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ORIGINAL

Delayed awakening after cardiac arrest: prevalence and risk factors in the Parisian registry

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Abstract

Purpose: Although prolonged unconsciousness after cardiac arrest (CA) is a sign of poor neurological outcome, limited evidence shows that a late recovery may occur in a minority of patients. We investigated the prevalence and the predictive factors of delayed awakening in comatose CA survivors treated with targeted temperature management (TTM).

Methods: Retrospective analysis of the Parisian Region Out-of-Hospital CA Registry (2008–2013). In adult comatose CA survivors treated with TTM, sedated with midazolam and fentanyl, time to awakening was measured starting from discontinuation of sedation at the end of rewarming. Awakening was defined as delayed when it occurred after more than 48 h.

Results: A total of 326 patients (71 % male, mean age 59 ± 16 years) were included, among whom 194 awoke. Delayed awakening occurred in 56/194 (29 %) patients, at a median time of 93 h (IQR 70–117) from discontinuation of sedation. In 5/56 (9 %) late awakeners, pupillary reflex and motor response were both absent 48 h after sedation discontinuation. In multivariate analysis, age over 59 years (OR 2.1, 95 % CI 1.0–4.3), post-resuscitation shock (OR 2.6 [1.3–5.2]), and renal insufficiency at admission (OR 3.1 [1.4–6.8]) were associated with significantly higher rates of delayed awakening.

Conclusions: Delayed awakening is common among patients recovering from coma after CA. Renal insufficiency, older age, and post-resuscitation shock were independent predictors of delayed awakening. Presence of unfavorable neurological signs at 48 h after rewarming from TTM and discontinuation of sedation did not rule out recovery of consciousness in late awakeners.

Keywords: Cardiac arrest, Prognosis, Therapeutic hypothermia

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Take-home message: Delayed awakening from coma after cardiac arrest is frequent, occurring in almost one-third of patients; renal insufficiency, older age. and post-resuscitation shock are independent predictors of delayed awakening. In patients presenting one or more of these factors, an observation period longer than the minimum recommended should be respected before neuroprognostication assessment.

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Introduction

About 80 % of patients resuscitated from cardiac arrest (CA) are comatose after return of spontaneous circulation (ROSC) because of severe anoxic-ischemic brain injury occurring during CA and resuscitation [1]. For these patients, a neuroprotective strategy based on targeted temperature management (TTM) between 32 and 36 °C for at least 24 h is recommended [2]. Unfortunately, a significant number of patients remain unconscious after rewarming from TTM and discontinuation of sedation. Most of these patients with prolonged unconsciousness will die, mainly following withdrawal of life-sustaining treatment (WLST) based on prognostication of a poor neurological outcome [3, 4].

Choosing the right timing for neuroprognostication is crucial to avoid, on the one hand, a premature WLST and, on the other hand, a futile prolongation of treatments in patients with no chance of recovery [5]. Current guidelines recommend that neuroprognostication should be performed not earlier than 72 h after ROSC [6]. This is based on evidence from the pre-TTM era showing that clinical examination is unreliable before this time point and that most of comatose CA survivors recover consciousness within 72 h after ROSC [7, 8]. However, 72 h must be interpreted as a minimum delay. Recent small cohort studies and case series [9–11] showed that in one-third of patients who awaken after CA, recovery of consciousness with a possible favorable neurological outcome occurs later than 72 h after ROSC and, in some patients, it may occur more than 10 days after ROSC.

Early identification of late awakeners would help establish the optimal timing for neuroprognostication and the appropriate duration of life-sustaining treatment in these patients. Unfortunately, in studies conducted until now the sample size was too small to allow the identification of specific characteristics associated with delayed awakening. Moreover, in these studies, factors that can affect prognostication, such as sedation and WLST timing and criteria, were not standardized. The aim of our study was to measure the incidence of delayed awakening and to identify the factors associated with it, in a large cohort of comatose CA survivors treated with TTM with a standardized protocol of care and prognostication.

Materials and methods

Population

This is a retrospective analysis of prospectively collected data from the Parisian Region Out-of-Hospital Cardiac Arrest Registry [12–14]. All consecutive adult patients who were admitted to the intensive care unit (ICU) of Cochin Hospital (Paris, France) in a coma (Glasgow coma scale [GCS] $\leq$ 8) after resuscitation from CA, from March 2008 to February 2013, were considered for inclusion.

Exclusion criteria were death from post-resuscitation shock within the first 48 h after ROSC and before a reliable neurological examination could be made, neurological cause of arrest, brain death, patients not treated with TTM, and repeated sedation after rewarming from TTM.

Patients' next of kin were informed that data were entered into a database for clinical research purposes. According to French law, our institutional review board waived the need for written informed consent.

Study protocol

The management protocol for patients admitted to our ICU after out-of-hospital CA has been previously described [4, 12, 15, 16] and did not change throughout the study period (electronic supplementary material, ESM 1). TTM was started immediately after ICU admission using forced external air. Body temperature was maintained at 32–34 °C for 24 h and subsequently rewarmed to 36 °C at a rate of 0.3 °C/h. The sedation protocol was based on the Richmond agitation-sedation scale (RASS). RASS is a standardized ten-point scale validated for the evaluation of arousal and agitation in ICU [17]. A value of −5 corresponds to no response to voice or physical stimulation, 0 corresponds to a patient alert and calm, while values above 0 measure agitation. Sedation was interrupted after rewarming and RASS was assessed every 3 h. ESM 2 reports the study timeline.

Post-resuscitation shock was defined as MAP less than 60 mmHg or a systolic blood pressure less than 90 mmHg sustained for more than 6 h after ROSC, despite adequate fluid loading, and requiring norepinephrine or epinephrine infusion [4].

Data collection

The following data were prospectively recorded for each patient: demographics, variables according to Utstein style [18], post-resuscitation shock, serum lactate, and creatinine level at admission. Renal insufficiency was defined as a glomerular filtration rate (GFR) less than 60 mL min^{-1} at admission, estimated using the simplified MDRD equation [19]. Obesity was defined as a body mass index over 30 kg m^{-2}. Clinical and non-convulsive seizures were treated with antiepileptic drugs (phenytoin, valproate, levetiracetam, phenobarbital). For sedative drugs the dose, the starting time, and the duration of infusion were recorded. Neurological status was assessed daily by ICU physicians from the day of rewarming until death or ICU discharge. A bedside clinical examination including GCS, pupillary light reflex, and cough reflex was performed daily.

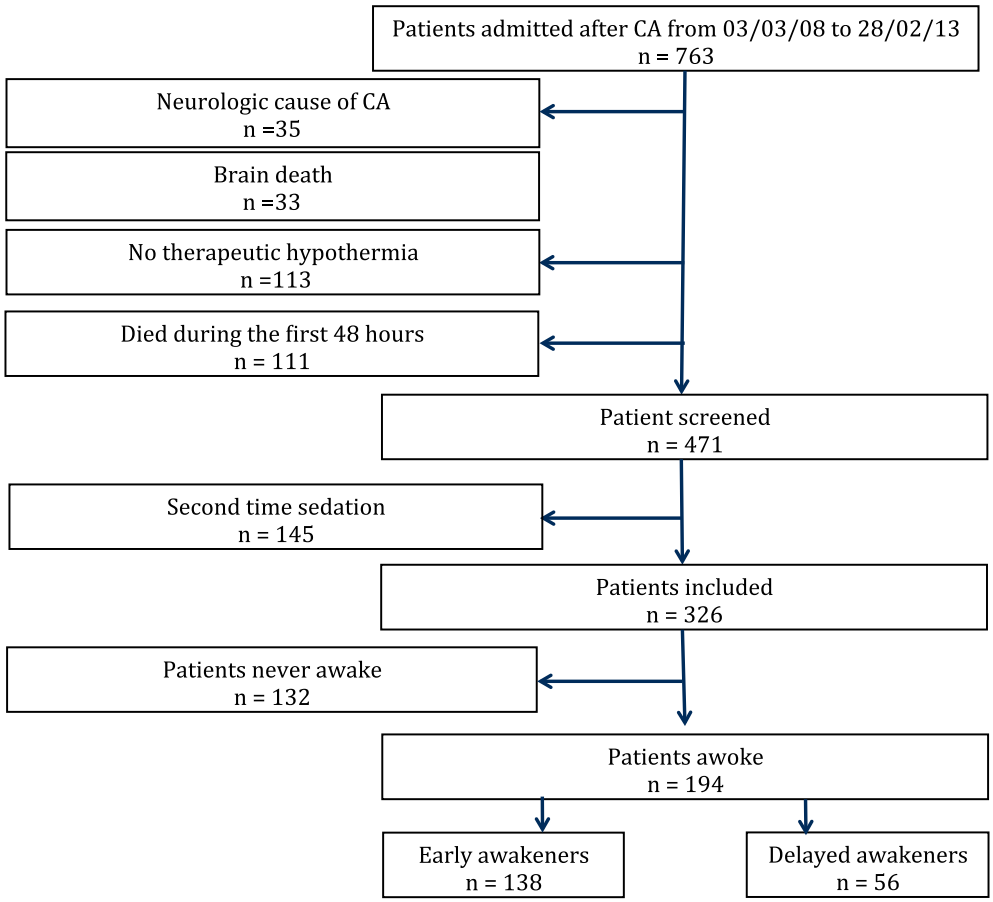

Fig. 1 Study flow chart

Neurological prognostication and criteria for WLST

In patients who were still comatose 48 h after discontinuation of sedation a multimodal prognostication protocol (ESM 3) was activated, including clinical examination (motor component of GCS, pupillary reflex, and corneal reflex), short-latency somatosensory evoked potentials (SSEPs), and electroencephalogram (EEG) performed 48 h after discontinuation of sedation. For patients with very long (>20 min) no-flow duration, we performed EEG and SSEPs earlier in order to detect signs of irreversible brain injury. WLST was considered in comatose patients with a GCS motor score 1 or 2 when one or more of the following conditions were present: (1) bilaterally absent pupillary and corneal reflexes; (2) bilaterally absent N20 SSEP waves; or (3) refractory status epilepticus. Status epilepticus was defined as refractory when it did not improve after treatment with two lines of major antiepileptic drugs (among phenytoin, valproate, levetiracetam, phenobarbital) [20].

Outcome assessment

The primary outcome of this study was delayed awakening. Awakening was defined as three consecutive RASS scores of at least −2 (patient awoke with eye contact to voice), as previously reported [21]. Time of awakening was set to the first of the three consecutive assessments. Delayed awakening was defined as persisting unconsciousness 48 h or more after discontinuation of sedation (ESM 2). Considering the duration of TTM (24 h for every patient) and the time allowed for rewarming, this cutoff was expected to occur around 12 h after the minimal time recommended by current guidelines, which is 72 h from ROSC [2, 6].

Neurologic outcome was measured using cerebral performance categories (CPC) [22] at ICU discharge. A favorable neurological outcome was defined as a good cerebral performance (CPC 1) or a moderate cerebral disability (CPC 2). Survival to hospital discharge was also measured.

Table 1 Baseline characteristics

Baseline characteristics	Population $n = 326$
Male sex, *n* (%)	231 (71)
Age, years mean (SD)	59 (16)
Public area, *n* (%)	123 (38)
Witnessed, *n* (%)	294 (90)
Bystander CPR before EMS arrival, *n* (%)	186 (57)
Initial shockable rhythm, *n* (%)	201 (62)
Use of epinephrine, *n* (%)	184 (56)
Dose of epinephrine, mg mean (SD)	4 (3.8)
Time from CA to CPR, min, median (IQR)	3 (0–6)
Time from CPR to ROSC, min, median (IQR)	15 (10–25)
Obesity, *n* (%)	48 (17)
Serum lactate at admission, mmol L^{-1}, mean (SD)	5.2 (4.1)
Post-resuscitation shock, *n* (%)	148 (45)
GFR < 60 mL min^{-1} at admission, *n* (%)	136 (42)
Renal replacement therapy, *n* (%)	151 (46)
Midazolam dose, mg kg^{-1} h^{-1}, median (IQR)	0.12 (0.08–0.18)
Fentanyl dose, µg kg^{-1} h^{-1}, median (IQR)	1.6 (1.0–2.3)
Seizures, *n* (%)	49 (15)
Awakening, *n* (%)	194 (60)
Discharged alive, *n* (%)	189 (58)
CPC 1–2	177 (94)
CPC 3–4	11 (6)
ICU length of stay, days, median (IQR)	6 (3.7–8.2)
Survivors	5.5 (3.5–8.2)
Non-survivors	6.4 (4.5–8.2)

CA cardiac arrest, *CPC* cerebral performance category (1 missing data), *CPR* cardiopulmonary resuscitation, *EMS* emergency medical service, *GFR* glomerular filtration rate, *ICU* intensive care unit, *IQR* interquartile range, *ROSC* return of spontaneous circulation, *SD* standard deviation

Statistical analysis

Continuous variables were summarized using medians and interquartile range, or means and standard deviation, as appropriate. We assessed normality using Shapiro–Wilk test. Categorical variables were reported as proportions. Missing data (<3 %; except for no-flow, 8 %) were handled using case-complete analysis.

In patients who awoke we investigated the association between delayed awakening and the relevant explanatory variables. These included patient demographics, Utstein variables [18], and factors likely to interfere with awakening (sedation, renal function, post-resuscitation shock). We used a binary outcome (early vs. delayed awakening). We performed χ^2 test for categorical variables, and Student *t* test, Mann–Whitney or Kruskal–Wallis test, when appropriate, for continuous variables. A multivariate analysis was performed using logistic regression including factors associated with delayed awakening in univariate analysis, with *P* values less than 0.15.

All tests were two-sided, with $P < 0.05$ considered statistically significant. We performed analysis using STATA/SE 14.0 (College Station, TX, USA).

Results

Patients

Among 763 patients admitted to the ICU after resuscitation from CA during the 5-year study period, 471 fulfilled the inclusion criteria. Of them, 145 needed further sedation after the initial interruption, including 91 for palliative sedation, 19 due to respiratory failure, and 14 to control seizure activity, leaving 326 patients in the final analysis (Fig. 1).

The baseline characteristics of the included patients are described in Table 1. Patients were mostly male (71 %), with mean age of 59 ± 16 years. Initial rhythm was shockable (i.e., ventricular fibrillation or pulseless ventricular tachycardia) in 201 (62 %) patients. Median intervals from collapse to cardiopulmonary resuscitation (CPR) and from CPR to ROSC were 3 and 15 min, respectively. A post-resuscitation shock occurred in 148 (45 %) patients. At admission, renal insufficiency (GFR < 60 mL min^{-1}) was found in 42 % of patients.

Sedation and awakening

Median dose of midazolam was 0.12 (IQR 0.08–0.18) mg kg^{-1} h^{-1}, and median dose of fentanyl was 1.6 (IQR 1.0–2.3) µg kg^{-1} h^{-1}. Median duration of infusion of sedative drugs was 34 h (IQR 30–41) (same for midazolam and fentanyl). The median time to awakening after discontinuation of sedation was 17 h (IQR 7–60) (Fig. 2).

Of the 326 included patients, 194 (60 %) regained consciousness during their ICU stay and 56 of them (29 %) had a delayed awakening. Among these 56 late awakeners, the motor component of the GCS was 1 or 2 (absent or extensor response) in 27/56 patients (48 %) and pupillary light reflex was absent in 9/56 patients (16 %) 48 h after sedation discontinuation. Regarding electrophysiology, EEG was performed in 29/56 patients: 26 patients had normal EEG reactivity, two had seizures, and one had absence of EEG background reactivity. In 11/56 patients SSEP were recorded, and all recordings showed N20 wave bilaterally present. In 5/56 late awakeners (9 %) both signs (motor GCS ≤ 2 and bilaterally absent pupillary reflexes) were present. These five "false positives" received high doses of sedation (mean dose of midazolam = 0.2 mg kg^{-1} h^{-1} and mean dose of fentanyl = 2.7 µg kg^{-1} h^{-1}) because of difficult mechanical ventilation. In addition, 3/5 had a cerebral CT scan, with normal results, 4/5 had an EEG, with reactive pattern, and 3/5 had a bilaterally present N20 SSEP wave.

The median time to regain consciousness after discontinuation of sedation was 10 h (IQR 6–23) for the early

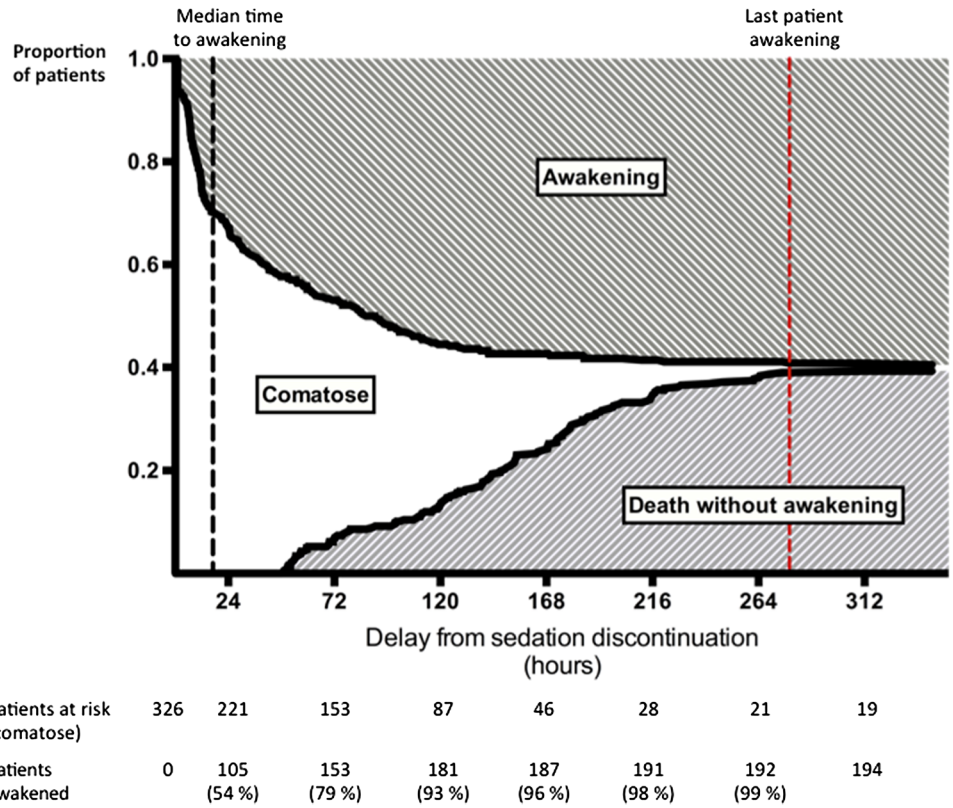

Fig. 2 Time course for awakening

awakeners and 93 h (IQR 70–117) for the late awakeners. Seven days after ROSC 13/56 late awakeners (23 %) were still comatose. The last awakener recovered consciousness 12 days after ROSC (278 h after discontinuation of sedation) (Fig. 2).

Among 194 awakeners, 189 (96 %) were discharged alive and 177 (91.2 %) had a favorable outcome (CPC 1–2 at ICU discharge). Early awakeners had a significantly higher rate of good neurological outcome than late awakeners (98 vs. 90 %; $P = 0.04$).

When considering every patient who fulfilled inclusion criteria (including those with repeated sedation), 234 patients awoke and 80 (34 %) had delayed awakening.

Factors associated with delayed awakening

Late awakeners were significantly older than early awakeners and had a higher incidence of post-resuscitation shock and renal insufficiency at admission (Table 2). Duration of sedation did not significantly differ ($P = 0.90$) between the two groups.

In multivariate analysis, age over 59 years (OR 2.1, 95 % CI 1.0–4.3; $P = 0.045$), post-resuscitation shock (OR 2.6, 95 % CI 1.3–5.2; $P = 0.008$), and renal insufficiency at admission (OR 3.1, 95 % CI 1.4–6.8; $P = 0.005$) were all independent predictors of a delayed awakening. We performed sensitivity analysis with different definitions of renal insufficiency, with consistent and homogenous results (ESM 4).

The proportion of late awakeners ranged from 12 % when none of these factors was present to 69 % when all these factors were present (Fig. 3).

Timing of death

All patients who did not awaken during their ICU stay died before hospital discharge, after a median time of 6.4 days (IQR 4.5–8.2). Among these patients, the cause of death was WLST in 101 patients (78 %). In eight of these (8 %), WLST was performed before 48 h from discontinuation of sedation because of prolonged duration of no-flow. In these patients, decision to perform early WLST was supported by refractory status epilepticus (5/8 patients) or bilateral absence of SSEP N20 wave (3/8), at a median of 1.5 days (range 1.4–1.8 days) after discontinuation of sedation.

Discussion

In our cohort, among comatose patients who recovered consciousness after CA, delayed awakening was

Table 2 Univariate analysis of delayed awakening

Variables	Early awakeners $n = 138$	Late awakeners $n = 56$	Univariate χ^2 or Student P
Male sex, *n* (%)	107 (78)	39 (70)	0.25
Age > 59 years, *n* (%)	47 (34)	34 (61)	0.001
Public area, *n* (%)	64 (46)	23 (41)	0.50
Witnessed, *n* (%)	131 (95)	52 (93)	0.57
Bystander CPR, *n* (%)	85 (62)	33 (59)	0.73
Initial shockable rhythm, *n* (%)	106 (77)	40 (71)	0.43
Use of epinephrine, *n* (%)	51 (37)	25 (45)	0.32
No flow > 3 min, *n* (%)	61 (44)	26 (46)	0.78
Low flow > 15 min, *n* (%)	50 (36)	20 (36)	0. 95
Post-resuscitation shock, *n* (%)	40 (29)	31 (55)	0.001
GFR < 60 mL min^{-1} at admission, *n* (%)	20 (14)	25 (45)	<0.001
Renal replacement therapy, *n* (%)	34 (25)	25 (45)	0.006
Etiology of cardiac arrest			0.14
Cardiac origin	114 (83)	41 (73)	
Anoxic origin	9 (7)	7 (13)	
Obesity, *n* (%)	10 (9)	9 (17)	0.12
Midazolam dose, mg kg^{-1} h^{-1} Median (IQR)	0.14 (0.09–0.20)	0.16 (0.09–0.21)	0.49
Fentanyl dose, µg kg^{-1} h^{-1} Median (IQR)	1.8 (1.1–2.7)	1.7 (1.2–2.6)	0.94
Duration of sedation, hours Median (IQR)	35 (31–41)	38 (30–42)	0.90
Seizure, *n* (%)	7 (5)	3 (5)	0.94
Discharged alive, *n* (%)	134 (97)	52 (93)	0.18
CPC 1–2	130 (98)	47 (90)	0.04
CPC 3–4	3 (2)	5 (10)	

CPC cerebral performance category (1 missing data), *CPR* cardio pulmonary resuscitation, *GFR* glomerular filtration rate, *IQR* interquartile range, *SD* standard deviation

common. In a significant number of these patients, awakening occurred over 1 week after ROSC. Renal impairment, older age, and initial shock were associated with a higher likelihood of delayed awakening.

The rate of delayed awakening we observed is in line with that reported in previous studies [8–11]. In the largest of those studies [9], 20/89 (22 %) comatose survivors of CA recovered consciousness after 72 h from ROSC. In two other studies including non-TTM-treated patients [8, 11], the rate of delayed awakening was 36 %. In comparison with previous investigations, however, our study has a larger sample size which allowed us to identify predictors of delayed awakening using multivariate analysis, while the adoption of consistent protocols both for post-resuscitation treatment (with 100 % of patients treated with TTM) and WLST should have reduced interference from confounders, making our results more reliable.

Our study showed that renal insufficiency on hospital admission, post-resuscitation shock, and older age were independently associated with a slower recovery of consciousness, and that the coexistence of these factors had an additive effect in increasing the risk of delayed awakening. All these predictors are associated with reduced clearance of sedative drugs, which suggests that the most likely explanation for delayed awakening in this population was residual sedation. Considering the cumulative effect, in patients with one or more risk factors, prognostication and especially WLST should be delayed later than 48 h after discontinuation of sedation. Furthermore, type and doses of sedation can influence time to awakening.

Among the predictors we identified, renal failure had the largest effect size. In patients with renal failure, midazolam and its active metabolite α-hydroxymidazolam accumulate after continuous infusion [23, 24]. Although we performed renal replacement therapy extensively in our patients, this may not have prevented midazolam and its active metabolites from accumulating since they are highly bound to plasma proteins [25] and are only minimally removed by hemodialysis or continuous veno-venous hemofiltration [26].

Post-resuscitation shock occurred in 45 % of patients in our study and was also associated with delayed awakening. Apart from being a consistent predictor of early acute renal failure in patients resuscitated from CA [12, 27–29], circulatory shock is associated with decreased clearance of drugs with high hepatic extraction like fentanyl [30].

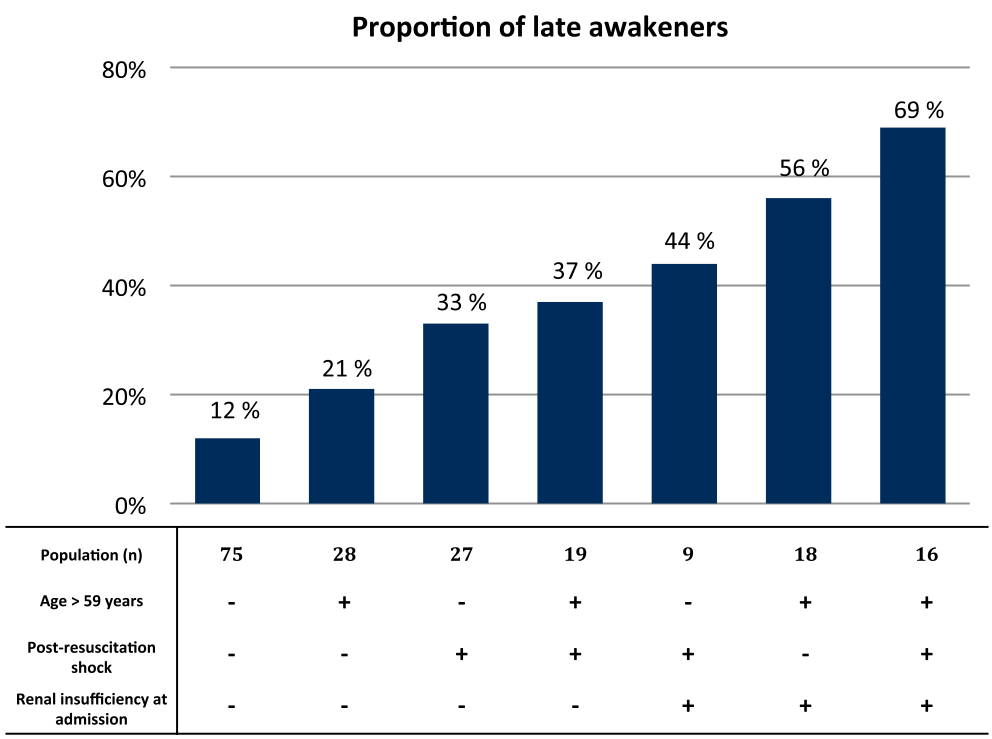

Fig. 3 Proportion of late awakeners, according to risk factors

The association between older age and delayed awakening we observed may also have been due, at least in part, to a prolonged effect of sedatives. Metabolic clearance of drugs from cytochrome P450 enzymes is up to 50 % lower in older compared with younger patients [31], and drugs with high hepatic extraction have shown a decreased clearance in the elderly because of a decreased hepatic blood flow [32]. In particular, the clearance of midazolam is significantly reduced starting from 50 years of age [33] and it decreases by almost 50 % above 60 years [34].

An additional reason for decreased drug clearance in our patients could have been TTM itself. Cytochrome P450 activity decreases by 7–22 % per degree Celsius below 37 °C [35]. The clearance of fentanyl is reduced by almost 50 % in comatose CA survivors during TTM [36]. Hypothermia may also double the duration of action of neuromuscular blocking drugs in these patients [37].

Although a decreased drug clearance appears to have been the most likely cause of delayed awakening in our patient population, alternative explanations can be considered. Late awakeners in our cohort could have suffered from a more severe, albeit still transient, hypoxic-ischemic brain injury than those who awoke early. In this case, the association of renal and circulatory failure with delayed awakening may be interpreted as a surrogate marker of a more severe ischemia–reperfusion injury rather than being causative. This is consistent with the fact that in our study neurological outcome was significantly worse in late versus early awakeners. However, key event characteristics like no-flow and low-flow times or initial cardiac rhythm did not differ between these two patient groups, so that this explanation appears to be less likely.

In our study, five late awakeners were unresponsive and had absent pupillary reflexes to light on prognostication assessment at 48 h after sedation discontinuation, which corresponds to a 9 % false positive rate for prediction of poor outcome using these clinical signs in late awakeners (7 % when considering patients with repeated sedation). This result is in line with that reported in recent studies [38] and it underlines the importance of excluding major confounders before prognostication assessment is made, especially as far as clinical examination is concerned. In order to reduce the risk of inappropriate WLST in these patients, a multimodal prognostication approach is also recommended whenever possible [2]. In particular, SSEPs and serum biomarkers are insensitive to sedation and can usefully complement prediction based on clinical examination.

Our study has some limitations. Firstly, as a result of its retrospective design, we could not report pharmacokinetic data, so that our interpretation of delayed awakening as a consequence of residual drug effect is only speculative. Future prospective studies based on assessment of plasma concentration–time profiles of sedatives and muscle relaxants will be needed to confirm this hypothesis. Secondly, we employed midazolam and fentanyl for sedation in our patients. Although these drugs are the most commonly used sedatives for TTM worldwide [39], the latest guidelines for post-resuscitation care [2] suggest using short-acting drugs for sedation after CA, in order to facilitate an earlier and more reliable prognostication assessment. Our results may therefore not be directly generalizable to centers where sedation with short-acting drugs has already been adopted. However, while the widespread adoption of these agents appears desirable, recent evidence [40] shows that the sedation regime used in our study largely reflects current practice. Thirdly, the single-center design of our study limits its external validity. Finally, the RASS scale we used has not been specifically designed to evaluate awakening from post-anoxic coma. However, no specific tool for this purpose is currently available. We believe that RASS measured every 3 h was sufficiently standardized and accurate to ensure reproducibility of our results. Moreover, 91 % of patients who awoke according to RASS measurement had favorable outcome, underlining the good reliability of RASS for the evaluation of neurological recovery.

Conclusions

Our study showed that an important fraction of comatose survivors of CA who recovered consciousness after TTM awoke more than 48 h after discontinuation of sedation. Factors associated with delayed awakening included renal insufficiency on admission, post-resuscitation shock, and older age. In patients presenting one or more of these factors, an observation period longer than the minimum recommended delay should be allowed before neuroprognostication assessment.

Electronic supplementary material

The online version of this article (doi:10.1007/s00134-016-4349-9) contains supplementary material, which is available to authorized users.

Abbreviations

CA: Cardiac arrest; CPC: Cerebral performance category; CPR: Cardiopulmonary resuscitation; EEG: Electroencephalography; ESM: Electronic supplementary material; GCS: Glasgow coma scale; GFR: Glomerular filtration rate; ICU: Intensive care unit; IQR: Interquartile range; RASS: Richmond agitation-sedation scale; ROSC: Return of spontaneous circulation; SD: Standard deviation; SSEP: Short-latency somatosensory evoked potentials; TTM: Targeted temperature management; WLST: Withdrawal of life-sustaining treatments.

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Compliance with ethical standards

Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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