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Cardiac Arrest in Patients Managed for Convulsive Status Epilepticus: Characteristics, Predictors, and Outcome

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Ethical approval: All procedures involving the patients complied with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments.

Drs. Legriel, Bresson, Dumas, and Cariou conceived, designed, and supervised the trial. Drs. Legriel, Bresson, Deye, Grimaldi, Sauneuf, Lesieur, Lascarrou, Argaud, Chelly, Beuret, Schnell, Chateauneuf, Holleville, Perier, Lemiale, Bruel, Cronier, Pichon, Mongardon, de-Prost, Dumas, and Cariou collected the data; and Dr. Legriel coordinated the data collection. Drs. Legriel, Bresson, Dumas, and Cariou analyzed and interpreted the data. Drs. Legriel and Dumas performed the statistical analysis. Drs. Legriel, Dumas, and Cariou wrote the first draft of the article. All authors approved the final version of the article.

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Objectives: Cardiac arrest is a catastrophic event that may arise during the management of convulsive status epilepticus. We aimed to report the clinical characteristics, outcomes, and early predictors of convulsive status epilepticus–related cardiac arrest.

Design: Retrospective multicenter study.

Setting: Seventeen university or university affiliated participating ICUs in France and Belgium.

Patients: Consecutive patients admitted to the participating ICUs for management of successfully resuscitated out-of-hospital cardiac arrest complicating the initial management of convulsive

status epilepticus between 2000 and 2015. Patients were compared with controls without cardiac arrest identified in a single-center registry of convulsive status epilepticus patients, regarding characteristics, management, and outcome.

Interventions: None.

Measurements and Main Results: We included 49 cases with convulsive status epilepticus–cardiac arrest and 235 controls. In the cases, median time from medical team arrival to cardiac arrest was 25 minutes (interquartile range, 5–85 min). First recorded rhythm was asystole in 25 patients (51%) and pulseless electrical activity in 13 patients (27%). A significantly larger proportion of patients had a favorable 1-year outcome (Glasgow Outcome Scale score of 5) among controls (90/235; 38%) than among cases (10/49; 21%; $p = 0.02$). By multivariate analysis, independent predictors of cardiac arrest were pulse oximetry less than 97% on scene (odds ratio, 2.66; 95% CI, 1.03–7.26; $p = 0.04$), drug poisoning as the cause of convulsive status epilepticus (odds ratio, 4.13; 95% CI, 1.27–13.53; $p = 0.02$), and complications during early management (odds ratio, 11.98; 95% CI, 4.67–34.69; $p < 0.0001$). Having at least one comorbidity among cardiac, respiratory, and neurologic (other than epilepsy) conditions predicted absence of cardiac arrest (odds ratio, 0.28; 95% CI, 0.10–0.80; $p = 0.02$).

Conclusions: In patients managed for convulsive status epilepticus, relative hypoxemia, on-scene management complications, and drug poisoning as the cause of convulsive status epilepticus were strong early predictors of cardiac arrest, suggesting areas for improvement. (*Crit Care Med* 2018; 46:e751–e760)

Key Words: cardiopulmonary resuscitation; coma/therapy; intensive care units; medical errors/adverse effect; status epilepticus; sudden death

Convulsive status epilepticus (CSE) is a common and life-threatening neurologic emergency associated with an about 20% hospital mortality rate (1, 2). The well-standardized management of CSE consists of on-scene initiation of antiepileptic drug (AED) therapy with subsequent adjustments based on the response. However, after treatment initiation, one third of CSE episodes have an unfavorable course (3). Thus, in addition to seizure refractoriness, some patients demonstrate persistent coma and/or potentially fatal systemic complications (4–8).

Cardiac arrest (CA) is among the most catastrophic early complication seen during CSE management. Factors that may contribute to CSE-related CA (CSE-CA) include comorbidities, severe systemic complications (particularly in the event of uncontrolled seizure activity [9–11]), injuries caused by the loss of consciousness and seizure, treatment complications, and cause of CSE.

Although CSE-CA is an event of considerable concern, few studies have assessed its characteristics and long-term survival and functional outcomes. More specifically, data on the factors contributing to CSE-CA are needed.

The objective of this retrospective study was to identify early factors associated with CA in adults managed for CSE and admitted to the ICU. Knowledge of such factors might help to identify areas for improvement in the management of CSE.

MATERIALS AND METHODS

Our local ethics committees ("Comité de Protection des Personnes de Paris, Ile de France VI; and Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé," February 17, 2016) approved this study (number 16/131) and waived the requirement for informed consent, in accordance with French law on retrospective studies of anonymized data.

Cases

Consecutive adults admitted between January 2000 and December 2015 to 2017 medical-surgical or surgical, university or university affiliated, French and Belgian ICUs with successfully resuscitated CA during CSE management were identified by searching the hospital databases for any of the following codes in the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision: CA (I46.9); status epilepticus (SE) (G41.0); SE, unspecified (G41.9); and other and unspecified convulsions (R56.8). Local investigators reviewed the medical records of the patients thus identified to select those meeting our eligibility criteria. Patients with CSE-CA (cases) were defined as experiencing CA within 24 hours after the initiation of CSE management, as validated by consensus between two of us (S.L., E.B.). Patients with CA before CSE management initiation were not included.

Historic Controls

Cases with CSE-CA were compared with 235 unmatched controls managed for CSE without CA at one of the participating ICUs (Versailles hospital CSE registry of data from previously published studies including Versailles hospital patients with CSE) during a comparable period (2005–2013). We also performed a sensitivity analysis comparing the 49 cases with 49 controls selected among the 235 historic controls. Each case was matched on a propensity score to a control.

Definitions

CSE was defined as either motor seizure activity for at least 5 minutes (continuous) or more than two motor seizures without full recovery of consciousness in the interval (intermittent) (12). CSE could be generalized from onset or initially focal with or without subsequent progression to bilateral CSE (13). Refractory SE was defined as a need for general anesthesia because of continuous or intermittent seizures despite treatment with an IV benzodiazepine (clonazepam or diazepam) and IV phenytoin/fosphenytoin, valproate, phenobarbital, or levetiracetam (14). Subtle SE was defined as a coma with or without subtle convulsive movements and with generalized or lateralized ictal discharges on the electroencephalogram (15).

Data Collection

For each case or control, a standardized form was used to collect demographic data, information on the history of epilepsy, characteristics of the current CSE episode (circumstances of onset, dates and times of onset and of seizure control, clinical features of the seizures, prehospital and hospital care providers, and

timing of AED and supportive treatments). We collected on-scene clinical findings recorded at any time during early CSE management (Glasgow Coma Scale [GCS] score, systolic blood pressure, heart rate, and pulse oximetry). Seizure duration was determined based on the prehospital, emergency department, and ICU records. Data related to CA were collected according to Utstein style guidelines (**Table 1**). We also collected results of etiologic investigations for CSE and CA (coronary angiography, chest and brain CT, lumbar puncture, MRI, and laboratory tests including a toxicology screen). Special attention was paid to complications related to CSE management (e.g., respiratory and/or cardiac side effects of AEDs, hemodynamic side effects of anesthetic drugs, and difficulties in airway management). The following data describing the ICU and hospital care were also collected: severity and description of organ failures according to the Simplified Acute Physiology Score II and Logistic Organ Dysfunction (LOD) score and use of mechanical ventilation, inotropic support, and/or renal replacement therapy.

Electronic supplementary material file 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/D537) describes the management of the cases.

Assessment of Short- and Long-Term Functional Outcomes

Short- and long-term functional outcomes were assessed using the Cerebral Performance Category (CPC) scale. The CPC was extracted from the hospital charts or determined by interviewing the patient or patient's next of kin, general practitioner, or neurologist at hospital discharge, then 90 days and 1 year after CSE onset. We defined a favorable outcome as a CPC of 1 or 2.

Statistical Analysis

Quantitative variables were described as median (interquartile range) and qualitative variables as number (%). We compared categorical variables using Fisher exact tests and continuous variables using Wilcoxon rank-sum tests. To identify associations between factors listed in **Table 2** and CA, the cases and controls were compared using logistic regression. Before performing logistic regression univariate analysis, all continuous variables were checked for log-linearity. Variables for which log-linearity was not found were transformed into dummy variables according to their median value. A multivariate model was built with variables that yielded *p* values lower than 0.20 by univariate analysis and/or were clinically relevant. The following variables were included into the multivariate model: age greater than 59 years; at least one comorbidity among cardiac, respiratory, and neurologic (other than epilepsy) comorbidities; previous history of epilepsy; GCS score greater than or equal to 6 at scene; pulse oximetry less than 97% at scene; generalized seizures; continuous (as opposed as intermittent) CSE; seizure duration greater than 85 minutes; refractory SE; time from seizure onset to intubation greater than 90 minutes; early management complications; and drug poisoning as a cause of CSE. The Le Cessie-van Houwelingen goodness-of-fit test and area under the receiver operating characteristics curve estimated by the *C*-statistic were computed on the final models.

TABLE 1. Main Characteristics of 49 Patients With Cardiac Arrest During Management of Convulsive Status Epilepticus

Patient Characteristics	*n* (%) or Median (IQR) Convulsive Status Epilepticus–*Related CA*, *n* = 49 (62.0%)
CA Utstein Criteria	
Age, yr	56 (41–66)
Male gender	26 (53.1)
Location at CA	
Home	12 (24.5)
Public place	6 (12.2)
Hospital	31 (63.3)
Arrest witnessed/monitored	46 (93.9)
First recorded rhythm	
Asystole	25 (51.0)
Pulseless electrical activity	13 (26.5)
Ventricular fibrillation/ventricular tachycardia	4 (8.2)
Other	7 (14.3)
Total number of defibrillations before ROSC	0 (0–0)
Total adrenaline dose before ROSC, mg	2 (0–5)
Antiarrhythmic drugs before ROSC	7 (14.3)
Sodium bicarbonate before ROSC	10 (20.4)
Time from collapse to	
Cardiopulmonary resuscitation (no flow), min	0 (0–0)
ROSC (no flow + low flow), min	6 (3–20)
Extracorporeal life support	4 (8.2)
Coronary angiography	0
Chest CT angiography	8 (16.3)
Lactate concentration at ICU admission, mmol/L	8.6 (4.9–14.8)
Targeted temperature management (32–36°C) on day 1	22 (45.8)

CA = cardiac arrest, IQR = interquartile range, ROSC = return of spontaneous circulation.

Associations of factors with CA occurrence are reported as odds ratios (ORs) with their 95% CIs. To test the robustness of our results, an exploratory analysis was carried out using a propensity score approach based on 1:1 pair matching when estimating the association between variables related to CSE and CSE-CA. We performed exact matching for each variable, with

TABLE 2. Factors Associated With Cardiac Arrest During Management for Convulsive Status Epilepticus

Factors Associated With CA During Management for CSE	*n* (%)		Univariate Analysis			Multivariate Analysis		
	CSE Without CA, *n* = 235 (82.7%)	CSE-Related CA, *n* = 49 (17.3%)	OR	95% CI	*p*	OR	95% CI	*p*
Demographic characteristics								
Male gender	128 (54.5)	26 (53.1)	1.06	0.57–1.96	0.86			
Age > 59 yr	122 (51.9)	20 (40.8)	0.64	0.34–1.19	0.16			
At least one comorbidity[a]	192 (81.7)	32 (65.3)	0.42	0.21–0.83	0.01	0.28	0.10–0.80	0.02
Chronic alcohol abuse	73 (31.1)	15 (30.6)	0.98	0.50–1.91	0.95			
Presumed ultimately fatal comorbidity[b]	44 (18.7)	11 (22.5)	1.26	0.60–2.65	0.55			
Previous history of epilepsy	96 (40.9)	22 (44.9)	1.18	0.63–2.19	0.60	2.42	0.91–6.67	0.08
Etiologic classification of previous epilepsy[c]								
Idiopathic or cryptogenic epilepsy	26 (27.1)	5 (22.7)	1					
Symptomatic genetic or acquired epilepsy	52 (54.2)	13 (59.1)	1.30	0.42–4.04	0.65			
Provoked epilepsy	18 (18.8)	4 (18.2)	1.16	0.27–4.90	0.84			
Use of chronic AED therapy	72 (75.0)	18 (81.8)	1.50	0.46–4.87	0.50			
Clinical findings at the scene								
Glasgow Coma Scale score ≥ 6	130 (55.3)	18 (37.5)	0.48	0.26–0.92	0.03			
Systolic blood pressure > 134 mm Hg (*n* = 269)	117 (51.3)	17 (41.5)	0.67	0.34–1.32	0.25			
Heart rate > 105 beats/min (*n* = 266)	113 (50.2)	20 (48.8)	0.94	0.49–1.84	0.87			
Pulse oximetry < 97% (*n* = 260)	93 (41.2)	24 (70.6)	2.70	1.22–6.25	0.02	2.66	1.03–7.26	0.04
Characteristics of CSE								
Out-of-hospital onset	139 (59.2)	30 (61.2)	1.09	0.58–2.05	0.79			
Witnessed onset	210 (89.4)	45 (91.8)	1.34	0.44–4.04	0.60			
Tonic-clonic seizure	175 (74.8)	38 (79.2)	1.28	0.60–2.73	0.52			
Generalized seizure	190 (80.9)	46 (93.9)	3.55	1.06–11.9	0.04			
Continuous (as opposed to intermittent)	130 (55.3)	21 (42.9)	0.60	0.32–1.12	0.11			
Seizure duration > 85 min	125 (53.2)	15 (30.6)	0.39	0.20–0.75	0.005	0.46	0.17–1.19	0.12
Time from seizure onset to medical team arrival > 30 min	128 (54.5)	22 (44.9)	0.68	0.37–1.26	0.22			
Drug poisoning as the cause of CSE	23 (9.80)	14 (28.6)	3.69	1.73–7.84	0.0007	4.13	1.27–13.53	0.02

(*Continued*)

TABLE 2.

(*Continued*). Factors Associated With Cardiac Arrest During Management for Convulsive Status Epilepticus

Factors Associated With CA During Management for CSE	*n* (%)		Univariate Analysis			Multivariate Analysis		
	CSE Without CA, *n* = 235 (82.7%)	CSE-Related CA, *n* = 49 (17.3%)	OR	95% CI	*p*	OR	95% CI	*p*
Management of CSE								
Benzodiazepine as first-line therapy	218 (93.2)	39 (88.6)	0.57	0.20–1.65	0.30			
"Classic" AED as first- or second-line therapy	131 (55.7)	30 (61.2)	1.25	0.67–2.35	0.48			
≥ 2 treatment lines needed to control CSE	90 (38.3)	14 (31.8)	0.88	0.65–1.20	0.41			
Refractory status epilepticus	84 (35.8)	15 (30.6)	0.79	0.41–1.54	0.49			
Time from seizure onset to intubation > 90 min (*n* = 243)	108 (55.1)	16 (34.0)	0.42	0.22–0.82	0.01			
Early adverse events related to CSE management	45 (19.2)	31 (63.3)	7.27	3.74–14.1	< 0.0001	11.98	4.67–34.69	< 0.0001
Side effect of AEDs/anesthetics	6 (12.2)	24 (49.0)	4.54	2.36–8.73	< 0.0001			
Airway management difficulties (*n* = 243)	4 (2.0)	9 (19.2)	11.4	3.33–38.8	0.0001			

AED = antiepileptic drug, CA = cardiac arrest, CSE = convulsive status epilepticus, OR = odds ratio.

[a]At least one comorbidity among cardiac (*n* = 139), respiratory (*n* = 84), and neurologic (other than epilepsy) comorbidities (*n* = 131).

[b]According to McCabe classification.

[c]Etiologic classification of previous epilepsy adapted from Shorvon (16).

Goodness-of-fit (Le Cessie-van Houwelingen) χ^2 *p*, 0.40/area under the receiver operating characteristics curve estimated by the *C*-statistic, 0.88.

no replacement, using a specified caliper distance of 0.2. The variables included in the propensity score were selected among the demographic and baseline CSE characteristics associated with CSE-CA by univariate logistic regression ($p < 0.20$) and/or were clinically relevant variables not thought to be related to CSE-CA. Five variables were included in the propensity score, namely, age greater than 59 years; at least one comorbidity among cardiac, respiratory, and neurologic comorbidities; previous history of epilepsy; continuous (as opposed to intermittent) CSE; and generalized seizure. Each of the 49 cases with CSE-CA was matched on the propensity score to a control with CSE but no CA. All tests were two tailed, and *p* values less than 0.05 were considered significant. Analyses were performed using R statistical software Version 3.3.3 (17).

RESULTS

Figure 1 is the patient flow chart. Of the 4,438 patients initially managed for an episode of CSE in the 17 participating hospitals during the 16-year study period, 49 patients (1.1%) with CA were included in the study.

Baseline Characteristics and Clinical Features of the Cases

There were 23 women and 26 men with a median age of 56 years (41–66 yr). A previous history of epilepsy was noted in 22 of 49 patients (45%) (Table 1). Most episodes (30/49; 62%) occurred out of hospital, and 45 of 49 (92%) were witnessed from their onset. All but 10 patients were still seizuring at medical team arrival. On-scene median GCS score was 3 (3–6). Details of CSE management are given in **electronic supplementary material file 2** (Supplemental Digital Content 2, http://links.lww.com/CCM/D538). Median time from seizure onset to AED initiation was 45 minutes (14–76 min), and median number of AED lines needed to control SE was 2 (1–3). CSE was refractory in 15 of 49 patients (31%). Total seizure duration was 45 minutes (22–95 min). Mechanical ventilation was needed in all but two patients.

Adverse events complicating the management of CSE occurred in 31 of 49 patients (63%). Side effects of AEDs developed in 24 of 49 patients (49%) and consisted of respiratory depression (*n* = 9; benzodiazepines, phenobarbital), cardiac arrhythmia (*n* = 8; phenytoin), and anesthetic-induced hypotension (*n* = 7). Airway management difficulties occurred in nine of 49 patients (19%).

Characteristics and Management of CA

Table 1 reports the main CA characteristics according to the Utstein style. Median time from CSE management initiation to CA was 25 minutes (5–85 min). At ICU admission, median LOD score was 13 (11–16), indicating a median of 4 (3–4) organ failures

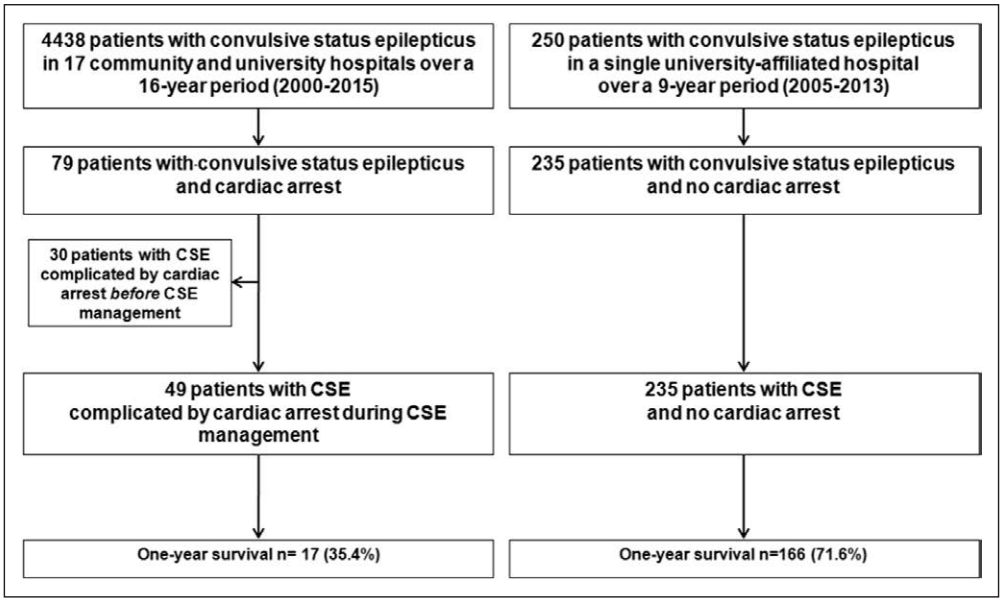

Figure 1. Patient flow chart. CSE = convulsive status epilepticus.

per patient. Post-CA shock developed in 32 patients (67%), who required vasopressors for a median duration of 2 days (1–4 d). Mechanical ventilation was used for 4 days (2–13 d). Finally, renal replacement therapy was required in 10 patients (20%). Targeted temperature management with a target of 32–36°C was used in 22 patients (46%), for a median of 28 hours (25–34 hr). Electroencephalogram monitoring was performed in 37 patients (76%).

Etiologic Investigations

Electronic supplementary material file 2 (Supplemental Digital Content 2, http://links.lww.com/CCM/D538) details the investigations performed to identify the causes of CSE and CA. In patients with CA, the most common cause of CSE was drug poisoning (14/49; 29%). The offenders were psychotropic drugs in nine patients (tricyclic antidepressants in five, neuroleptics in two, and various combinations in two), recreational drugs in two patients (cocaine and amphetamine in one patient each), and prescribed medications in three patients (antibiotic, mycophenolate mofetil, and local anesthetic in one patient each). The other main causes of CSE in the cases were acute alcohol ingestion in nine of 49 patients (18%), vascular disease in seven patients (14%), metabolic disorders in six patients (12%), and withdrawal of chronic AED therapy in five patients (10%). The cause of CSE remained undetermined despite extensive investigations in five of 49 patients (10%).

The most common mechanisms of CA were a systemic complication of CSE in 48 of 49 patients (98%), a complication of CSE management in 31 of 49 patients (63%), the cause of CSE in 12 patients (24%), patient-related factors in four patients (8%), and injuries related to the loss of consciousness and seizuring in one patient.

Short- and Long-Term Functional Outcomes

Overall in-hospital mortality was 61% (30/49), and an additional patient died during the 1-year follow-up period, yielding an overall 1-year mortality rate of 63%. Of the 30 in-hospital deaths, 16 occurred after treatment limitation decisions, eight were due to multiple organ failure induced by post-CA shock, and six were related to brain death. The 1-year mortality rate was significantly lower in the controls than in the cases (28.8% vs 64.6%). The proportion of patients with a favorable 1-year functional outcome (CPC score of 1–2) was significantly higher in the controls (56.7% vs 27.8%; $p = 0.0002$).

Determinants of CSE-CA

Table 2 reports the results of the univariate and multivariate analyses comparing the 49 cases and 235 controls. By multivariate analysis (**Fig. 2**), the only variable significantly associated with absence of CA was having at least one comorbidity among cardiac, respiratory, and neurologic comorbidities (OR, 0.28; 95% CI, 0.10–0.80; $p = 0.02$). Three variables were associated with CA, namely, low pulse oximetry (< 97%) on scene (OR, 2.66; 95% CI, 1.03–7.26; $p = 0.04$), drug poisoning as the cause of CSE (OR, 4.13; 95% CI, 1.27–13.53; $p = 0.02$), and adverse events complicating the management of CSE (OR, 11.98; 95% CI, 4.67–34.69; $p < 0.0001$). The sensitivity analysis comparing the 49 cases with CSE-CA to 49 propensity score–matched controls with CSE, and no CA produced comparable results (**Table 3**). Variables significantly associated with CSE-CA were as follows: GCS score less than 6 ($p = 0.03$), pulse oximetry less than 97% ($p = 0.004$), seizure duration less than 85 minutes ($p = 0.0001$), drug poisoning as the cause of CSE ($p = 0.04$), and early adverse events related to CSE management ($p < 0.0001$).

DISCUSSION

To our knowledge, this study provides the first detailed information on CA as a complication arising during the management of CSE. Although CA occurred in only 1.1% of all patients with CSE, this complication was associated with major adverse effects on both survival and long-term functional outcomes. We identified four factors independently associated with CA; these factors were linked to the patients' health profile, systemic impact of CSE, early management, and cause of CSE, respectively.

The characteristics of our patients were consistent with previous reports of critically ill patients with CSE. CSE occurred predominantly in out-of-hospital settings and was usually witnessed from the onset (17). All patients received early on-scene symptomatic IV AED therapy concomitantly with prompt and extensive investigations to identify the cause, as well as life-supporting measures as needed. Thus, time from seizure onset

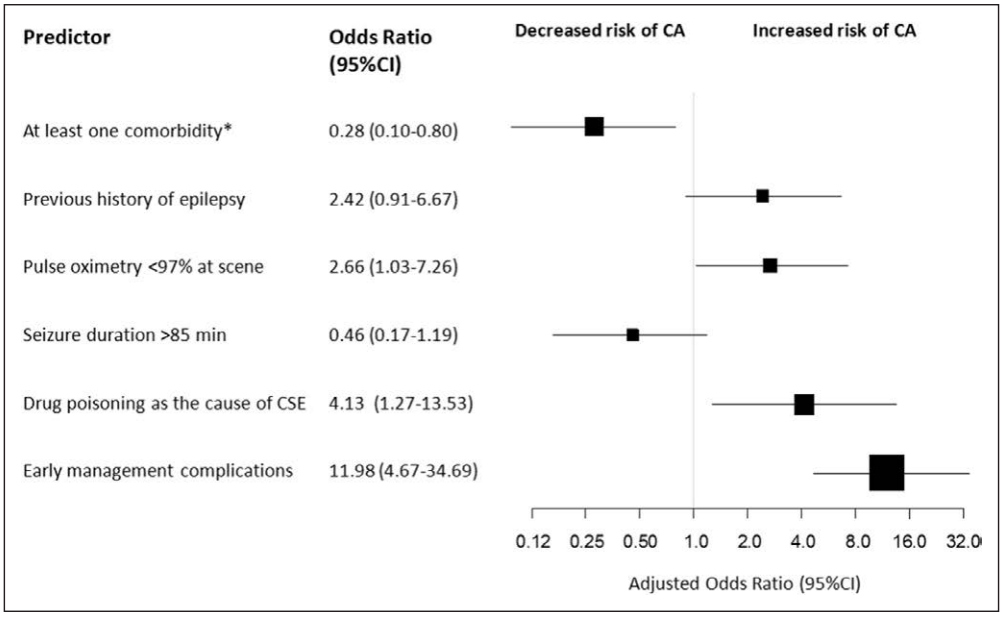

Figure 2. Odds ratios for cardiac arrest (CA). *Data marker* sizes reflect the relative size of each covariate. *Error bars* indicate 95% CIs of odds ratios. *At least one comorbidity among cardiac, respiratory, and neurologic (other than epilepsy). CSE = convulsive status epilepticus.

to first drug administration was 45 minutes (14–76 min) (18). However, as previously described, median total seizure duration was as long as 45 minutes (22–95 min) (15, 18–20). Extensive diagnostic investigations were performed. Cerebral imaging and electroencephalogram monitoring were available for all patients. The electroencephalograms were interpreted by neurophysiologists, and neurologists assessed the patients as needed. Finally, a cause of CSE was detected in 88% of patients (18, 19, 21). CSE-CA is a rare event about which data are scarce. Two main approaches can be distinguished. The first likens CSE-CA to sudden unexpected death in epilepsy (SUDEP), defined as sudden and unexpected death in a patient with epilepsy in the absence of an underlying anatomic or toxicologic cause of death. SUDEP is the leading cause of epilepsy-related deaths in patients with epilepsy (22). However, SUDEP occurs in the absence of ongoing seizures (23). The other approach is based chiefly on scant data from retrospective cohorts of patients with CA due to neurologic causes, in which ictal causes are merely reported. In a study of 21,175 patients with out-of-hospital CA due to any cause, only 0.2% had CSE-CA (24). In a smaller population of 270 patients with CA, the cause was epilepsy in 0.4% of cases (25). Of 253 patients with SE, five (2%) died at the acute phase (26), and of 41 patients with in-hospital SE episodes, 25 died, including nine during the acute seizure phase (3). However, these data are scant and come only from patients with in-hospital SE. Furthermore, no study focused on CA complicating the management of patients with CSE.

Our case-control comparison indicates a far worse prognosis in patients with CA. Thus, 1-year mortality was more than twice as high in the cases than in the controls. Good function (CPC score of 1–2) was twice as common in the controls than the cases. The consistency of these findings with ICU mortality rates and long-term functional outcomes in previous studies of CSE support the external validity of our study (1, 4, 5, 18, 19). The strong associations linking CSE-CA to adverse outcomes highlight the importance of identifying risk factors for CA, in order to devise potential strategies for improvement.

Four factors were independently associated with CA during the management of CSE, including three associated with a higher risk of CA. Among these three factors, adverse events of CSE management offer the greatest room for improvement. These adverse events included respiratory and cardiac side effects of AEDs, hemodynamic side effects of anesthetics, and airway management difficulties. Many AEDs have been reported to be associated with potentially life-threatening complications. For example, IV phenytoin—a drug with class IB antiarrhythmic properties—can induce cardiac arrhythmia, arterial hypotension, cardiogenic shock, or CA, even with recommended dosages and administration rates (27–32). Anesthetics used for the induction or maintenance treatment of refractory SE may cause hemodynamic failure, a complication frequently reported with pentothal (33). Furthermore, these systemic complications, potentiated by the use of highly sympatholytic and vasodilating hypnotic agents such as thiopental sodium, promote ventilation-induced cardiovascular collapse (33). Finally, no specific data on intubation difficulties in CSE are available. Among patients requiring emergent mechanical ventilation, 8% had intubation difficulties and 3% died within 30 minutes after intubation (34). Furthermore, both sustained seizure activity, and causes of CSE can induce acute destabilization of comorbidities, thereby promoting the occurrence of complications and treatment intolerance. Drug poisoning as the cause of CSE independently predicted CA in our study. The underlying mechanism may involve interactions between the drugs of overdose and AEDs, particularly as ongoing seizure activity can impair the tolerance of aggressive AED therapy (35). Another predictor of CA in our study was on-scene pulse oximetry less than 97% during early CSE management, which may reflect the burden of systemic complications of CSE (9–11, 36). Respiratory failure is among the most frequent systemic complications of CSE, being encountered in about 80% of cases, and has been reported to be independently associated with mortality (17, 37). The association we found between early relative hypoxemia during CSE management and CA may be explained by a higher risk of cardiac arrhythmias in patients with longer peri-ictal hypoxemia

TABLE 3. Variables Associated With Cardiac Arrest During Management for Convulsive Status Epilepticus in 49 Cases and 49 Controls Matched on a Propensity Score

Cases vs Matched Controls	*n* (%) CSE-Related CA Cases, *n* = 49	CSE Without CA Matched Controls, *n* = 49	*p*
Demographic characteristics			
Male gender	23 (46.9)	26 (53.1)	0.69
Age > 59 yr	20 (40.8)	20 (40.8)	1.00
At least one comorbidity[a]	32 (65.3)	32 (65.3)	1.00
Chronic alcohol abuse	15 (30.6)	12 (24.5)	0.65
Presumed ultimately fatal comorbidity[b]	11 (22.5)	9 (18.4)	0.80
Previous history of epilepsy	22 (44.9)	22 (44.9)	1.00
Etiologic classification of previous epilepsy[c]			0.85
Idiopathic or cryptogenic epilepsy	5 (22.7)	6 (27.3)	
Symptomatic genetic or acquired epilepsy	13 (59.1)	11 (50.0)	
Provoked epilepsy	4 (18.2)	5 (22.7)	
Use of chronic AED therapy	18 (81.8)	16 (72.7)	1.00
Clinical findings at the scene			
Glasgow Coma Scale score ≥ 6	18 (37.5)	30 (61.2)	0.03
Systolic blood pressure > 134 mm Hg (*n* = 40)	17 (41.5)	27 (56.3)	0.20
Heart rate > 105 beats/min (*n* = 39)	20 (48.8)	25 (52.1)	0.83
Pulse oximetry < 97% (*n* = 33)	24 (70.6)	18 (37.5)	0.004
Characteristics of CSE			
Out-of-hospital onset	30 (61.2)	31 (63.3)	1.00
Witnessed onset	45 (91.8)	44 (89.8)	1.00
Tonic-clonic seizure	38 (79.2)	43 (87.8)	0.29
Generalized seizure	46 (93.9)	46 (93.9)	1.00
Continuous (as opposed to intermittent)	21 (42.9)	21 (42.9)	1.00
Seizure duration > 85 min	15 (30.6)	35 (71.4)	0.0001
Time from seizure onset to medical team arrival > 30 min	22 (44.9)	28 (57.1)	0.31
Drug poisoning as the cause of CSE	14 (28.6)	5 (10.2)	0.04
Management of CSE			
Benzodiazepine as first-line therapy	39 (88.6)	45 (93.8)	0.47
"Classic" AED as first- or second-line therapy	30 (61.2)	27 (55.1)	0.68
≥ 2 treatment lines needed to control CSE	14 (31.8)	15 (30.6)	1.00
Refractory status epilepticus	15 (30.6)	13 (26.5)	0.82
Time from seizure onset to intubation > 90 min (*n* = 39)	16 (34.0)	22 (56.4)	0.05
Early adverse events related to CSE management	31 (63.3)	7 (14.3)	< 0.0001
Side effect of AEDs/anesthetics	24 (49.0)	7 (14.3)	0.0004
Airway management difficulties (*n* = 39)	9 (19.2)	0	0.003

AED = antiepileptic drug, CA = cardiac arrest, CSE = convulsive status epilepticus.
[a]At least one comorbidity among cardiac, respiratory, and neurologic comorbidities.
[b]According to McCabe classification.
[c]Etiologic classification of previous epilepsy adapted from Shorvon (16).

(38). Finally, in our study, having at least one cardiac, respiratory, or neurologic comorbidity (other than epilepsy) unexpectedly predicted absence of CA. One possible explanation is that patients with such comorbidities are easily identified by emergency teams, who then implement special precautions. Such an explanation, if true, would suggest that improved management may decrease the risk of CSE-CA. Interestingly, the univariate analysis done for the sensitivity study identified two additional factors of potential interest associated with CA, namely, on-scene GCS score less than 6 ($p = 0.03$) and seizure duration less than 85 minutes ($p = 0.0001$). That worse consciousness impairment associated with CA may be related to the respiratory disturbances seen in patients with impaired consciousness. The association with shorter seizure duration may be related to the fact that once CA occurs, seizuring stops.

Our study has several limitations. First, the extent to which our findings apply to the full spectrum of patients with CSE is unclear. Our patients were admitted to 17 ICUs over a 16-year period, and their management may have varied across centers and over time. However, we believe our study provides a faithful picture of the management of patients with CSE, since guidelines for defining and managing both CSE and CA have changed little in recent years. Second, only patients requiring ICU admission for CSE were included. This population may not reflect the overall population of patients with CSE. However, our focus was CSE-CA, which consistently requires ICU admission if the patient recovers spontaneous cardiac activity. Third, it would have been methodologically more satisfying to study a single cohort of patients with and without CA during CSE management. However, the very low prevalence of CSE-CA precluded such an approach. Finally, to test the robustness of our results, we performed a sensitivity analysis comparing the 49 cases with CSE-CA to 49 propensity score–matched controls with CSE and obtained comparable results.

In conclusion, CA occurred during the management of CSE in only 1.1 % of patients with CSE admitted to the ICU and was associated with significantly worse survival and long-term functional outcomes. In our patients, early predictors of CA were on-scene relative hypoxemia, on-scene adverse events of CSE management, and drug poisoning as the cause of CSE. Knowledge of these risk factors may suggest areas for improving the on-scene management of CSE.

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