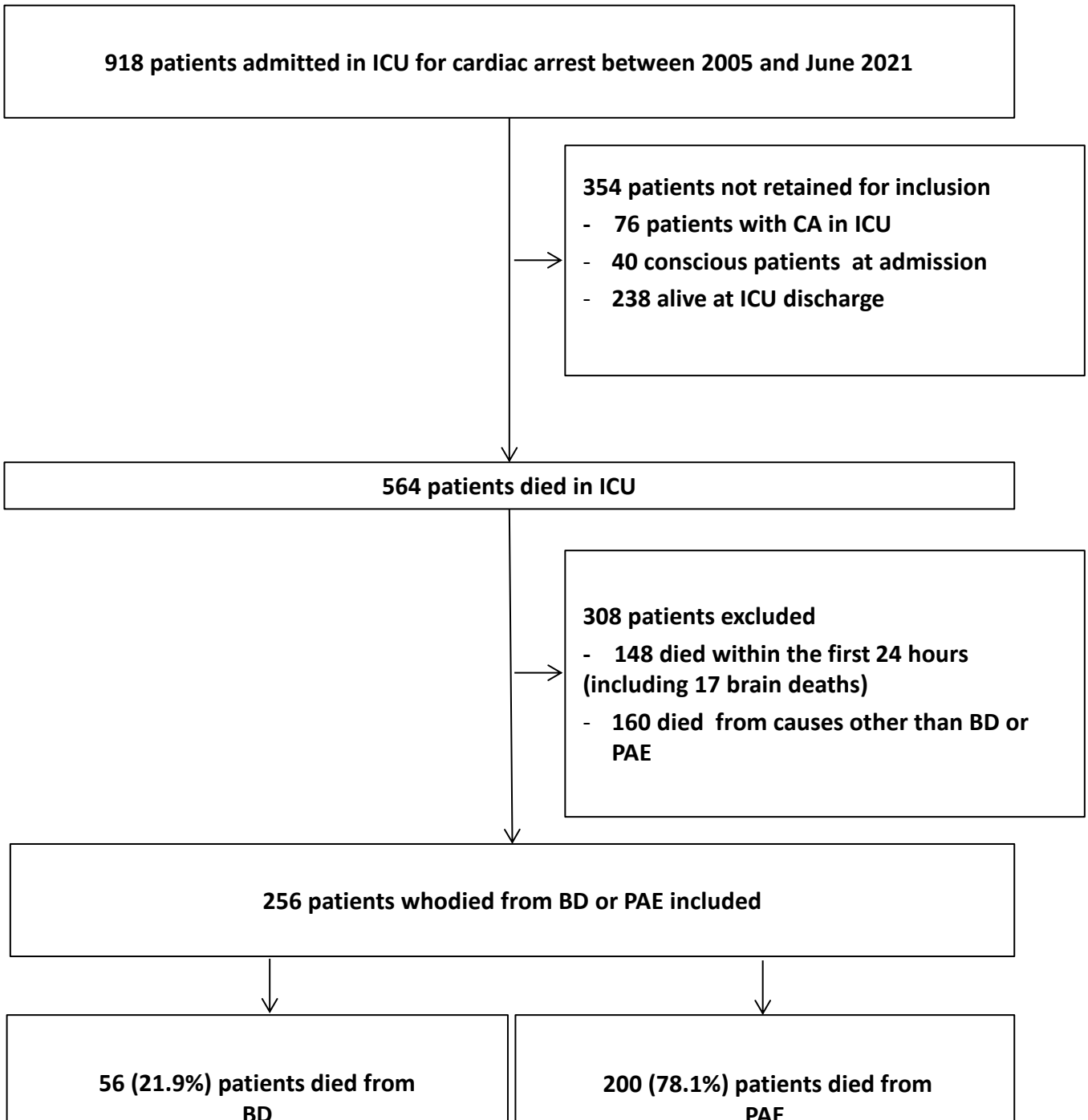
Figure 1 Study flow chart

Abbreviations: BD = brain death; CA = cardiac arrest; ICU = intensive care unit; PAE = post-anoxic encephalopathy.



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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.

Marine Paul, MD [1,2], Charles Hickel, MD[1], Gilles Troché, MD[1], Virginie Laurent, MD[1], Olivier Richard, MD[3], Sybille Merceron, MD[1], and Stéphane Legriel, MD, PhD[1,2,4]

[1] Intensive Care Unit, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France

[2] AfterROSC Study Group, Paris, France

[3] SAMU 78, Centre Hospitalier de Versailles - Site André Mignot, Le Chesnay, France 4

[4] University Paris-Saclay, UVSQ, INSERM, CESP, Villejuif, France

Correspondent

Marine Paul, MD

Intensive Care Department, Centre Hospitalier de Versailles - Site André Mignot, 177 Rue de Versailles, 78150 Le Chesnay, France

mpaul@ght78sud.fr

Twitter: @Marine_PAUL

ORCID: 0000-0002-0717-9555

Abstract

Objective : TTM, through its physiological effects on intracranial pressure, may impede the progression to BD in severe anoxic brain injury post-cardiac arrest. We examined whether there is a negative association between the use of TTM and the occurrence of BD after CA.

Design : Monocentric, retrospective study.

Setting: ICU, Versailles Hospital, France.

Participants : Comatose survivors of CA who died from BD or post-anoxic encephalopathy (PAE) after 24 hours.

Main outcome measures : PAE deaths corresponded to WLST due to irreversible post-anoxic coma or vegetative state according to prognostication guidelines. BD corresponded to the cessation of cerebral vascularization secondary to intra-cranial hypertension. The diagnosis of BD was definite by clinical diagnosis of deep coma Glasgow Coma Scale 3, loss of all brainstem reflexes, and the demonstration of apnea during a hypercapnia test. Cerebral 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 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 (OR 1.08, 95% CI 0.51–2.32). Factors associated with BD included a total duration of no-flow plus low-flow exceeding 30 minutes, CA due to neurological causes or hanging and a high arterial partial pressure of carbon dioxide (PaCO2) 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.

Key words: cardiac arrest, brain death, targeted temperature management, post-anoxic encephalopathy, organ donor.

Strengths and limitations of this study

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- This study addresses a unique aspect of 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-center, retrospective design may limit generalizability and restricts 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 post-anoxic encephalopathy (PAE).[2]

Targeted Temperature Management (TTM) has been widely debated in recent years as a potential neuroprotective treatment for CA patients [3,4]. TTM may reduce neuroinflammation secondary to ischemia-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 [5,6]. In severe anoxic brain injury post-cardiac arrest, progression to brain death (BD) occurs in approximately 10–12% of cases.[7]. For these patients, TTM may reduce brain edema and intracranial pressure, potentially preventing progression to brain death 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-cardiac arrest, TTM might influence progression to brain death, and consequently, the pool of potential organ donors.

This study examines the potential association between TTM and progression to brain death in this specific population

Methods

This single-center, retrospective, observational cohort study was conducted using a prospectively collected dataset from Versailles hospital (NCT03594318). Data collection was approved by the Ethics Committee of the French Intensive Care Society (#CESRLF 20-41) which waived the requirement for written consent in accordance with French law on retrospective studies of anonymized data. The study is reported according to the STROBE statement.

Patient and public involvement

Patients were not involved in the research.

Study Setting and ICU Management

The management protocol for patients admitted to our 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 Artic Sun®, was used. was set at 33°C for comatose patients after out-of-hospital cardiac arrest (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. Rewarming was gradual, in increments of 0.25–0.5°C, done passively before 2016 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 mmHg. 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[8–11].

Study Objective

Our objective was to investigate an independent negative association between TTM and BD in a population of post-cardiac arrest 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

We defined PAE as cases where patients died following withdrawal of life-sustaining therapy (WLST) due to irreversible neurological injury, in accordance with prognostication guidelines. [8–10]. 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 apnea demonstrated during a hypercapnia test, in which arterial partial pressure of carbon dioxide ($PaCO_2$) rises to ≥50 mmHg (6.6 kPa) after 10 minutes of disconnection. Additional confirmatory tests, such as cerebral CT angiography or two 30-minute isoelectric and unreactive electroencephalograms taken 4 hours apart, were also used to confirm BD.[12–14]

Data Collection

Demographic characteristics and CA data were prospectively collected in an electronic database according to the Utstein style[15]. 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 (C.H. and M.P.) with a third author (S.L.) 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 post-resuscitation shock, use of TTM, and secondary brain insult parameters (e.g., minimum and maximum serum sodium, temperature, MAP, and PaCO2 between days 1 and 2 after admission, excluding PaCO2 from the apnea test for BD diagnosis). Only TTM lasting ≥24 hours was considered complete. While Witten et al. grouped BD and PAE together as neurological deaths, we opted to dichotomise these as PAE due to neurological WLST and BD [2].

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 interquartile ranges (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 Chi-square 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 odds ratios (OR) with 95% confidence intervals (CI). 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, version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org; accessed March 13, 2021).

Data Availability

The anonymized datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and 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 cardiac arrest (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=0.005) and 54.3% received TTM for ≥24 hours (44.6% in the BD group

and 57.0% in the PAE group, p=0.10). Fifty-six 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) and 7 days (5–9), respectively.

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

Table 1 Patient Characteristics

N (%) or Median (interquartile range)				
	Total (N = 256)	**Brain death (N = 56)**	**PAE (N = 200)**	***p* value**
Age, y	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 edema 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, mmHg				
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
Natremia 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, mmHg				
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
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

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

The cause of CA differed significantly between the two groups, with more neurological causes and hangings in the BD group ($p < 0.001$). 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%), $p < 0.001$). The CT scans were conducted at a median (IQR) of 3 hours [2–11] post-cardiac arrest, with no significant difference between the groups.

Although TTM for ≥24 hours was used less frequently in the BD group compared to the PAE group (44.6% vs 57.0%), this difference was not statistically significant ($p = 0.10$). 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 EEGs confirming isoelectric EEG.

Factors Independently associated with BD

TTM ≥24 hours was not significantly associated with brain death (BD) in either univariate analysis (OR 0.61, 95% CI 0.35–1.10, p = 0.14) or multivariate analysis (OR 1.08, 95% CI 0.51–2.32, p = 0.80; see Table 2). The following factors were independently associated with an increase in BD: no-flow plus low-flow duration >30 minutes (OR 3.17, 95% CI 1.48–7.23, *p* = 0.004), CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49–17.90, *p* < 0.001) and a high $PaCO_2$ between days 1 and 2 after admission >45 mmHg (6 kPa) (OR 3.92, 95% CI 1.82–9.00, *p* < 0.001). After exclusion of patients managed with TTM 36°C, the association between TTM 33 and BD was still not statistically significant (OR 0,43, 95% CI 0.16–1.17, p=0.093) (ESM).

Table 2 Factors associated with brain death by multivariable analysis[a]

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

Abbreviations: CI = confidence interval; TTM = targeted temperature management; MAP: mean arterial pressure; OR = odds ratio; $PaCO_2$ = arterial partial pressure of carbon dioxide.

[a]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 mmHg, maximal arterial carbon dioxide between days 1 and 2 after admission >45 mmHg, maximal natremia day 1 >143 mmol/L. Goodness-of-fit Hosmer-Lemeshow test, *p* = 0.82; area under the receiver operating characteristics curve estimated by the C-statistic = 0.81.

Discussion

This retrospective analysis of 256 patients with severe anoxic brain injuries following cardiac arrest, 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 cardiac arrest duration of more than 30 minutes, a CA due to neurological causes or hanging, and a maximum PaCO2 of over 45 mmHg (6 kPa) between days 1 and 2 post-admission.

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 edema 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-cardiac arrest deaths are due to brain death, occurring at a mean delay of 3 days post-ROSC, and over 40% of brain-dead patients are potential organ donors.[7,21] 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-cardiac arrest patients who progress to brain death 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 0.51–2.32, p = 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 1,056 patients, with 15.2% patients progressing to BD, TTM was not associated with BD when compared to patients who died from other causes. [24,25] Compared to these studies, our work uniquely focuses on a homogenous 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 minutes 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 minutes is a risk factor for progression to BD .[25] 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 mmHg (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.[4] A prospective, multicenter, randomized phase of 1700 post-CA patients found that therapeutic mild hypercapnia during the first 24 hours ($PaCO_2$ 50–55 mmHg (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 mmHg (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 multicenter study indicates a U-shaped association between $PaCO_2$ and in-hospital mortality, with higher risk associated with $PaCO_2$ levels below 35 mmHg (4.6 kPa) or above 55 mmHg (7.3 kPa), though specific causes of death were not detailed.[27]

We acknowledge several limitations in our study, which should be viewed as an exploratory analysis rather than definitive evidence. First, the retrospective design of the outcome analysis limits our ability to establish causal relationships between TTM and brain death. 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. [15,16] Although in our sensitivity analysis considering only patients managed with TTM 33°C excluding patients managed at TTM 36, we still did not find a significant association between TTM and BD. Thirdly, this is a single-center 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 neurosurgery in the hospital. However, our recruitment represents a vast geographic area of western Paris. Fourthly, the population was restricted to patients who died from BD or PAE, which does not allow us to compare our population with the literature nor to answer the question of the incidence of post-CA BD. But we wanted to explore the association on the most severely brain injured CA patients. For this reason, we did not include patients who were discharged alive, as their neurological impairment was by definition less severe, and currently, based on the literature, we cannot question the neuroprotective effect of TTM in this patient population. Fifthly, it cannot be excluded that self-fulfilling prophecy limits the results of the study. 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 minimized the potential effect of shorter durations of TTM on the primary outcome. In the same aspect, the fact that we used TTM 33 and 36°C 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-cardiac arrest patients in whom TTM may offer limited benefit or even potential harm. Such studies could contribute to refining treatment strategies and optimizing patient care.

Glossary

BD = brain death; **CA** = cardiac arrest; **CI** = confidence interval; **CPR** = cardiopulmonary resuscitation; **ICU** = intensive care unit; **IQR** = interquartile range; **MAP** = mean arterial pressure; **OHCA** = out-of-hospital cardiac arrest; **OR** = odds ratio; **$PaCO_2$** = arterial partial pressure of carbon dioxide; **PAE** = post-anoxic encephalopathy; **ROSC** = return of spontaneous circulation; **TTM** = targeted temperature management; **WLST**= Withdrawal of life-sustaining therapy.

Declarations

Contributors

Study conception and design: MP, CH, SL

Data collection : MP, CH, SL

Analysis and interpretation of results: MP , SL

Draft manuscript preparation: CH MP

All authors reviewed the results and approved the final version of the manuscript.

Marine PAUL (MP) serves as guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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Patient and Public Involvement statement

Patients were not involved in the research.

Conflict of interest statement:

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Author contributions

Marine Paul and Charles Hickel wrote the first draft of the paper. All authors approved the final version of the manuscript.

MP: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

CH: Major role in the acquisition of data, Drafting/revision of the manuscript for content, including medical writing for content;

GT: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

VL: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

OR: Major role in the acquisition of data

SM: Major role in the acquisition of data Drafting/revision of the manuscript for content, including medical writing for content;

SL: Major role in the acquisition of data, Study concept or design, Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data;

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Figure 1 Study flow chart

Abbreviations: BD = brain death; CA = cardiac arrest; ICU = intensive care unit; PAE = post-anoxic encephalopathy.