



Clinical Paper

Neuromuscular blockade during therapeutic hypothermia after cardiac arrest: Observational study of neurological and infectious outcomes[☆]



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ABSTRACT

Introduction: Neuromuscular blockade (NMB) is widely used during therapeutic hypothermia (TH) after cardiac arrest but its effect on patient outcomes is unclear. We compared the effects of NMB on neurological outcomes and frequency of early-onset pneumonia in cardiac-arrest survivors managed with TH.

Methods: We retrospectively studied consecutive adult cardiac-arrest survivors managed with TH in a tertiary-level intensive care unit between January 2008 and July 2013. Patients given continuous NMB for persistent shivering were compared to those managed without NMB. Cases of early-onset pneumonia and vital status at ICU discharge were recorded. To avoid bias due to between-group baseline differences, we adjusted the analysis on a propensity score.

Results: Of 311 cardiac-arrest survivors, 144 received TH, including 117 with continuous NMB and 27 without NMBs. ICU mortality was lower with NMB (hazard ratio [HR], 0.54 [0.32; 0.89], $p = 0.016$) but the difference was not significant after adjustment on the propensity score (HR, 0.70 [0.39; 1.25], $p = 0.22$). The proportion of patients with good neurological outcomes was not significantly different (36% with and 22% without NMB, $p = 0.16$). Early-onset pneumonia was more common with NMB (HR, 2.36 [1.24; 4.50], $p = 0.009$) but the difference was not significant after adjustment on the propensity score (HR, 1.68 [0.90; 3.16], $p = 0.10$).

Conclusions: Continuous intravenous NMB during TH after cardiac arrest has potential own effects on ICU survival with a trend increase in the frequency of early-onset pneumonia. Randomised controlled trials are needed to define the role for NMB among treatments for TH-induced shivering.

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1. Introduction

Cardiac arrest occurs in 250,000–300,000 individuals each year in Europe.¹ Only 5–35% of these patients leave the hospital alive

with minimal to moderate neurological impairments.² Two studies established the beneficial effect in cardiac-arrest survivors of therapeutic hypothermia (TH) with a target core temperature of 32–34 °C.^{3,4} TH is now the standard of care for cardiac-arrest survivors, according to recommendations issued by the International Liaison Committee for Resuscitation (ILCOR) and European Resuscitation Council (ERC)⁵ and is widely used in Europe and throughout the world.^{6,7}

The optimal modalities of TH, however, remain unclear. Thus, uncertainty exists about the optimal time of hypothermia induction, rate of cooling, duration of hypothermia, target temperature, and rate of rewarming. During the induction and warming phases, a physiological reaction mediated by the hypothalamus may result in

Abbreviations: ICU, intensive care unit; NMB, neuromuscular blocker/blockade; ROSC, return of spontaneous circulation; SD, standard deviation; TH, therapeutic hypothermia; TOF, train of four.

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shivering.⁸ Shivering increases metabolic needs and body temperature, thus counteracting the beneficial effects of TH. Many drugs and physical factors can be used to decrease shivering. Sedatives and neuromuscular blockers (NMBs) were used routinely in the two studies that established the benefits of TH.^{3,4} Routine NMB administration not only decreases shivering, but also facilitates both the rapid achievement and the maintenance of the target temperature. However, recently developed active cooling techniques can be used to reach the target temperature without administering NMBs.^{9,10} Finally, in combination with these techniques, the administration of fluids at 4 °C facilitates TH induction.^{11–13}

NMB therapy has limitations in cardiac-arrest survivors. NMBs do not suppress the central hypothalamic activation by cold that is responsible for shivering but merely eliminate the peripheral response.⁸ NMB therapy is associated with an increased risk of pneumonia¹⁴ and with critical-illness neuromyopathy and its attendant morbidity.¹⁵ NMB therapy precludes sedation-depth monitoring and may therefore unnecessarily delay the neurological evaluation when sedation is too deep or increase the risk of posttraumatic stress disorder when sedation is too superficial.¹⁶

In our intensive care unit (ICU), since 2008, we have not used NMBs routinely in patients receiving TH. The aim of this study was to compare neurological outcomes and the frequency of early-onset pneumonia in cardiac-arrest survivors managed with TH and either continuous intravenous NMB therapy for shivering or no NMB therapy.

2. Materials and methods

We conducted an observational retrospective study of cardiac-arrest survivors managed using TH. According to French legislation (articles L.1121-1 paragraph 1 and R1121-2, Public Health Code), neither informed consent nor ethics committee approval was required.

2.1. Study population

The study was performed in the medical/surgical ICU of the regional hospital centre in La Roche-Sur-Yon, France, which serves a population of over 600,000. We included consecutive patients admitted to the ICU between January 2008 and July 2013 who met the following criteria: age 18 years or older; out-of-hospital cardiac arrest or in-hospital cardiac arrest followed by sustained recovery of spontaneous circulation (ROSC) defined as the presence of palpable pulses for >20 min; coma defined as a Glasgow Coma Scale (GCS) score ≤ 8 at ICU admission; and presence of criteria for using TH as defined in the written protocol of our ICU. We included both patients with shockable rhythms (ventricular fibrillation and ventricular tachycardia) and patients with non-shockable rhythms (electromechanical dissociation and asystole) according to Utstein Style criteria.¹⁷ Exclusion criteria were recovery of consciousness before ICU admission, pregnancy, clinical diagnosis of brain death at ICU admission, and treatment-limitation decision at ICU admission based on factors indicating a poor prognosis.

2.2. Management of cardiac-arrest survivors

2.2.1. Therapeutic hypothermia (TH)

TH was induced in all patients with shockable rhythms and in those patients with non-shockable rhythms whose ROSC time was shorter than 30 min.¹⁸ TH was induced by infusion of isotonic saline at 4 °C. Core body temperature was maintained at 33 °C for 24 h using either an external active method (cold tunnel or blanket, Artic Sun BARD Medical, Louisville, CO, USA) or an internal active method (CoolGard catheter, Alsius/Zoll, Voisin le

Bretonneux, France) depending on availability of each. Controlled warming from 33 °C to 37 °C was then performed with a target temperature-increase rate of 0.3–0.5 °C per hour. Inadequate cooling was defined as a core temperature above 34 °C and overshoot cooling as a core body temperature less than 32 °C during the maintenance phase.

2.2.2. Shivering and neuromuscular blockade

All patients were sedated with midazolam (Panpharma, Luitré, France) and fentanyl (Renaudin, Itxassou, France). Doses were adjusted to obtain a Richmond Agitation Sedation Scale score of –5.¹⁹ Persistent shivering was treated according to a four-step protocol established in our ICU.

- Step 1, single intravenous bolus of a hypnotic agent and an opioid²⁰ in a dose that depended on the infusion rates of hypnotic and opioid drugs (i.e., midazolam 5-mg intravenous bolus if the continuous midazolam infusion rate was 5 mg/h);
- Step 2, 2-fold increases in the infusion rates of the hypnotic agent and opioid;
- Step 3, intravenous bolus of 10 mg of the NMB cisatracurium (Nimbex®, GlaxoSmithKline, Marly-Le-Roy, France);
- and Step 4, continuous cisatracurium infusion in an initial dose of 10 mg/h, allowing train-of-four monitoring (Innervator NS252, Fisher & Paykel, Auckland, Australia) with a target of ≤ 1 twitch; during re-warming, the infusion was stopped when core body temperature increased above 35 °C.

2.3. Data collection

All data were abstracted from the computerised patient files (CareVue Chart, Philips, France). The following were collected: age; gender; GCS score at admission, Simplified Acute Physiology Score II (SAPS II) after 24 h; history of hypertension, diabetes, and smoking; characteristics of the cardiac arrest (cardiac or non-cardiac cause, no-flow and low-flow durations, and whether ST was elevated immediately after the cardiac arrest); whether coronary angiography was performed; whether coronary angioplasty was performed successfully; occurrence of early-onset pneumonia (<48 h); ICU stay duration; mechanical ventilation duration; and vital status at ICU discharge.

2.3.1. Outcome measures

The neurological outcome was assessed based on the Cerebral Performance Categories (CPC) score after 3 months, which was determined by calling each patient's usual physician. The CPC is a validated scale that classifies outcomes into five categories and is widely used in studies of cardiac-arrest patients.²¹ Lower scores indicate better performance and scores of 3 or higher indicate severe disability or death. For our study, we dichotomised the CPC scores into two groups, good neurologic function (CPC 1 and 2) and poor neurologic function (CPC 3–5), as done in earlier studies.³ Data were entered into a study database and checked for completeness and accuracy.

Pneumonia was suspected in patients with compatible pulmonary auscultation signs, leukopenia $<4000/\text{mm}^3$ or leucocytosis $>10000/\text{mm}^3$, and a new chest radiograph infiltrate. The diagnosis was confirmed by a quantitative bacteriological culture of a protected distal respiratory specimen ($>10^3$ cfu/mL); when no such specimen was collected, diagnostic confirmation relied on purulence of the tracheal aspirates with hypoxaemia ($\text{PaO}_2/\text{FiO}_2 < 300$) not explained by pulmonary oedema, pulmonary embolism, or atelectasis. Body temperature was not taken into account for suspecting early onset pneumonia, as the patients were receiving TH. Isolated microorganisms were routinely subjected to antibiotic susceptibility testing. Pneumonia

diagnosed within 48 h after intubation was defined as early-onset pneumonia.²² Pneumonia diagnosed after 48 h of mechanical ventilation was defined as ventilator-associated pneumonia (VAP).

2.4. Statistical analysis

Descriptive statistics were computed for all baseline features of the overall population and of the groups with and without continuous NMB therapy (NMB+ and NMB–, respectively). Frequency and percentages were determined for categorical data and mean \pm standard deviation (SD) or median and interquartile range for continuous data. Comparisons of the groups managed with and without NMBs (NMB+ and NMB– groups) relied on the two-tailed *t*-test or non-parametric Wilcoxon test for continuous data and on the chi-square test or Fisher exact test for categorical data. Because 28-day ventilator-free days, 28-day ICU-free days, mechanical ventilation (MV) duration, and ICU length of stay were not normally distributed, they were analysed using the non-parametric Wilcoxon test. Blood lactate level changes over time were compared between groups using a linear mixed model after logarithmic transformation. Crude proportions of patients with early-onset pneumonia and with a good neurological outcome (CPC 1–2 after 3 months) were compared using chi-square tests. Because death competed with early-onset pneumonia, a sensitivity analysis was performed using competing-risk analysis. Survival to ICU discharge rates were estimated using the Kaplan–Meier method and compared using the log rank test. Multivariate analyses were performed with adjustment on a propensity score to eliminate potential bias due to baseline differences between groups. The propensity score was estimated using a logistic regression model in which NMB exposure was the dependent variable and age, shockable rhythm, PO₂/FiO₂ ratio, no-flow time, low-flow time, and witnessed cardiac arrest were covariates. Values of *p* less than 0.05 were considered significant unless stated otherwise. Imputation of missing data was not performed. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and R 3.0.2 (<http://www.r-project.org>).

3. Results

3.1. Study patients and comparison of the two groups

Fig. 1 is the patient flowchart. Of 311 cardiac-arrest patients admitted during the study period, 167 were not included, for the following reasons: no TH (*n* = 136), brain death at ICU admission (*n* = 15), and no ROSC (*n* = 16). This left 144 patients for the study, including 117 (81%) given NMB therapy during TH and 27 (19%) managed without NMB therapy. Table 1 lists the main patient characteristics in the two groups. The only statistically significant baseline difference between the two groups was for age, which was older in the NMB– group (*p* = 0.014). Witnesses cardiac arrest, shockable rhythm, no-flow time, and low-flow time were not significantly different between the two groups. Coronary angiography was performed in 74 (63%) NMB+ patients and 13 (48%) NMB– patients. Core temperatures were similar at ICU admission and 12 h later (*p* = 0.23). Also similar were the cooling methods used (*p* = 0.90) and time needed to reach the target temperature (*p* = 0.85) (Table 2).

3.2. Early-onset pneumonia, 3-month neurological status, and survival (Table 3)

The crude proportion of patients with early-onset pneumonia was significantly higher in the NMB+ group than in the NMB– group (64% vs. 33%; *p* = 0.005) even after handling death as a competing event (HR 2.36 [1.24; 4.50], *p* = 0.009) (Table 3). The difference was

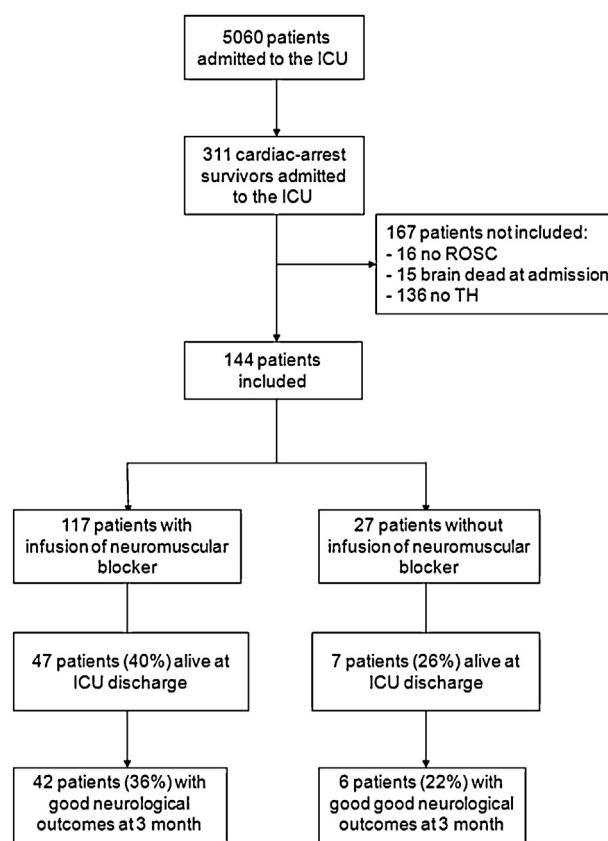


Fig. 1. Flowchart.

not significant after adjustment on the propensity score (*n* = 120, HR 1.68 [0.9; 3.16], *p* = 0.10). Of 84 patients with early-onset pneumonia, 54 had bacteria recovered from respiratory specimens (Table 4).

Continuous NMB infusion was associated with a non-significant increase in MV duration (4.0 days [2.3; 6.9] in the NMB+ group vs. 3.6 days [2.0; 4.5] in the NMB– group; *p* = 0.057) and a significant increase in ICU stay length (5.1 days [2.9; 9.7] in the NMB+ group vs. 4.0 days [2.2; 5.8] in the NMB– group); *p* = 0.049). Ventilator-free days and ICU-free days by day 28 did not differ between the two groups (Table 3).

Variations in serum lactate levels did not differ between the groups. ICU mortality was lower in the NMB+ group compared to the NMB– group (HR = 0.54 [0.32; 0.89], *p* = 0.016). However, the between-group difference for ICU survival was not significant after adjustment on the propensity score (*n* = 120, HR = 0.70 [0.39; 1.25], *p* = 0.22) (Table 3 and Fig. 2). The proportion of patients with a good neurological outcome after 3 months was not significantly different between the NMB+ and NMB– groups (Table 3).

4. Discussion

Most patients in our study required continuous NMB therapy for suppression of shivering during TH despite the use of a stepwise protocol, in keeping with a previous descriptive study.⁶ The Kaplan–Meier analysis, but not the propensity-score analysis, showed a significant increase in ICU survival in patients given NMB compared to those managed without NMB. The proportion of patients alive after 3 months with a CPC of 1 or 2 was not significantly different between these two groups. After adjustment on the propensity score, NMB therapy was associated with non-significant increases in early-onset pneumonia and ICU stay length.

NMB therapy was used routinely in the two studies that established the efficacy of TH in cardiac-arrest survivors:

Table 1
Baseline characteristics of the groups managed with and without continuous intravenous neuromuscular blocker therapy.

	NMB+ (n = 117)	NMB– (n = 27)	p value
Age in years, mean ± SD	58.5 ± 14.6	66.2 ± 12.7	0.014*
Males, n (%)	94 (80%)	19 (70%)	0.30
Witnessed cardiac arrest, n (%)	101 (86%)	25 (59%)	0.53
Location at cardiac arrest, n (%)			0.35
Home	37 (32%)	11 (41%)	
Public place	59 (50%)	14 (52%)	
In the hospital	21 (18%)	2 (7%)	
Hypertension, n (%)	67 (57%)	15 (55%)	1.00
Diabetes, n (%)	15 (13%)	6 (22%)	0.23
Smoker, n (%)	43 (37%)	5 (18%)	0.08
Shockable rhythm, n (%)	76 (65%)	12 (44%)	0.08
Cardiac cause, n (%)	88 (75%)	17 (63%)	0.23
ST segment elevation, n (%)	39 (33%)	8 (30%)	0.82
No-flow duration in min, mean ± SD	3.9 ± 5.2	2.4 ± 3.2	0.08
Low-flow duration in min, mean ± SD	23.5 ± 19.9	27.0 ± 14.3	0.42
SAPS II at ICU admission, mean ± SD	67.3 ± 16.4	73.2 ± 13.8	0.09
GCS score at ICU admission, mean ± SD	3.5 ± 0.9	3.7 ± 1.4	0.47
Post-resuscitation shock, n (%)	78 (66%)	20 (74%)	0.50
STEMI, n (%)	39 (33%)	8 (30%)	0.82
Coronary angiogram, n (%)	74 (63%)	13 (48%)	0.19
Successful angioplasty, n (%)	40 (34%)	9 (33%)	1.00
PaO ₂ /FiO ₂ ratio, median [Q1; Q3]	238.0 [153.0; 340.0]	233.0 [137.0; 340.0]	0.87

NMB, neuromuscular blocker therapy by continuous intravenous infusion during therapeutic hypothermia; SAPS II, Simplified Acute Physiology Score version II; ICU, intensive care unit; GCS, Glasgow Coma Scale; STEMI, ST-elevation myocardial infarction.

Table 2
Characteristics of therapeutic hypothermia in the groups managed with and without continuous intravenous neuromuscular blocker therapy.

	NMB+ (n = 117)	NMB– (n = 27)	p value
Core temperature at H0, mean ± SD	35.4 ± 1.5	35.0 ± 1.2	0.20
Core temperature at H12, mean ± SD	33.5 ± 0.9	33.8 ± 1.2	0.23
Cooling method, n (%)			
Internal active method (CoolGard™)	88 (76%)	20 (74%)	0.90
External active method (Cold tunnel or Artic Sun™)	29 (24%)	7 (26%)	
Time from ICU admission to target temperature, in min	365.1 (±334.1)	351.4 (±384.9)	0.85
Overshoot cooling, ^a n (%)	16 (14%)	3 (11%)	1.00
Inadequate cooling, ^b n (%)	40 (34%)	13 (48%)	0.19
Lactate at H0, median [Q1; Q3]	2.9 [1.9; 5.0]	4.0 [2.2; 6.2]	0.22
Lactate at H12, median [Q1; Q3]	1.9 [1.4; 4.1]	3.2 [1.5; 4.2]	0.32
Lactate at H24, median [Q1; Q3]	1.5 [1.1; 2.4]	1.4 [1.0; 2.7]	0.86

H0, time of ICU admission.

^a Core temperature lower than 32 °C.

^b Core temperature higher than 34 °C.

pancuronium was injected every 2 h in one study³ and vecuronium as needed to suppress shivering in the other.⁴ Several experimental and clinical arguments support routine NMB therapy during the cooling phase of TH.²³ In patients with acute respiratory distress syndrome requiring mechanical ventilation, muscle relaxants improved oxygenation.²⁴ In cardiac-arrest survivors, better oxygenation would be expected to lower the risk of secondary brain injury due to systemic factors and to avoid regional hyperoxia,

particularly affecting the brain, which may have deleterious effects after cardiac arrest.²⁵ In addition, the haemodynamic tolerance of NMBs is good^{26,27} compared with analgesics or sedatives, which are the alternatives for combatting shivering,²³ although no well-designed comparative trials are available.²⁸

However, a recent literature review does not support routine NMB therapy during TH,²³ and American Heart Association guidelines specify that the “Duration of NMB agents should be kept to

Table 3
Outcomes in the groups managed with and without continuous intravenous neuromuscular blocker therapy.

	NMB+ (n = 117)	NMB– (n = 27)	p value
Early-onset pneumonia, n (%)	75 (64%)	9 (33%)	0.005*
Ventilator-associated pneumonia, n (%)	6 (5.1%)	2 (7.4%)	– ^b
Nosocomial urinary tract infection, n (%)	4 (3.4%)	0 (0%)	– ^b
Nosocomial bacteraemia, n (%)	11 (9.4%)	1 (3.7%)	– ^b
MV duration in days, median [Q1; Q3]	4.0 [2.3; 6.9]	3.6 [2.0; 4.5]	0.057
ICU stay length in days, median [Q1; Q3]	5.1 [2.9; 9.7]	4.0 [2.2; 5.8]	0.049*
Ventilator-free days by D28, median [Q1; Q3]	0.0 [0.0; 22.1]	0.0 [0.0; 23.0]	0.37
ICU-free days by D28, median [Q1; Q3]	0.0 [0.0; 17.8]	0.0 [0.0; 18.8]	0.39
Good neurological outcome ^a , n (%)	42 (36%)	6 (22%)	0.26

NMB, neuromuscular blocker; MV, mechanical ventilation; ICU, intensive care unit; D28, day 28 after ICU admission.

^a Cerebral Performance Category 1 or 2, 3 months after cardiac arrest.

^b The sample size was too small for statistical testing.

§ Pneumonia diagnosed within 48 h after intubation was defined as early-onset pneumonia and pneumonia diagnosed after 48 h of mechanical ventilation as ventilator-associated pneumonia.

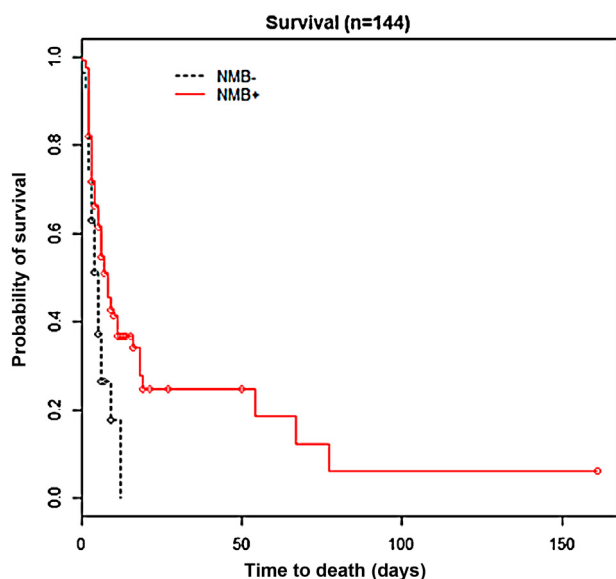


Fig. 2. ICU survival curve.

Table 4

Bacteria recovered in 54 of 84 patients with early-onset pneumonia.

Bacteria recovered	n = 54
Gram-positive cocci	
<i>Staphylococcus aureus</i>	16
<i>Streptococcus pneumoniae</i>	6
Other (<i>Corynebacterium</i> , group B streptococci)	4
Gram-negative bacteria	
<i>Haemophilus influenzae</i>	15
<i>Escherichia coli</i> (ESBL, n = 2)	6
<i>Enterobacter aerogenes</i>	3
<i>Klebsiella pneumoniae</i>	3
<i>Hafnia alvei</i>	3
<i>Proteus vulgaris</i>	2
<i>Aerococcus viridans</i>	1
<i>Serratia marcescens</i>	1
<i>Aeromonas sobria</i>	1
<i>Pseudomonas aeruginosa</i>	1
<i>Citrobacter freundii</i>	1
<i>Citrobacter koseri</i>	1
More than one species	7

ESBL, extended-spectrum beta-lactase production.

a minimum or avoided altogether".⁵ NMBs have several unwanted effects in cardiac-arrest patients. First, they preclude clinical monitoring for seizures or status epilepticus, in which early treatment improves the likelihood of survival with good function.²⁹ Second, NMBs do not inhibit the central controller linked to central hypothalamus receptors. Thus, they suppress shivering only by inhibiting the motor response and consequently only partially decrease the metabolic demand of the brain.³⁰ Third, NMB therapy can mask inadequate sedation, which may cancel out the expected benefits from TH. Finally, NMBs increase the risk of ICU-acquired neuromyopathy, although to a small degree compared to corticosteroids,³¹ particularly when used for short periods as during TH.²⁴

Our results are in accordance with the only previous report that routine NMB therapy was beneficial during TH in cardiac-arrest survivors. A post hoc analysis of data from an observational study found that routine NMB administration for 24 h after ROSC was associated with a significant increase in survival (odds ratio, 7.23; 95% confidence interval, 1.56–33.38) and with a significant improvement in lactate clearance.³² The absence of significant beneficial effects of NMB therapy on ICU survival and 3-month

neurological outcome in our study may be ascribable to inadequate statistical power, particularly for the analysis adjusted on the propensity score. Shivering may be linked chiefly to the development of infectious complications (pneumonia in most cases) rather than to a physiological cerebral response. Alternatively, shivering may indicate relative preservation of brain function: thus, an observational study found better neurological outcomes in patients with than without shivering during TH for cardiac arrest.³³ In our study, early-onset pneumonia was not significantly more common in the group given NMB therapy. NMBs may decrease the clearance of respiratory secretions or increase the duration of mechanical ventilation by inducing muscle weakness.³⁴ We used cisatracurium, whose anti-inflammatory effects³⁵ may impair immune responses within the lung, thereby increasing the risk of bacterial pneumonia.^{34,36,37} Finally, variations in the use of NMBs may explain the conflicting results about the risk of infection associated with TH.^{22,38}

Our study has several limitations. The patients were identified retrospectively and the number of patients managed without NMB was small, albeit consistent with earlier reports.^{32,33} Continuous NMB infusion was only used when persistent shivering occurred, according to a protocol that was easy to apply, even by nurses and residents. The definition of persistent shivering was not standardised, and the Bedside Shivering Assessment Scale was not used,³⁹ although TOF monitoring was performed to assess neuromuscular blockade depth. However, the reliability of TOF monitoring in patients with hypothermia,²³ and more generally in the ICU, has been challenged.⁴⁰ Hypothermia may potentiate the effect of NMBs.⁴¹ We had no specific protocol for managing bacterial pneumonia after cardiac arrest. However, no changes in the ICU team occurred during the study period. The frequency of early-onset pneumonia in our study is consistent with earlier data.²² Because of the observational design of our study, the better prognosis of NMB+ group may be ascribable to selection bias. However, all patients received TH (i.e., none had early treatment-limitation decisions) and acute illness severity as assessed by the SAPS II was not significantly different between the two groups. Last, our study lacked sufficient power to draw definitive conclusions about patient outcomes. Nevertheless, our study is the first to report the effects of NMB treatment for shivering according to a pre-established protocol during TH for cardiac arrest. The data were carefully collected and analysed, thus providing reliable results.

5. Conclusion

NMB therapy to suppress shivering was given to most patients despite the use of a step-wise protocol specifically designed to limit NMB use. Our results suggest a beneficial effect of continuous intravenous NMB therapy on survival of patients treated with TH after cardiac arrest. However, NMB therapy was also associated with a non-significant increase in the frequency of early-onset pneumonia. Adequately powered randomised controlled trials are warranted to assess the risk/benefit ratio of NMB therapy during TH after cardiac arrest, especially in the new era of targeted temperature management.

Conflict of interest statement

The authors declare that they have no competing interests.

Authors' contributions

JBL was responsible for the study concept and design; JBL, JCL, MF, JR, KB, CL, AY, CB, MHL, MF, LML, and IV for data acquisition;

JBL, ALG, JD, and JCL for data analysis and interpretation;
 JBL, JCL, GC, and JR for drafting the manuscript; and
 JBL and JR for interpreting the data and critically revising the
 manuscript for important intellectual content.
 All authors read and approved the final manuscript.

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