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Clinical paper

Delirium after cardiac arrest: Phenotype, prediction, and outcome[☆]



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Abstract

Aim: To establish incidence, phenotype, long-term functional outcome, and early EEG predictors of delirium after cardiac arrest.

Methods: This is an ad hoc analysis of a prospective cohort study on outcome prediction of comatose patients after cardiac arrest. Patients with recovery of consciousness, who survived until hospital discharge, were subdivided in groups with and without delirium based on psychiatric consultation. Delirium phenotype and medical treatment were retrieved from patient files. All other data were prospectively collected. We used univariate analyses of baseline and early EEG characteristics for identification of possible delirium predictors. Association of delirium with neurological recovery at six months was analyzed with multinomial logistic regression analysis.

Results: Of 233 patients, 141 survived until hospital discharge, of whom 47 (33%) were diagnosed with delirium. There were no differences in baseline characteristics between patients with and without delirium. All delirious patients were treated with relatively high dosages of psychopharmaceuticals, mostly haloperidol and benzodiazepine agonists. Prevalent characteristics were disturbed cognition, perception and psychomotor functioning (98%). Half of the patients had language disorders or shouting. Delirium was associated with longer ICU and hospital admission, and more frequent discharge to rehabilitation centre or nursing home. There was a trend towards poorer neurological recovery. EEG measurements within 12 h after cardiac arrest could predict delirium with 91% specificity and 40% sensitivity.

Discussion: Delirium is common after cardiac arrest, and probably leads to longer hospitalization and poorer outcome. Optimal treatment is unclear. Early EEG holds potential to identify patients at risk.

Keywords: Delirium, cardiac arrest, Postanoxic encephalopathy, Postanoxic coma, Neurological recovery, Electroencephalogram

Introduction

Patients who survive a comatose state after cardiac arrest are at risk of delirium. Delirium is a clinical syndrome defined by disturbances in

cognition and behaviour in medically ill patients. The diagnosis of delirium is based on fluctuating disturbances in attention, awareness, and cognition, without a direct cause, such as specific medical conditions or neurocognitive disorders. The disturbances should not occur during a severely reduced level of arousal, such as coma.^{1–3}

[☆] This study was conducted at the Rijnstate hospital, Arnhem, The Netherlands, in collaboration with the department of Clinical Neurophysiology of the University of Twente, Enschede, The Netherlands.

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The reported incidence of delirium is 30–80% in patients admitted to an intensive care unit (ICU)^{4,5} and up to 100% in cardiac arrest survivors treated with mild therapeutic hypothermia.⁶ The origin of delirium is often multifactorial. In patients after cardiac arrest, both postanoxic encephalopathy and treatments like induced hypothermia or sedative medication may play a role. In critically ill patients, delirium is associated with higher mortality, prolonged hospitalization, and an increased risk of cognitive impairment after discharge.⁵

Most patients after cardiac arrest have neurological disturbances as a result of postanoxic encephalopathy and many have delirious symptoms during the first weeks after resuscitation. However, patients after cardiac arrest are classically excluded from delirium studies. This results in a lack of information about the phenotype, risk factors and optimal treatment of delirium after cardiac arrest. Confusion, disorientation, attention deficits, psychomotor agitation, hallucinations, sleep-wake cycle disturbance, and affective symptoms are often observed after myocardial infarction.⁷ It is unknown whether these represent true delirium, where treatment with antipsychotic medication may improve outcome, or are a direct expression of postanoxic encephalopathy, where treatment may be futile or interfere with the recovery of the postanoxic brain.

Identification of patients at risk may help early diagnosis and treatment of the delirium. Clinical predictors of delirium include an advanced age, intensive smoking, daily use of alcohol, pre-existent cognitive impairment, and a preceding period of sedation, coma, or mechanical ventilation.^{4,7,8} Various EEG characteristics have been described in relation to delirium, either during or preceding delirium. These include slowing of the dominant frequency,^{9,10} time spent in burst suppression patterns,^{11–13} and measures of functional connectivity.¹⁴

With this study, we estimate incidence of delirium in patients that recover from coma after cardiac arrest. We describe the delirium phenotype, treatment, and association with long-term functional outcome. In addition, we investigate if particular EEG features in the comatose phase are predictive of delirium after recovery of consciousness.

Methods

This is an ad hoc analysis of a multicentre prospective cohort study on EEG for outcome prediction of comatose patients after cardiac arrest. Methods for data collection have been described previously,¹⁵ and part of the data of patients included up to November 2017 have been used in earlier publications.^{15–25} In short, we applied prospective patient inclusion and collection of demographic, baseline, clinical, EEG, and outcome data. For the current analysis we used data from patients in the Rijnstate hospital (Arnhem, The Netherlands) collected between January 2015 and December 2018.

Patients

We included consecutive patients who were admitted to the ICU department in a comatose state after cardiac arrest and survived till discharge from the primary hospital. Exclusion criteria were concomitant acute stroke, traumatic brain injury, and progressive neurodegenerative disease. All patients had continuous EEG registrations starting as soon as possible after arrival at the ICU, up to awakening or a minimum of 72 h after cardiac arrest. During this comatose phase, patients were mostly treated with propofol and morphine, sometimes complemented with midazolam.

Delirium

Patients with recovery of consciousness, who survived until hospital discharge, were subdivided in groups with and without delirium based on psychiatric consultation. In Rijnstate hospital, according to local hospital protocols, diagnosis and treatment of delirium are always done by a consulting hospital psychiatrist. The psychiatrist confirms or rejects the diagnosis of delirium based on the DSM-V criteria, and is in the lead with regard to medical treatment of delirium. Patients were included in the delirium group if a psychiatrist was consulted during hospital stay, and delirium was diagnosed, and at least one of the following criteria was reported in the patient's file: disturbances of consciousness, disturbances of cognition, or perceptual disturbances.

Of patients that were included in the delirium group, we collected data on delirium symptoms and medication from patient hospital files. Presence or absence of characteristics of delirium was scored according to the DSM-V,^{1,2} and the ICD-10 Version: 2016, section F05,^{26,27} complemented with additional details of these characteristic symptoms, based on our own expertise with patients after cardiac. Characteristics are summarized and explained in Table 1. We collected which pharmaceuticals were used to treat delirium, the average maximal dose of these pharmaceuticals, the mean duration of treatment, and whether treatment was continued after discharge from the primary hospital.

Outcome

Our primary outcome measure was neurological recovery, defined as the Cerebral Performance Category (CPC-score) measured six months after cardiac arrest. CPC scores were obtained using a telephone interview based on a Dutch translation of the EuroQol-6D questionnaire. Other outcome measures were duration of stay at the ICU, duration of hospital admission, and discharge destination.

EEG registration and analysis

Continuous EEG registrations were performed using a Nihon Kohden device (VCM Medical, Leusden, The Netherlands), using 21 silver/silver chloride electrodes according to the international 10–20 system, and a sampling frequency of 500 Hz. Recordings were started as soon as possible after arrival at the ICU and continued for three to five days, or until the patient regained consciousness or died.

We extracted five-minute EEG epochs at 12, 24, 48 and 72 h after resuscitation from the EEG using an automated algorithm.²³ If the EEG epoch at one of these hours was unavailable, we used an available EEG epoch at the closest hour within a range of 2 h. All epochs were referenced to the longitudinal bipolar montage and pre-processed to remove EEG channels containing artefacts due to muscle activity, flat signals, and unrealistically high amplitude peaks, using an automated artefact rejection algorithm.²¹ EEG epochs were included for further analysis when at least 12 artefact-free channels were available. The EEG signals of these channels were bandpass (0.5–30 Hz) filtered with a zero-phase sixth order Butterworth filter. We extracted 90-s epochs from these filtered five-minute EEG segments, to remove filtering edge effects at the beginning and the end of the segment.

With data from these EEG epochs, we calculated two EEG features: the scaled alpha-to-delta ratio (sADR) and the background continuity index (BCI). The sADR was defined as the ratio between the

Table 1 – Characteristics of delirium according to the ICD-10 and additional details.

	Characteristic	Definition
ICD-10 criteria	Impairment of consciousness and attention	A decreased level of consciousness with reduced ability to direct, focus, sustain, and shift attention.
	Global disturbance in cognition and perception	This includes problems with forming of new long-term memories, impairments of abstract thinking and comprehension, possible illusions and disorientation in place, time and person.
	Psychomotor disturbances	This can be subdivided in psychomotor activation (restlessness, repetitive movements, frequent changes of position) and psychomotor retardation (staring, slow and little movements).
	Disturbances of the sleep-wake cycle	Varying from insomnia to reversion of the sleep-wake cycle.
Additional details	Emotional disturbances	Includes symptoms like depression, anxiety, fear, apathy or anger.
	Extreme restlessness	Motor restlessness necessitating bodily fixation to the bed or chair, because of danger for the patient or medical staff. This includes falling and walking away with getting lost.
	Disinhibition	Lack of restraint, resulting a.o. in poor risk assessment, impulsive behaviour and disregard of social conventions.
	Language disorder	Problems in producing and/or understanding spoken language. Bilingual patients may temporarily forget one of their languages.
	Wandering	Restlessness resulting in inability to stay in the room and wandering from the department and an abnormal urge to move.
	Shouting	Intentional shouting aiming to get something.
	Aggression	Verbal or physical aggression to medical staff, family member or other patients.
	Incontinence	Urinary or faecal continence problems
	Paranoia	Anxious or fearful feelings and thoughts, often related to threat or conspiracy.
	Hallucinations	Visual or auditory hallucinations.
	Head shaking	Constant shaking with the head.
	Excessive drinking	Excessive fluid intake, obsession with drinking.

EEG power in the alpha band (8–13 Hz) and delta band (1–4 Hz), scaled between –1 and 1, given by:

$$sADR = \frac{\alpha - \delta}{\alpha + \delta} \quad (1)$$

where α represents the EEG power in the alpha band and δ the EEG power in the delta band. The power spectral density was estimated using Welch's method with 50% overlap and a Hamming window length of 2 s.²³ The BCI was defined as the fraction of EEG signal that was not spent in suppression.²¹ Suppression was defined as segments of at least 500 ms with amplitudes $<10 \mu V$.

All data analyses were performed with MATLAB (2019, MathWorks Inc., Natick, USA).

Statistical analysis

Baseline and clinical characteristics, duration of stay at the ICU, and duration of hospital admission are presented in a descriptive way for patients with and without delirium. For analysis of differences between groups of patients with and without delirium we used chi-squared tests for ordinal variables and Mann–Whitney U tests for continuous variables using SPSS 22 (IBM Corp., Armonk, NY). Differences in outcome between both groups were analyzed by multinomial logistic regression analysis with MATLAB.

We compared sADR and BCI at 12, 24, 48 and 72 h after resuscitation between patients with and without delirium using Mann–Whitney U tests in MATLAB. A preliminary logistic regression model for prediction of delirium, based on sADR and BCI, was created at the time point with largest group differences. Discriminative values of this

model are expressed as the area under the receiver-operator characteristics (ROC) curve (AUC). Sensitivity and specificity to predict delirium were estimated at the optimal cut-off, by minimizing a cost-function to the ROC. For all comparisons, a p -value <0.05 was considered statistically significant.

Table 2 – Baseline characteristics of patients after cardiac arrest who recovered from coma and survived until hospital discharge.

	Delirium ($n=47$)	No delirium ($n=94$)	p -value
Male	40 (85%)	78 (83%)	0.48
Age (year)	61 (10)	62 (12)	0.33
Cardiac cause	43 (91%)	90 (96%)	0.25
Shockable rhythm	45 (96%)	84 (89%)	0.17
Poor outcome ^a	9 (19%)	13 (14%)	0.27
Propofol in first 24 h	45 (96%)	87 (93%)	0.72
Max. Propofol dose (mg/kg/h)	2.93 (0.98)	2.78 (1.13)	0.53
Midazolam in first 24 h	13 (28%)	47 (50%)	0.07
Max. Midazolam dose ($\mu g/kg/h$)	138 (99.2)	126 (84.9)	0.79
Morphine in first 24 h	47 (100%)	91 (97%)	0.55
Max. Morphine dose ($\mu g/kg/h$)	24.6 (4.45)	28.1 (15.2)	0.58

p -values were obtained using two-sided chi-square tests for nominal variables and Mann–Whitney U tests for continuous variables. Nominal variables are presented as n (%). Continuous variables are presented as mean (standard deviation).

^a Poor outcome defined as a Cerebral Performance Category (CPC) score 3–5 at six months after cardiac arrest.

Results

During the inclusion period, 233 comatose patients after cardiac arrest were admitted. All patients were treated with 24–72 h of targeted temperature management (33 °C until January 2014, 36 °C since February 2014) after arrival at the ICU department. Of these patients, 141 (61%) survived up to discharge from the primary hospital and were included in the current analysis. Delirium was diagnosed in 47 (33%) of the survivors. There were no differences in baseline characteristics between surviving patients with and without delirium (Table 2).

Delirium phenotype and treatment

The incidence of delirium symptoms in the delirium group is presented in Fig. 1. Treatment is presented in Table 3. Pharmacological treatment was applied to all delirious patients. Most patients were treated with multiple antipsychotic drugs (median (IQR) number of drugs: 3 (2)). Of note, this indicates treatment after the comatose state

on de ICU and cardiac care unit (CCU), in 'awake' patients, prescribed by a consulting psychiatrist. In 21 patients (45%), anti-delirium treatment was continued after discharge from the primary hospital. Mann–Whitney *U* tests revealed that dosages of the most often prescribed drugs, haloperidol, lorazepam, oxazepam, temazepam, and zopiclone, showed no statistically significant association with outcome at six months after cardiac arrest.

Discharge and outcome

Patients with delirium stayed significantly longer on intensive care units (delirium (median (IQR)) 6(9) days, non-delirium 3(4) days, $p < 0.01$) and in the hospital (Delirium (median (IQR)) 24(21) days, non-delirium 15(15) days, $p < 0.01$). Due to transfer to another hospital, total stay at ICU was unknown for 5 patients, total stay in hospital was unknown for 7 patients. Patients with delirium were more often discharged to a rehabilitation centre (delirium 19%, non-delirium 3%, $p < 0.01$) or chronic nursing home (delirium 15%, non-delirium 4%, $p = 0.03$), Supplementary Table 1). Patients with delirium had a

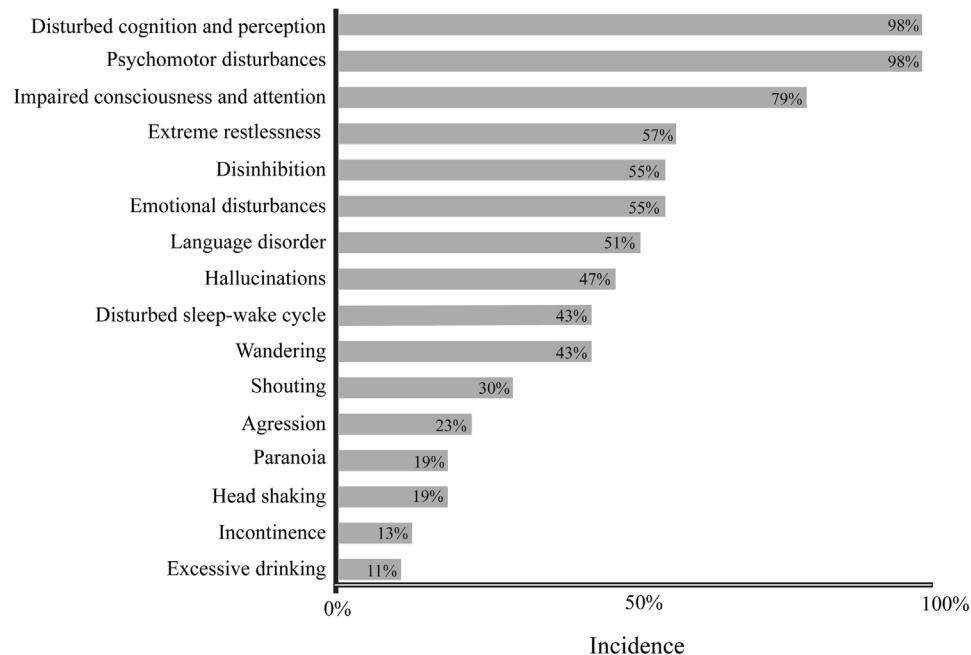


Fig. 1 – Incidence of clinical characteristics present in the delirium group.

Table 3 – Medication to suppress delirious symptoms in the delirium group.

	Number of patients <i>n</i> (%)	Highest dose (mg/day) Mean (SD)	Days of use in hospital Mean (SD)	Continued after discharge <i>n</i> (%)
Haloperidol	45 (96%)	7.8 (5.2)	9.6 (6.9)	12 (26%)
Lorazepam	24 ((51%)	2.5 (3.0)	7.4 (6.0)	1 (2%)
Oxazepam	24 (51%)	30.2 (31.1)	6.2 (7.36)	5 (11%)
Zopiclone	24(51%)	7.5 (0.0)	6.3 (5.89)	4 (9%)
Temazepam	11 (23%)	11.8 (4.1)	9.5 (8.54)	4 (9%)
Valproic acid	5(11%)	1420 (239)	16.0 (2.92)	0 (0%)
Diazepam	3 (6%)	6.7 (2.9)	1.3 (0.577)	0 (0%)
Clonazepam	1 (2%)	0.50 (–)	3.0 (–)	0 (0%)
Zolpidem	1 (2%)	10.0 (–)	5.0 (–)	0 (0%)
Quetiapine	1 (2%)	200.0 (–)	21.0 (–)	1 (2%)
Risperdal	1(2%)	2.00 (–)	6.0 (–)	0 (0%)

larger chance of a poor outcome than patients without delirium, but this difference was not statistically significant ($p=0.15$ for ordinal analysis of any shift in the direction of a poorer outcome on the CPC, $p=0.19$ for proportion of patients with CPC1, $p=0.32$ for the proportion of patients with CPC 1 or 2, Fig. 2).

EEG analysis

At 12 h after cardiac arrest, the median sADR was lower in patients with delirium -0.82 (IQR: -0.90 to -0.68) than in patients without delirium (-0.59 (IQR: -0.77 to -0.14), $p<0.01$). The median BCI at 12 h after cardiac arrest was also significantly lower for patients with delirium (0.59 (IQR: 0.39 – 0.78)) than for patients without delirium (0.89 (IQR: 0.53 – 0.98), $p=0.02$). Later measurements showed only a significantly lower median sADR for patients with delirium (-0.78 (IQR: -0.88 to -0.56)) than for patients without delirium (-0.69 (IQR: -0.81 to -0.35), $p=0.03$, supplementary Table 2).

The ROC curve of a predictive model based on sADR and BCI at 12 h after cardiac arrest discriminated between patients with and without delirium with an area under the curve of 0.76 (0.62 – 0.88 95%CI) and predicted poor outcome with a sensitivity of 40% (19 – 62% 95%CI) at a specificity of 91% (75 – 97 95%CI, Fig. 3).

Discussion

We confirm that the incidence of delirium amongst survivors after cardiac arrest is high. In our study, one third of patients recovering from a comatose state had clinical symptoms classifying as delirium. Disturbances of cognition or perception and psychomotor disturbances were present in almost all delirious patients. Characteristic features included prominent restlessness, with aggression, wandering, or getting lost, with danger for the patient himself or others. Half of the patients had language disorders or shouting. Head shaking or excessive drinking were present in 10 – 20% of the patients. All patients were treated with anti-psychotic drugs, mostly with more than one drug, in relatively high doses. Delirium was associated with longer stay in ICU and hospital. There was a trend towards poorer functional recovery.

In general, delirium is associated with higher mortality, longer intensive care and hospital stay, and a larger chance of cognitive impairments after discharge.^{5,28} This corresponds with our results, showing significantly longer hospitalization of patients with delirium. Our lack of statistical significance with regard to functional recovery at six months is probably related to the limited sensitivity of the CPC to detect long term cognitive disturbances.

Our results are in line with the only previous study on delirium after cardiac arrest, where the reported incidence was even higher.⁶ Apparently, psychomotor, cognitive, and mental disturbances are common after cardiac arrest, especially in the first days to weeks after recovery of consciousness in patients that survive the comatose phase.⁶ This combination of clinical symptoms may classify as delirium according to DSM-V and ICD-10 and give rise to treatment with anti-psychotic drugs. However, in patients after cardiac arrest, these symptoms are probably often a direct expression of postanoxic encephalopathy and/or reperfusion damage. With postanoxic encephalopathy, effects of (high doses of) anti-psychotic and sedative drugs are uncertain.

A more extended differential diagnosis should probably be considered with delirious symptoms in patients after cardiac arrest.

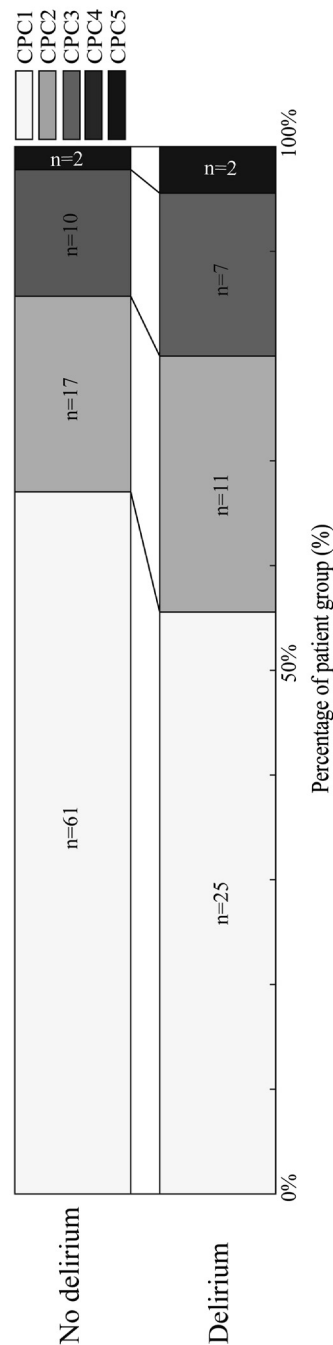


Fig. 2 – Outcome at 6 months after cardiac arrest for patients with and without delirium, classified according to the Cerebral Performance Category (CPC). p -value of difference between both groups assessed by multinomial logistic regression analysis is 0.15 .

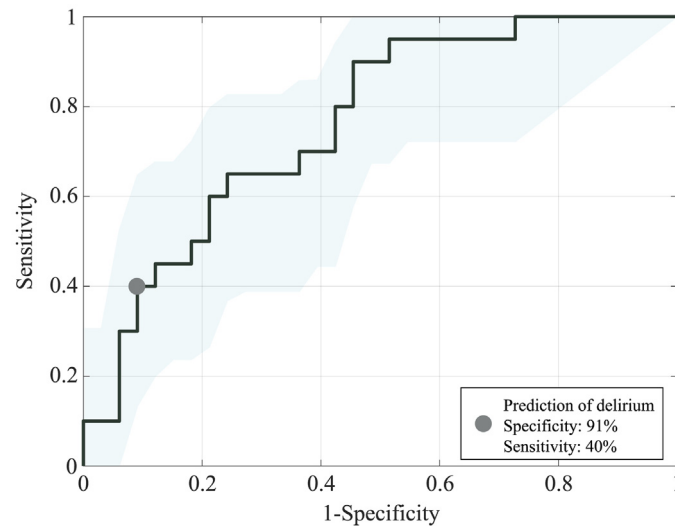


Fig. 3–ROC curve of logistic regression model, containing sADR and BCI at 12 h after cardiac arrest, to predict delirium. The area under the curve is 0.76 (0.62–0.88 95%CI). At 91% specificity (75–97% 95%CI) delirium could be predicted with 40% sensitivity (19–62% 95%CI).

EEG studies have shown that a non-convulsive status epilepticus is present in 10–20% of the patients during the comatose phase.^{22,29} Impaired consciousness with psychomotor disturbances and restlessness may be caused by epileptic seizures, as well.³⁰ However, systematic EEG measurements of delirious patients after cardiac arrest are scarce. The typical feature of excessive drinking could be a sign of Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH). This syndrome may arise from various factors present in patients after cardiac arrest, such as encephalopathy, pneumonia, vasopressin, and narcotic drugs.³¹ Non-convulsive seizures and SIADH require a different treatment than plain delirium.

The EEG within 24 h after resuscitation allows reliable prediction of poor or good outcome of approximately half of all comatose patients after cardiac arrest.^{15,23} Here we show that early EEG patterns may be predictive of delirium in patients that recover from coma. In accordance with prediction of long term outcome, apparently, predictive values are especially high within the first 24 h after cardiac arrest. A lower sADR and lower BCI were seen more often in the patients developing a delirium. Smaller values of the sADR and BCI reflect EEG patterns that are relatively slow and discontinuous.²¹ This implies a more severe postanoxic encephalopathy, that is apparently associated with a larger likelihood of developing a delirium. Further research in a larger cohort with strict screening for delirium is necessary to confirm predictive values of models based on the EEG.

Our study has certain limitations. First, we only diagnosed delirium when a hospital psychiatrist was consulted because of a suspected delirium. This may have led to inclusion of delirious patients in the non-delirium group, when a psychiatrist was never consulted, especially in patients with hypoactive delirium.^{4,6} Also, development of delirium after hospital discharge from the primary hospital is missed. Otherwise, diagnosis by a consulting psychiatrist has probably contributed to a high specificity of the diagnosis of delirium.

Second, this prospective cohort study focussed on prediction of neurological outcome after cardiac arrest.^{15,23} The study did not include prospective collection of clinical data on delirious symptoms. Delirious symptoms were collected retrospectively, from patient files.

Therefore, the list of delirious symptoms may be incomplete. Third, we did not include extensive cognitive follow up.

Conclusion

In conclusion, delirium is common after cardiac arrest and characterized by prominent psychomotor disturbances. It is unknown to which extent delirious symptoms represent a direct expression of postanoxic brain damage. Specific causes, such as non-convulsive seizures and SIADH, need to be excluded. To establish optimal diagnoses and treatment, prospective studies with follow up of cognitive functioning are needed.

Conflict of interest

MvP is co-founder of clinical science systems, providing software for EEG recording and analysis.

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Authors' contribution

Hanneke M. Keijzer: conceptualization; methodology; software; formal analyses; writing original draft. Marjolein Klop: methodology; software; formal analyses; writing – review & editing. Michel J.A.M. van Putten: methodology; supervision; writing – review & editing. Jeannette Hofmeijer: conceptualization; methodology; supervision; writing – review & editing.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.resuscitation.2020.03.020>.

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