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Association between targeted temperature management and reduction of brain death post cardiac arrest

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3 4 5	1	Association between targeted temperature management and reduction of
5 6 7	2	brain death in severe anoxic brain injured patients post cardiac arrest
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38	17	What is already known on this topic ? Targeted temperature management could theoretically
40 41	18	limit the evolution to brain death after cardiac arrest decreasing intracranial pressure.
42	19	What is our hypothesis? Some patients with very severe anoxic brain injuries may have been
43 44	20	at risk of progressing towards brain death, but the application of therapeutic hypothermia could
45	21	have prevented this progression, potentially reducing the pool of potential organ donors post
46 47 48	22	cardiac arrest.
49	23	What this study adds ? In this study, targeted temperature management during 24 h after CA
50 51	24	was not associated with evolution to brain death (BD). But BD was associated with longer no-flow
52	25	plus low-flow time, a neurological injury or hanging as the cause of CA, and high PaCO ₂ between
53 54	26	days 1 and 2 after admission.
55 56	27	How this study might affect research, practice or policy? Further studies are warranted to
57 58 59	28	find subgroups of post-CA patients for whom TTM is especially beneficial or futile.
60	29	

30 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 (PaCO₂) 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.

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57 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.

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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 O₂ 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].

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113 Study Objective

114 Our objective was to search for an independent negative association between TTM and BD in 115 a population of very severe brain damaged patients post CA.

116 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 (PaCO₂) 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]

136 Data Collection

Demographic characteristics and data related to CA were prospectively collected in an
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Page 7 of 22

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defibrillations, and administration of epinephrine. The final etiology of CA was so reported, with classification of patients into five groups (cardiac, respiratory, neurolog hanging, or other cause) by two authors (C.H. and M.P.) who were blinded from each of and a third (S.L.) in case of disagreement. This classification is intended to isolate cardiac sts at higher risk of intracranial hypertension such as neurological causes or hanging. In-IC riables were also collected: post-resuscitation shock, use of TTM, secondary brain insult meters (e.g., minimal and maximal serum sodium, temperature, MAP, and PaCO₂ betwe ays 1 and 2 after admission, excluding the PaCO₂ after the apnea test for BD diagnosis). y a TTM ≥24 hours was considered complete. While Witten et al. described cause of ath into five categories, pooling BD and PAE in the same group of neurological death e choose to dichotomize PAE with neurological withdrawal of life-sustaining therapy and]. To further investigate the association of TTM with BD we recorded: depth and duration TM, date of death, and cerebral oedema on the CT scan during the first day of admission. bral oedema was collected from the report of radiologist in the medical record of each patie and CT were not reanalyzed. When reports mentioned a loss of gray-white matter differen on or a brain swelling or a cerebral oedema we considered a presence of cerebral oedema

Statistical Analysis

Values are presented as medians and interguartile ranges (IQRs) o imbers and percentages, as appropriate. Univariate comparisons between patients who from BD or PAE were performed using the Mann–Whitney U test for continuous variab and the Chi-square or Fisher's exact tests for categorical variables, as appropriate. To ide ndependent association between TTM≥ 24 and BD, we compared subjects with BD and ect with PAE using univariate analysis then logistic regression. Before performing the multiv ble analysis, non-log-linear variables were transformed into dummy variables according heir median value. Non-collinear variables that yielded p values < 0.05 by univariate analysis, TTM \geq 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 Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, Al training, and similar technologies.

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> 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).

176 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.

181 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.

1 187 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

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[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 PaCO₂, 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.

208 Factors Independently associated with BD

TTM \geq 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 PaCO₂ 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).

216 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 \geq 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 PaCO₂ >45 mmHg (6 kPa) between days 1 and 2 after admission were independently associated with increased likelihood of BD.

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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 PaCO₂ 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 \ge 24 hours. TTM \ge 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,

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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.

27 263

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 PaCO₂ >45 mmHg (6 kPa) during between days 1 and 2 after admission was also associated with progression to BD. PaCO₂ 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 (PaCO₂ 50-55 mmHg (6.6-7.3 kPa)) attenuated neuron-specific

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enolase release compared with normocapnia (PaCO₂ 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 PaCO₂ 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 PaCO₂ 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.

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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

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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.

316 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.

5 323 Glossary

- 7 324 **BD** = brain death; **CA** = cardiac arrest; **CI** = confidence interval; **CPR** = cardiopulmonary
- ⁹ 325 resuscitation; **ICU** = intensive care unit; **IQR** = interquartile range; **MAP** = mean arterial
- ¹ 326 pressure; **OHCA** = out-of-hospital cardiac arrest; **OR** = odds ratio; **PaCO**₂ = arterial partial
- ³ 327 pressure of carbon dioxide; **PAE** = post-anoxic encephalopathy; **ROSC** = return of
- $\frac{1}{2}$ 328 spontaneous circulation; **TTM** = targeted temperature management; **WLST** = Withdrawal of
- 329 life-sustaining therapy.
- **Declarations**
- 52 331 Acknowledgement
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- ⁶⁰ 335 **Conflict of interest statement:**

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one of the authors has any conflicts of interest to declare.

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- arine Paul and Charles Hickel wrote the first draft of the paper. All authors approved the
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- H: Major role in the acquisition of data, Drafting/revision of the manuscript for content,
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- cluding medical writing for content;
- .: Major role in the acquisition of data, Study concept or design, Drafting/revision of the
- anuscript for content, including medical writing for content; Analysis or interpretation of
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	Total (N = 256)	Brain death (N = 56)	PAE (N = 200)	p val
Age, y	63 (53–75)	58 (45–65)	65 (55–76)	<0.
Male	167 (65.2)	32 (57.1)	135 (67.5)	0.20
OHCA	214 (83.6)	50 (89.3)	164 (82.0)	0.2
Public place at CA	129 (50.4)	34 (60.7)	95 (47.5)	0.0
Arrest witnessed/monitored	199 (77.7)	36 (64.3)	163 (81.5)	0.0
Bystander CPR	64 (25.0)	13 (23.2)	51 (25.5)	0.7
Shockable first recorded rhythm	83 (32.4)	9 (16.1)	74 (37.0)	0.0
Total number of defibrillations before ROSC	0 (0–2.0)	0 (0–2.0)	0 (0–2.3)	0.0
Use of epinephrine	222 (86.7)	49 (87.5)	173 (86.5)	0.8
Total epinephrine dose before ROSC, mg	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.9–4.0)	0.5
Time from CA to CPR (no-flow), min	5 (0–11)	6 (2–15)	5 (0–10)	0.3
Time from CA to ROSC (low-flow), min	21 (15–30)	26 (20–36)	20 (15–30)	0.0
No-flow + low-flow, min (n = 245)	30 (20-40)	36 (28–45)	30 (20–37)	0.0
Cerebral edema on initial CT scan (n=120)	36/120 (30.0)	18/32 (56.3)	18/88 (20.5)	<0
Time to CT scan, hours after CA	3 (2-11)	3 (2-11)	3 (2-4)	0.4
admission, mmol/L	5.7 (3.2–8.1)	6.4 (4.8–9.4)	5.4 (2.9–7.5)	0.0
Cardiaa	05 (27 1)	15 (26 9)	90 (40 0)	<0
Boopirotony	$\frac{90}{62}(37.1)$	10 (20.0)	<u> </u>	
Neurological	02 (24.4)	11 (19.0)	$\frac{51(25.5)}{6(2.0)}$	
	22 (8.6)	0(16.1)	13 (6 5)	
	$\frac{22}{60}$ (0.0)	9(10.1)	<u> </u>	
First temperature at admission °C	36.2 (36.0-37.0)	36.0 (34.5-36.9)	36 3 (35 1- 37 2)	0 1
TTM	213 (83 2)	38 (67 9)	175 (87 5)	<u> </u>
Time to TTM target hours after CA	<u>2 13 (03.2)</u> 6 (3-7)	5 (3-10)	6 (3-9)	<u> </u>
Duration of TTM hours	<u>26 (20–31)</u>	25 (20-29)	26 (20-32)	0,0
TTM >12 hours	192 (75 0)	34 (60 7)	158 (79 0)	0.0
TTM >24 hours	139 (54 3)	25 (44 6)	114 (57 0)	0.0
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)	0.7
Body temperature between days 1 and 2 after admission, °C	20,100 (20.0)	0.20 (2110)		0.1
Minimal	33.0 (32.1–34.0)	33.0 (31.9–34.5)	33.0 (32.1–34.0)	0.7
Maximal	37.0 (36.4–37.9)	37.4 (36.7–38.0)	37.0 (36.4–37.8)	0.0
PaCO ₂ between days 1 and 2 after admission, mmHg		2		
Minimal	29.0 (26.0–32.0)	29.0 (26.5–35.0)	29.0 (26.0–33.0)	0.5
Maximal Natremia between days 1 and 2 after admission. mmol/L	45.0 (39.0–54.0)	50.0 (42.0–59.0)	44.0 (39.0–52.0)	0.0
Minimal	137.0 (134.8–140.0)	138.0 (135.0–142.0)	137.0 (134.0–140.0)	0.0
Maximal	143.5 (139.0–146.0)	145.0 (141.0–148.0)	143.0 (139.0–144.0)	<0
MAP between days 1 and 2 after admission, mmHg				
Minimal	59 (51–64)	57 (50–62)	59 (51–64)	0.3
Maximal	114 (102–128)	124 (106–141)	113 (101–125)	0.0
Post-resuscitation shock	188 (73.4)	42 (75.0)	146 (73.0)	0.8
Continued epinephrine use	100 (39.1)	26 (46.4)	74 (37.0)	0.2
Renal replacement therapy	37 (14.5)	5 (8.9)	32 (16.0)	0.2
Time between admission and death	6 (4–9)	4 (2–5)	7 (5–9)	<0

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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	1.93 (0.93-4.03)	0.077
Maximal natremia between days 1 and 2 after admission >143 mmol/L	1.93 (0.93–4.03)	0.07

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

^aVariables 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. To be teries only



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 lifesupport 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

	Multivaria	ate analysis	
-	OR (95	5%CI)	P valu
TTM >24h	1.07 (0.50)-2.32)	0.
Age > 63 vears	0.70 (0.32	2-1.53)	0.4
Shockable first recorded rhythm	0.42 (0.15	5-1.05)	0.074
No-flow + low-flow >30 min	3.06 (1.42	2-7.00)	0.00
Neurological cause of cardiac arrest or hanging	5.18 (1.89	9-15.1)	0.00
Maximal MAP between day $1-2 > 114 \text{ mmHg}$	1 49 (0 7))-3 17)	0
Maximal arterial carbon dioxide between day $1-2 > 45$ mmHg	3.81 (1.76	5- 8.8 1)	0.00
Maximal natremia day $1-2 > 143$ mmol/L	1.96(0.94	4-4.14)	0.07
ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36°	is in a sub group of pat	ients receiving	
ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36°	is in a sub group of pat	ients receiving	_
ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36° TTM 33° >24 hours	ois in a sub group of pat) OR (95% CI) 0,43 (0.16–1.17)	ients receiving p value 0.093	-
ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36° TTM 33° >24 hours Shockable first recorded rhythm	bis in a sub group of pat OR (95% CI) 0,43 (0.16–1.17) 0.48 (0.17–1.24)	ients receiving p value 0.093 0.14	-
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ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36° TTM 33° >24 hours Shockable first recorded rhythm No-flow + low-flow >30 minutes Neurological cause of cardiac arrest or hanging Maximal PaCO2 between days 1 and 2 after admission >45 mmHa	OR (95% CI) 0,43 (0.16–1.17) 0.48 (0.17–1.24) 2.54 (1.11–6.18) 5.64 (2.06–16.40) 3.65 (1.58, 9.16)	ients receiving p value 0.093 0.14 0.031 <0.001 0.004	
ESM 3: Factors associated with brain death by multivariable analys TTM 33° vs no TTM (after exclusion of patients receiving TTM 36° TTM 33° >24 hours Shockable first recorded rhythm No-flow + low-flow >30 minutes Neurological cause of cardiac arrest or hanging Maximal PaCO2 between days 1 and 2 after admission >45 mmHg	is in a sub group of pat OR (95% CI) 0,43 (0.16–1.17) 0.48 (0.17–1.24) 2.54 (1.11–6.18) 5.64 (2.06–16.40) 3.65 (1.58–9.16)	ients receiving p value 0.093 0.14 0.031 <0.001 0.004 	

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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.

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Keywords:	Out-of-Hospital Cardiac Arrest, Brain Injuries, Death, Sudden, Cardiac





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2 3 4	1	Impact of Targeted Temperature Management on Progression to Brain Death
5 6	2	after Severe Anoxic Brain Injury Following Cardiac Arrest: An Observational
7 8	3	Study.
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1 ว		
2 3	30	Abstract
4 5	31	Objective : This study explores whether TTM in severe anoxic brain injury post-cardiac arrest
6	32	might be futile. We hypothesized that TTM could, through its physiological effects on
/ 8	33	intracranial pressure, impede the progression to BD potentially impacting organ donation
9 10	34	opportunities, without improving neurological outcomes. We investigated whether there is a
10	35	negative association between the use of TTM and the occurrence of BD after CA.
12 13		
14	36	Design : Monocentric, retrospective study.
15 16		
17	37	Setting: ICU, Versailles Hospital, France.
18 19	20	Participants : Comptose survivors of CA who died from BD or post-apovic encephalopathy
20	30	(PAE) after 24 hours
21	55	
23 24	40	Main outcome measures : PAE deaths corresponded to WLST due to irreversible post-
25	41	anoxic coma or vegetative state according to prognostication guidelines. BD corresponded to
26 27	42	the cessation of cerebral vascularization secondary to intra-cranial hypertension. The
28	43	diagnosis of BD was definite by clinical diagnosis of deep coma Glasgow Coma Scale 3, loss
29 30	44	of all brainstem reflexes, and the demonstration of apnea during a hypercapnia test. Cerebral
31 32	45	CT scan or two isoelectric and unreactive electroencephalograms were used to confirm BD.
33	46	To identify the independent association between TTM and BD, we conducted a multivariable
34 35	47	logistic regression analysis.
36		
37 38	48	Results : Out of 256 patients included between 2005 and 2021, 54.3% received TTM for at
39 40	49	for at least 24 hours, and 56 patients (21.9%) died from BD. In the multivariable analysis,
40 41	50	TTM for 24 hours or more was not associated with a decrease in BD (OR 1.08, 95% CI 0.51-
42 43	51	2.32). Factors associated with BD included a total duration of no-flow plus low-flow
44	52	exceeding 30 minutes, CA due to neurological causes or hanging and a high arterial partial
45 46	53	pressure of carbon dioxide (PaCO2) between days 1 and 2 after admission.
47		
48 49	54	Conclusions: This exploratory analysis of post-CA patients with severe anoxic brain injury
50 51	55	did not find an association between TTM ≥24 hours and a reduction in BD. Further studies
52	56	are needed to identify specific subgroups of post-CA patients for whom TTM may be
53 54	57	especially tutile or even harmful.
55	58	Key words: cardiac arrest brain death targeted temperature management post-anoxic
56 57	59	encephalopathy, organ donor.
58		
60	60	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

70 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).

85 We hypothesize that in patients with very severe anoxic brain injuries post-cardiac 86 arrest, TTM could potentially prevent progression to brain death, thereby reducing the pool of

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

90 Methods

91 This single-center, retrospective, observational cohort study was conducted using a 92 prospectively collected dataset from Versailles hospital (NCT03594318). Data collection was 93 approved by the Ethics Committee of the French Intensive Care Society (#CESRLF 20-41) 94 which waived the requirement for written consent in accordance with French law on 95 retrospective studies of anonymized data. The study is reported according to the STROBE 96 statement.

97 Patient and public involvement

98 Patients were not involved in the research.

100 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 since2005[8–11].

8 116

117 Study Objective

118 Our objective was to investigate an independent negative association between TTM and BD 119 in a population of post-cardiac arrest patients with very severe anoxic brain injury.

16 120 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.

37 130 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 (PaCO₂) rises to \geq 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]

58 140 Data Collection

Page 7 of 20

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characteristics and CA data were prospectively collected in an electronic Demograph database ad ording to the Utstein style[15]. Information included age, gender, CA setting, initial rhythn time from collapse to cardiopulmonary resuscitation (CPR) initiation (no-flow) time from C initiation to ROSC (low-flow), presence of a witness, number of defibrillations, and adminis tion of epinephrine. The final aetiology of CA was also reported, with patients ive groups (cardiac, respiratory, neurological, hanging, or other causes) by two classified int blinded auth s (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 uses or hanging. neurological

Additional in U variables were collected, including post-resuscitation shock, use of TTM, and secondary b n insult parameters (e.g., minimum and maximum serum sodium, temperature, MAP, and F O2 between days 1 and 2 after admission, excluding PaCO2 from the apnea test for BD of gnosis). Only TTM lasting ≥24 hours was considered complete. While Witten et al. grouped and PAE together as neurological deaths, we opted to dichotomise these as PAE due to urological WLST and BD [2].

ore the association between TTM and BD, we recorded the depth and duration To further ex of TTM, date f death, and presence of cerebral oedema on the CT scan from the first day of admission. ebral oedema was identified based on radiologist reports in patient records; CT scans were t reanalysed. Reports indicating loss of grey-white matter differentiation, brain swelling, or ebral oedema were classified as showing cerebral oedema.

47 161 Statistical Analysis

Values are esented as medians with interguartile ranges (IQRs) or as numbers with s appropriate. Univariate comparisons between patients who died from BD and percentages those who d from PAE were conducted using the Mann–Whitney U test for continuous variables ar the Chi-square or Fisher's exact test for categorical variables, as appropriate. To identify an independent association between TTM \ge 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 \geq 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

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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.

198Table 1 shows the characteristics of patients according to their progression to BD or PAE.199Patients who died from BD were younger (58 vs 65 years, p < 0.001) and had a lower frequency200of witnessed CA (64.3% vs 81.5%, p = 0.006) and initial shockable rhythm (16.1% vs 37.0%,201p = 0.003) compared to those who died from PAE. Median (IQR) no-flow plus low-flow duration202was longer in the BD group (36 [28–45] vs 30 [20–37] minutes, p = 0.001), and admission203lactate levels were higher (6.4 [4.8–9.4] vs 5.4 [2.9–7.5] mmol/L, p = 0.003).

204 Table 1 Patient Characteristics

N (%) or Median (interquartile range)		D a la set	545	
	(N = 256)	(N = 56)	PAE (N = 200)	<i>p</i> 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
ТТМ	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

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_	36°C	29/139 (20.9)	6/25 (24.0)	23/114 (20.2)	0.70
	Body temperature between days 1				
-	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				0.020
_	admission, mmHg				
_	Minimal	29.0 (26.0–32.0)	29.0 (26.5–35.0)	29.0 (26.0–33.0)	0.50
-	Maximai Natromia botwoon days 1 and 2 aftor	45.0 (39.0–54.0)	50.0 (42.0–59.0)	44.0 (39.0–52.0)	0.009
	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)	<0.00
	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)	0.30
-	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,	6 (4–9)	4 (2–5)	7 (5–9)	<0.00
າດເ	days"	CPP - cardionulmonan	requisitation: ICLL - int	tonsivo caro unit: IOP -	
207	interguartile range: MAP = mean art	erial pressure: OHCA =	out-of-hospital cardiac	arrest: $PaCO_2 = arterial$	l partia
208	pressure of carbon dioxide; $PAE = p$	ost-anoxic encephalopa	athy; ROSC = return of	spontaneous circulation	; TTM
209	= targeted temperature managemen	nt. 🚺 · · ·			
210	* Time between admission and deat	h corresponds to the da	ate of brain death diagno	osis in BD patients	
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212	The cause of CA differed sign	ificantly between th	ne two groups, with	more neurological o	cause
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2							
3 4	227	Factors Independently associated with BD					
5 6	228	TTM ≥24 hours was not significantly associated with brain death (BD) in either univariate					
7 8	229	analysis (OR 0.61, 95% CI 0.35–1.10, p = 0.14) or multiva	riate analysis (OR 1.	08, 95% CI			
9 10	230	0.51–2.32, p = 0.80; see Table 2). The following factors we	re independently asso	ociated with			
11 12	231	an increase in BD: no-flow plus low-flow duration >30 minute	es (OR 3.17, 95% CI 1	.48–7.23, <i>p</i>			
13 14	232	= 0.004), CA due to neurological cause or hanging (OR 6.49	9, 95% CI 2.49–17.90	, <i>p</i> < 0.001)			
15 16	233	and a high $PaCO_2$ between days 1 and 2 after admission >4	45 mmHg (6 kPa) (OF	R 3.92, 95%			
17 18	234	CI 1.82–9.00, $p < 0.001$). After exclusion of patients manage	d with TTM 36°C, the	association			
19 20 21	235	between TTM 33 and BD was still not statistically significa	nt (OR 0,43, 95% CI	0.16–1.17,			
21 22 23	236	p=0.093) (ESM).	p=0.093) (ESM).				
24 25	237 238	Table 2 Factors associated with brain death by multivariable	analysis ^a				
26			OR (95% CI)	p value			
27		TTM >24 hours	1.08 (0.51–2.32)	0.80			
28		Shockable first recorded rhythm	0.43 (0.16–1.03)	0.068			
29		No-flow + low-flow >30 minutes	3 17 (1 48–7 23)	0.004			
30		Neurological cause of cardiac arrest or hanging	6 49 (2 49–17 90)	<0.001			
21		Maximal PaCO, between days 1 and 2 after admission >45 mmHg	3 92 (1 82_9 00)	<0.001			
51		Maximal natromia botwoon days 1 and 2 after admission >1/3	1.02(1.02 0.00)	0.077			
32		maximar natrenna between days 1 and 2 arter admission > 145	1.00 (0.00-4.00)	0.077			
33	220	Abbreviations: CL = confidence interval: TTM = targeted temperature man	agement: MAP: mean arte	rial pressure:			
34	235	$\Delta D = odds ratio: PaCO = arterial partial pressure of earbon diavide$	agement, MAF. mean alte	nai pressure,			
35	240	$OR = 0003$ ratio, $FaCO_2$ = alterial partial pressure of Carbon dioxide.	62 years abaakabla first r	agordad			
36	241	rbuthm, po flow + low flow >20 min, pourological course of cardiac arrest of	v honging maximal MAD h				
22	242	1 and 2 after admission >114 mmHq, maximal arterial earban diavide bat	woon days 1 and 2 offer ad	mission >45			
3/	245	mmHa maximal natromia day 1 >142 mmal/L. Coodpass of fit Heamer L	ween days 1 and 2 after ad monopoly toot $p = 0.82$; or	1111551011 ~43			
38	244	receiver exercising observations output optimated by the C statistic = 0.82	p = 0.62, an	ea under the			
39	245	receiver operating characteristics curve estimated by the C-statistic = 0.6					
40	246						
41							
42 43	247	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.

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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 PaCO₂ 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

Page 13 of 20

BMJ Open

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. PaCO₂ plays a crucial role in managing secondary

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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 (PaCO₂ 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 (PaCO₂ 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 PaCO₂.[29] Furthermore, a recent multicenter study indicates a U-shaped association between PaCO₂ and in-hospital mortality, with higher risk associated with PaCO₂ 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 PaCO₂, 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

Page 15 of 20

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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

Glossary

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.

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3 4	365	BD = brain death; CA = cardiac arrest; CI = confidence interval; CPR = cardiopulmonary
5 6	366	resuscitation; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial
7 8	367	pressure; OHCA = out-of-hospital cardiac arrest; OR = odds ratio; PaCO ₂ = arterial partial
9 10	368	pressure of carbon dioxide; PAE = post-anoxic encephalopathy; ROSC = return of
11 12	369	spontaneous circulation; TTM = targeted temperature management; WLST = Withdrawal of
13 14 15	370	life-sustaining therapy.
15 16 17	371	Declarations
17 18 19	372	Contributors
20 21	373	Study conception and design: MP, CH, SL
22	374	Data collection : MP, CH, SL
23 24	375	Analysis and interpretation of results: MP , SL
25 26	376	Draft manuscript preparation: CH MP
27 28	377	All authors reviewed the results and approved the final version of the manuscript.
29 30	378	Marine PAUL (MP) serves as guarantor and accepts full responsibility for the work and/or the
31 32	379	conduct of the study, had access to the data, and controlled the decision to publish.
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44 45	385	Patients were not involved in the research.
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11 12	396	MP: Major role in the acquisition of data, Study concept or design, Drafting/revision of the
13 14 15	397	manuscript for content, including medical writing for content; Analysis or interpretation of
15 16 17	398	data;
17 18 19	399	CH: Major role in the acquisition of data, Drafting/revision of the manuscript for content,
20 21	400	including medical writing for content;
22 23	401	GT: Major role in the acquisition of data Drafting/revision of the manuscript for content,
24 25	402	including medical writing for content;
26 27	403	VL: Major role in the acquisition of data Drafting/revision of the manuscript for content,
28 29	404	including medical writing for content;
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34 35 26	407	including medical writing for content;
30 37 38	408	SL: Major role in the acquisition of data, Study concept or design, Drafting/revision of the
39 40	409	manuscript for content, including medical writing for content; Analysis or interpretation of
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18	520	Figure 1 Study flow chart
19 20	520	Abbraviationa: $DD = brain death: CA = cardiae arreat: C = intensive care unit: DAE = next energies$
21 22	521	Abbreviations: BD = brain death, CA = cardiac arrest, ICO = intensive care unit, PAE = post-anoxic
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Association of Targeted Temperature Management on Progression to Brain Death after Severe Anoxic Brain Injury Following Cardiac Arrest: An Observational Study.

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2 3 4	1	Association of Targeted Temperature Management on Progression to Brain
5 6	2	Death after Severe Anoxic Brain Injury Following Cardiac Arrest: An
7 8	3	Observational Study.
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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
Strengths and limitations of this study
2

Page 4 of 19

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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

68 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 specific population

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

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 (PaCO₂) rises to \geq 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**

Page 7 of 19

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Demographic characteristics d CA data were prospectively collected in an electronic database according to the Ut in style[15]. Information included age, gender, CA setting, initial rhythm, time from collar to cardiopulmonary resuscitation (CPR) initiation (no-flow) time from CPR initiation to RC (low-flow), presence of a witness, number of defibrillations, and administration of epineph e. The final aetiology of CA was also reported, with patients classified into five groups (car c, respiratory, neurological, hanging, or other causes) by two blinded authors (C.H. and M. with a third author (S.L.) resolving any disagreements. This classification aimed to isolat CAs at higher risk of intracranial hypertension, such as neurological causes or hangin

Additional in-ICU variables we ollected, including post-resuscitation shock, use of TTM, and secondary brain insult parame s (e.g., minimum and maximum serum sodium, temperature, MAP, and PaCO2 between da 1 and 2 after admission, excluding PaCO2 from the apnea test for BD diagnosis). Only T lasting \geq 24 hours was considered complete. While Witten et al. grouped BD and PAE toge r as neurological deaths, we opted to dichotomise these as PAE due to neurological WLS nd BD [2].

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

, 161 Statistical Analysis

Values are presented as me ans with interquartile ranges (IQRs) or as numbers with ariate comparisons between patients who died from BD and percentages, as appropriate. l those who died from PAE we conducted using the Mann–Whitney U test for continuous variables and the Chi-square Fisher's exact test for categorical variables, as appropriate. To identify an independent association between TTM \ge 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 \geq 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

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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.

198Table 1 shows the characteristics of patients according to their progression to BD or PAE.199Patients who died from BD were younger (58 vs 65 years, p < 0.001) and had a lower frequency200of witnessed CA (64.3% vs 81.5%, p = 0.006) and initial shockable rhythm (16.1% vs 37.0%,201p = 0.003) compared to those who died from PAE. Median (IQR) no-flow plus low-flow duration202was longer in the BD group (36 [28–45] vs 30 [20–37] minutes, p = 0.001), and admission203lactate 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)	Tratel	Dusta de ette	DAE	
	1 Otal	Brain death $(N = 56)$		p
	(N = 250)	(de - N)	(N = 200)	value
Age, y	63 (53–75)	58 (45–65)	65 (55–76)	<0.00
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	0 (0–2.0)	0 (0–2.0)	0 (0–2.3)	0.053
before ROSC				
Use of epinephrine	222 (86.7)	49 (87.5)	173 (86.5)	0.80
Total epinephrine dose before	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.9–4.0)	0.50
ROSC, mg				
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),	21 (15–30)	26 (20–36)	20 (15–30)	0.006
min				
No-flow + low-flow, min (n = 245)	30 (20–40)	36 (28–45)	30 (20–37)	0.001
Cerebral edema on initial CT scan	36/120 (30.0)	18/32 (56.3) 🛛 🗠	18/88 (20.5)	<0.00
(n=120)				
Time to CT scan, hours after CA	3 (2-11)	3 (2-11)	3 (2-4)	0.4
Lactate concentration on ICU	5.7 (3.2–8.1)	6.4 (4.8–9.4)	5.4 (2.9–7.5)	0.003
admission, mmol/L				
Final identified cause of CA				<0.00
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
ТТМ	213 (83.2)	38 (67.9)	175 (87.5)	< 0.00
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

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_					
_	36°C	29/139 (20.9)	6/25 (24.0)	23/114 (20.2)	0.70
ا ن_	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
 	PaCO₂ 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				
_	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)	<0.00
-	MAP between days 1 and 2 after				0.00
	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) 6 (1-9)	<u>(0.9)</u> (2.5)	32 (10.0) 7 (5_0)	0.20
	have*	0 (4-9)	+ (2-3)	1 (0-9)	~ 0.00
06	Abbreviations: CA = cardiac arrest: (CPR = cardiopulmonary	resuscitation: ICU = int	tensive care unit. IOR =	
07	interquartile range; MAP = mean art	erial pressure; OHCA =	out-of-hospital cardiac	arrest; PaCO ₂ = arterial	l partia
80	pressure of carbon dioxide; PAE = p	ost-anoxic encephalopa	athy; ROSC = return of :	spontaneous circulation	; TTM
.09	= targeted temperature management	it. 🚺			
10	* Time between admission and deat	h corresponds to the da	te of brain death diagno	osis in BD patients	
11					
12	The cause of CA differed sign	ificantly between th	e two groups, with	more neurological c	ause
12	The cause of CA differed sign	ificantly between th	e two groups, with	more neurological c	ause
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3 4	227	Factors Independently associated with BD
5 6	228	TTM ≥24 hours was not significantly associated with brain death (BD) in either univariate
7 8	229	analysis (OR 0.61, 95% CI 0.35-1.10, p = 0.14) or multivariate analysis (OR 1.08, 95% CI
9 10	230	0.51-2.32, p = 0.80; see Table 2). The following factors were independently associated with
11 12	231	an increase in BD: no-flow plus low-flow duration >30 minutes (OR 3.17, 95% CI 1.48–7.23, p
13 14	232	= 0.004), CA due to neurological cause or hanging (OR 6.49, 95% CI 2.49–17.90, <i>p</i> < 0.001)
15 16 17	233	and a high $PaCO_2$ between days 1 and 2 after admission >45 mmHg (6 kPa) (OR 3.92, 95%
17 18 10	234	CI 1.82–9.00, $p < 0.001$). After exclusion of patients managed with TTM 36°C, the association
20 21	235	between TTM 33 and BD was still not statistically significant (OR 0,43, 95% CI 0.16-1.17,
22 23	236	p=0.093) (ESM).
24	227	Table 2 Factors associated with brain death by multivariable analysis

Table 2 Factors associated with brain death by multivariable analysis^a

3		
	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	1.93 (0.93-4.03)	0.077
mmol/L		

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 >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.

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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 PaCO₂ 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

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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.

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Interestingly, a maximum PaCO₂ >45 mmHg (6 kPa) between days 1 and 2 after admission was also associated with progression to BD. PaCO₂ 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 (PaCO₂ 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 (PaCO₂ 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 PaCO₂ and in-hospital mortality, with higher risk associated with PaCO₂ levels below 35 mmHg (4.6 kPa) or above 55 mmHg (7.3 kPa), though specific causes of death were not detailed.[27]

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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.

336 Conclusion

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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.

¹ 345 **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; PaCO₂ = arterial partial pressure of carbon dioxide; PAE = post-anoxic encephalopathy; ROSC = return of

- 350 spontaneous circulation; **TTM** = targeted temperature management; **WLST**= Withdrawal of
- 4 351 life-sustaining therapy.
- 6 352 Declarations
- 8 353 **Contributors**
- ⁰ 354 Study conception and design: MP, CH, SL
- 2 355 Data collection : MP, CH, SL
- 4 356 Analysis and interpretation of results: MP , SL
- 6 357 Draft manuscript preparation: CH MP
- All authors reviewed the results and approved the final version of the manuscript.
- $\frac{1}{50}$ 359 Marine PAUL (MP) serves as guarantor and accepts full responsibility for the work and/or the
- 52 360 conduct of the study, had access to the data, and controlled the decision to publish.
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56 57	389	SL: Major role in the acquisition of data, Study concept or design, Drafting/revision of the
58 59	390	manuscript for content, including medical writing for content; Analysis or interpretation of
60	391	data;

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8 9	481	
10 11	482	
12 13	483	Figure 1 Study flow chart
14 15	484	Abbreviations: BD = brain death; CA = cardiac arrest; ICU = intensive care unit; PAE = post-anoxic
16	485	encephalopathy.
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Page 20 of 19

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