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Futility After Cardiac Arrest: Another One Bites the Dust*

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Prognostication after sudden cardiac arrest used to be easy. Outcomes were uniformly dismal: epidemiologic studies in the 1990s reported survival to discharge in fewer than 5% of cases in New York and other U.S. cities (1). The primary role of the intensivist was to continue cardiopulmonary support while giving families enough time to come to terms with tragedy. Neurologists were taught that coma from hypoxic-ischemic injury was untreatable and irrecoverable.

Targeted temperature management (TTM) for the treatment of cerebral reperfusion injury after cardiac arrest has since changed everything (2, 3). Hypoxic-ischemic encephalopathy is now a treatable disease. The publication of the first two landmark trials in 2002 have been followed by a multitude of single-center studies, demonstrating a consistent pattern of improved outcome among cardiac arrest patients treated with hypothermia (4). Although a recent trial showed that outcomes are similarly excellent whether patients are cooled to either 33°C or 36°C (5), cooling after cardiac arrest is clearly here to stay. With the advent of TTM, there is new hope, and outcomes have been steadily improving.

But with a new game comes new rules, especially regarding prognostication (6). Intensivists and neurologists have learned to address prognosis only after a trial of maximally aggressive therapy before declaring neurological futility and recommending withdrawal of life support. This strategy was incorporated into the TTM trial, which may in part explain the remarkable 47% overall rate of good outcome in this study.

The most authoritative evidence-based guideline for predicting prognosis after cardiac arrest was published in 2006 by the American Academy of Neurology (7). The upshot was a list of clinical and laboratory criteria that were felt to define an iron-clad "no-hope" situation. However, the studies used to support these findings were conducted before therapeutic hypothermia came into widespread use.

Since 2006, a series of isolated reports of good neurological recovery have challenged the foundation of evidence supporting various no-hope criteria after cardiac arrest in patients who have been cooled. This process began with reports of good outcome in small numbers of patients with absent motor responses on day 3 or later (8), peak neuron-specific enolase levels exceeding the previously validated cut-point of 33 μg/L (9, 10), and bilaterally absent N20 responses on median nerve somatosensory-evoked potentials (11). We now know that exceptions to these conventional no-hope criteria can occur.

Myoclonic status epilepticus (MSE) has long been considered a catastrophic finding among victims of cardiac arrest (12, 13). The 1994 article (13) that firmly established this concept

*See also p. 965.

Key Words: cardiac arrest; hypoxic-ischemic encephalopathy; myoclonic status epilepticus; prognosis

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described 40 patients with MSE out of a consecutive series of 107 comatose survivors after cardiac arrest. All of the patients with MSE died, compared with a 30% recovery rate (i.e., the ability to follow verbal commands) among the 67 patients without MSE. The conclusion was that "myoclonus status in postanoxic coma should be considered an agonal phenomenon that indicates devastating neocortical damage. Its presence in comatose patients after cardiac arrest must strongly influence the decision to withdraw life support."

The tenet that MSE is irrecoverable was challenged by the study by Rossetti et al (14) in 2009. Three patients with MSE who had preserved brainstem reflexes and reactivity to stimuli on electroencephalography (EEG) recovered consciousness. A later article from the Netherlands reported that nine of 79 patients (12%) with post–arrest myoclonus treated with hypothermia survived with good outcomes (15).

If these studies represented the first cracks in a longstanding dogma, the landmark article published in this issue of *Critical Care Medicine* by Seder et al (16) crashes the walls down, and another one bites the dust. If these findings are further replicated, it means much more than "rare exceptions to the rule can occur." It might also mean that for the past 20 years, we have gotten it wrong.

In a large multinational database spanning 34 nations, of 2,532 cardiac arrest patients, 88% underwent TTM and 18% exhibited myoclonus. Survival with good recovery occurred in 9% of those with myoclonus (44 of 471) (16). Survival with recovery from coma was associated with the absence of epileptiform activity on EEG (15% vs 2%), as well as younger age, a shockable initial rhythm, witnessed arrest, and shorter time to return of spontaneous circulation.

The greatest weakness of this study is the lack of detailed information regarding the myoclonus itself. We have no idea of the duration, intensity, or distribution of the myoclonus and cannot differentiate between rare and isolated, purely stimulus-induced, or status myoclonus. In our experience, clinicians have very poor interobserver agreement when describing adventitious movements after cardiac arrest; terms such as myoclonus, seizures, twitches, dyskinesias, and the like are used almost interchangeably. Further research is needed to develop a detailed nosology for abnormal movements after cardiac arrest. Similarly, the study by Seder et al (16) lacks detail about EEG abnormalities beyond the presence or absence of epileptiform activity and electrographic seizures.

Despite these weaknesses, this important study challenges the widespread belief that MSE after cardiac arrest implies certain doom. These patients deserve to be offered a trial of aggressive life support and treatment of their myoclonic seizures, especially if brainstem reflexes are intact, the EEG is reactive to stimuli, and if epileptiform discharges are absent. The most eye-popping finding of all in the study is the fact that 78% of patients with myoclonus who died had a do-not-resuscitate order, compared with only 7% of those who survived ($p < 0.001$).

The study by Seder et al (16) in this issue of *Critical Care Medicine* has the potential to change clinical practice around the world. These findings need to be replicated in a study with high-quality centralized reads of EEG findings and the movements themselves, to put us on more solid ground. But until then, do not rush to judgment when confronted with MSE after cardiac arrest. Instead, roll up your sleeves: get an emergency EEG, start treating the seizures aggressively (we suggest starting with valproic acid and a midazolam infusion), and tell the family to hang on—it's too soon to tell.

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Neurologic Outcomes and Postresuscitation Care of Patients With Myoclonus Following Cardiac Arrest*

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Objectives: To evaluate the outcomes of cardiac arrest survivors with myoclonus receiving modern postresuscitation care.

Design: Retrospective review of registry data.

Setting: Cardiac arrest receiving centers in Europe and the United States from 2002 to 2012.

Patients: Two thousand five hundred thirty-two cardiac arrest survivors 18 years or older enrolled in the International Cardiac Arrest Registry.

Interventions: None.

Measurements and Main Results: Eighty-eight percent of patients underwent therapeutic hypothermia and 471 (18%) exhibited myoclonus. Patients with myoclonus had longer time to professional cardiopulmonary resuscitation (8.6 vs 7.0 min; $p < 0.001$) and total ischemic time (25.6 vs 22.3 min; $p < 0.001$) and less often presented with ventricular tachycardia/ventricular fibrillation, a witnessed arrest, or had bystander cardiopulmonary resuscitation. Electroencephalography demonstrated myoclonus with epileptiform activity in 209 of 374 (55%), including status epilepticus in 102 of 374 (27%). Good outcome (Cerebral Performance Category 1–2) at hospital discharge was noted in 9% of patients with myoclonus, less frequently in myoclonus with epileptiform activity (2% vs 15%; $p < 0.001$). Patients with myoclonus with good outcome were younger (53.7 vs 62.7 yr; $p < 0.001$), had more ventricular tachycardia/ventricular fibrillation (81% vs 46%; $p < 0.001$), shorter ischemic time (18.9 vs 26.4 min; $p = 0.003$), more witnessed arrests (91% vs 77%; $p = 0.02$), and fewer "do-not-resuscitate" orders (7% vs 78%; $p < 0.001$). Life support was withdrawn in 330 of 427 patients (78%) with myoclonus and poor outcome, due to neurological futility in 293 of 330 (89%), at 5 days (3–8 d) after resuscitation. With myoclonus and good outcome, median ICU length of stay was 8 days (5–11 d) and hospital length of stay was 14.5 days (9–22 d).

Conclusions: Nine percent of cardiac arrest survivors with myoclonus after cardiac arrest had good functional outcomes, usually in patients without associated epileptiform activity and after prolonged hospitalization. Deaths occurred early and primarily after withdrawal of life support. It is uncertain whether prolonged care would yield a higher percentage of good outcomes, but myoclonus of itself should not be considered a sign of futility. (*Crit Care Med* 2015; 43:965–972)

Key Words: arrest; cardiac; myoclonic; myoclonus; seizure; status epilepticus

***See also p. 1136.**

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Myoclonus, described as brief, involuntary twitching of a muscle or a group of muscles, is a common manifestation of neurological injury after cardiac arrest, and its clinical meaning, prevalence, and treatment are much debated. Pathophysiological correlates to myoclonus after cardiac arrest include cortical injury, injury to deep white matter tracts, and injury to the deep gray matter structures (1). Animal research shows that injury to the ventrolateral

thalamus is associated with clinical myoclonus (2, 3), and functional imaging of patients that survive cardiac arrest with late myoclonus shows increased fludeoxyglucose uptake in the same area (4). The prevalence of such injuries may depend on the duration of circulatory arrest (no-flow interval), duration and severity of hypoperfusion (low-flow interval), relative contribution of hypoxemia, presence or absence of focal cerebrovascular stenosis, microvascular disease, the severity of reperfusion injury after restoration of blood flow, and other factors. Biochemically, myoclonus after cardiac arrest is associated with decreased spinal fluid serotonin, and in rat models, seratonin replacement ameliorates myoclonus (5–7). Some authors have suggested that "subcortical" myoclonus may differ from "cortical myoclonus" (8–10), and recent work confirmed that myoclonus after cardiac arrest may originate from either cortical or subcortical injury (11), yet this nomenclature has not been validated with physiologic or autopsy studies, and remains problematic.

Generalized myoclonus after circulatory arrest is often called "status myoclonus," characterized by coma, sustained (> 30 min) bilateral muscle twitching, and predominantly poor outcomes (12–17). Although cortical electroencephalography (EEG) discharges are frequently seen in status myoclonus, simultaneous electrical discharges have not been required in most descriptions to make the diagnosis (1, 6, 15, 16), and it is unclear if status myoclonus with epileptiform discharges has a different prognosis than status myoclonus without EEG correlates (6, 11, 14, 18–21). By contrast, the so-called Lance-Adams Syndrome is described as an intention or action myoclonus, occurring later, typically in awake patients after cardiac arrest or severe hypoxia, and associated with better functional outcomes (2, 6, 22, 23). A histopathological comparison of these entities has not been undertaken, and distinguishing the clinical entities can be difficult. Unanticipated recovery of patients exhibiting early myoclonus after resuscitation is the subject of multiple case reports but occurs rarely (15, 24–28). This unexpected recovery is of concern, since most inpatient deaths after cardiac arrest are due to withdrawal of life support (29, 30), and confusion about the classification of postcardiac arrest myoclonus might contribute to incorrect prognostication and unnecessary deaths.

In 1985, prior to the routine utilization of targeted temperature management (TTM), Levy et al (16) reported 90% poor neurological outcomes in patients with myoclonus after cardiac arrest. Two widely cited articles followed, describing no survivors in large case series among patients with status myoclonus (12, 13), referred to as an "agonal" phenomenon (12). These articles were a basis for 2006 Guidelines issued by the American Academy of Neurology, which offered a strong opinion of futility when status myoclonus was present after an arrest (31). We now attempt to characterize the prevalence, neuromonitoring practices, outcomes, and mode and timing of death among patients with myoclonus after cardiac arrest in a large registry population, most of whom received TTM. We also describe the patient characteristics and hospital course of survivors, in an effort to give clinicians a sense of the time frame for awakening, suggesting how long it might be reasonable to wait for recovery of neurologic function.

MATERIALS AND METHODS

This observational, registry-based study of cardiac arrest survivors was conducted in the International Cardiac Arrest Registry (INTCAR). INTCAR is a secure, web-based database involving 34 sites in Europe and the United States. The core INTCAR dataset is composed of 87 de-identified data points with standardized definitions, focusing on elements of post–cardiac arrest care. Research approval is obtained locally, and sites must maintain institutional review board approval for data collection and participation. INTCAR approved this registry-based project, and data analyses were performed at Maine Medical Center. See **Appendix 1** for participating sites.

Patients

Two thousand five hundred and thirty-two patients included unconscious (Glasgow Coma Scale motor score < 6), adult (≥ 18 yr old) patients admitted to the ICU after in- or out-of-hospital cardiac arrest. The study period was 2002–2012. Centers were asked to register all patients consecutively, and each treated patients according to its own therapeutic protocols, cardiac care pathways, and temperature management equipment.

Dataset

Data collection regarding patient characteristics, comorbidities, cardiac arrest–related factors, and time points followed the Utstein recommendations (32–34). Cardiac arrest data were recorded from ambulance and emergency medical services records, using standardized definitions. The database provided automatic range checks, and all entries were manually reviewed for plausibility and logic. Site investigators were contacted to clarify data when appropriate. On-site monitoring was not performed.

Data related to intensive care management and adverse events were recorded according to a predefined protocol. The use of electroencephalogram, including limited or continuous recordings, was identified, and dominant EEG background patterns, epileptiform activity including periodic discharges, electrographic seizures, and electrographic status epilepticus were recorded. Abnormal movements, including convulsions and myoclonus, were also recorded. We further assessed the utilization of TTM and other treatments, all adverse events, utilization of "do-not-resuscitate" orders, and the withdrawal of life support.

Patients with myoclonus who were also reported to have periodic epileptiform discharges, seizures, or status epilepticus on EEG were considered to have "myoclonus with epileptiform activity," whereas those with EEG monitoring who had no epileptiform activity were classified as having "myoclonus without epileptiform activity." Many patients with myoclonus did not undergo EEG, and so this distinction could not be made for all patients. Timing, persistence, and location of the myoclonus is not reported, so status myoclonus could not be distinguished from occasional myoclonic jerks or a late action myoclonus.

Outcome Measurement

The primary outcome was neurological function at hospital discharge, assessed in terms of Cerebral Performance Category (CPC): CPC 1 indicates no or minor neurologic disability, able to work; CPC 2 indicates moderate neurologic disability, able to work in a sheltered environment; CPC 3 indicates severe neurologic disability, dependent on others for daily activities; CPC 4 indicates coma or vegetative state; and CPC 5 indicates dead. Classifications of CPC 1 or 2 were regarded as good neurologic outcomes.

Statistical Analysis

Proportions are expressed as percentages. Continuous data are expressed as mean and SD or as medians with interquartile ranges where nonnormal distributions were identified. Differences of proportions were assessed using a chi-square test. Continuous variables were compared using Student *t* test or Mann-Whitney-Wilcoxon rank-sum test as appropriate. Categorical variables were compared using a chi-square test. Two-tailed tests of significance were used, and *p* value less than or equal to 0.05 was considered significant.

RESULTS

Of 2,532 patients in the Registry, 471 (19%) were observed to have myoclonus (**Fig. 1**). **Table 1** compares characteristics of cardiac arrest survivors with myoclonus with those without, whereas **Table 2** compares the characteristics of patients with myoclonus and good functional outcome with those with myoclonus and poor functional outcome.

Thirty-nine percent of patients in the total cohort and 374 of 471 patients with myoclonus (79%) underwent some kind of EEG monitoring—either intermittent or continuous (**Table 3**). Of these, 194 underwent continuous EEG, and 180 had only intermittent EEG. Among patients with myoclonus who underwent EEG monitoring, 209 of 374 (55%) had epileptiform activity, meeting criteria for "myoclonus with epileptiform activity." Of these, 102 of 374 (27%) had electrographic status epilepticus.

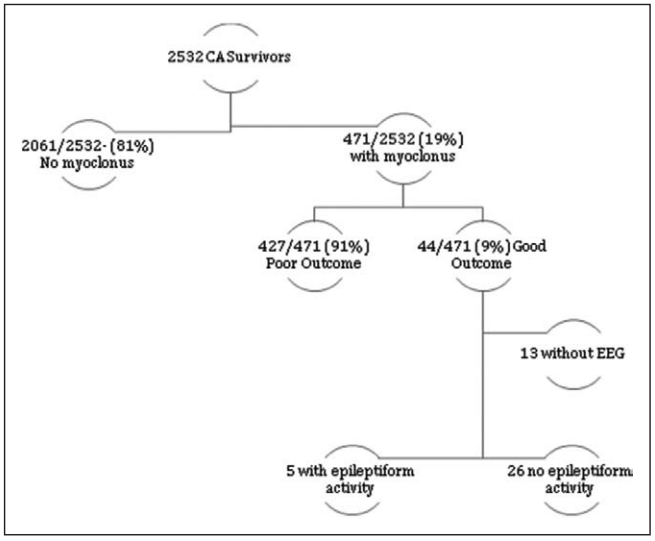

Figure 1. Myoclonus patients In the registry. CA = cardiac arrest, EEG = electroencephalography, Good outcome = Cerebral performance category of 1 or 2 at hospital discharge, Poor outcome = Cerebral performance category of 3, 4, or 5 at hospital discharge.

Forty-four patients with myoclonus (9%) were described as CPC 1 or CPC 2 (good outcome) at hospital discharge (**Table 4**). EEG was performed in 31 of 44 patients with myoclonus and good outcome, and "myoclonus without epileptiform activity" was reported in 26 of 31 (84%) while five patients (**Table 5**) had "myoclonus with epileptiform activity," including two with electrographic status epilepticus. Among the 374 patients with EEG monitoring and myoclonus, CPC of 1 or 2 was reported in five of 205 patients (2%) with "myoclonus with epileptiform activity" and 26 of 170 patients (15%) with "myoclonus without epileptiform activity" ($p < 0.001$). **Table 6** describes EEG findings and outcomes of the overall registry population.

DISCUSSION

This is the first article to describe the prevalence, EEG findings, and outcomes of patients with myoclonus after cardiac arrest in a large, multicenter registry cohort largely treated with TTM. The prevalence of myoclonus (18%) was lower than described in the pre-TTM era (16) and similar to two recent series treated with hypothermia (11, 35). Myoclonus was associated with many factors related to brain injury severity, including longer total ischemic time, a nonshockable initial heart rhythm, unwitnessed arrest, and lack of bystander cardiopulmonary resuscitation (CPR). Yet, the magnitude of these differences was not profound. Patients with "myoclonus without epileptiform activity" had better outcomes than those with "myoclonus with epileptiform activity," yet even when epileptiform activity was present, a small number, including two with electrographic status epilepticus, did well. Twenty-one percent of patients with myoclonus after cardiac arrest did not undergo EEG monitoring, which limits the completeness of our analysis, but also speaks to many clinicians' point of view that when myoclonus is present after cardiac arrest, EEG is not required to interpret its significance. Although most patients with myoclonus had poor outcomes, 89% of these died due to withdrawal of life support at a median of only 5 days postresuscitation and at 3 days or less in 25%. Conversely, patients with myoclonus with good outcome had a median ICU stay of 8 days and 14.5 days of hospitalization, raising the question of whether life support might have prematurely been withdrawn in some of those that died early.

This is also the first study to report a significant distinction in outcomes between cardiac arrest survivors with myoclonus and the presence or absence of associated epileptiform activity on EEG. Our findings differ from studies performed in the pre-TTM era in which the prevalence of myoclonus was described as 30–40% (14, 16). In our cohort, the prevalence of myoclonus was 19%, which agrees with a recent single-center Dutch experience (11), and is slightly lower than the 23–28% rate seen in the TTM Trial (35). Although it is impossible to know if the patients in these cohorts were similar, one possible explanation for the decreased prevalence of myoclonus compared to historical cohorts is less severe brain injury due to the utilization

TABLE 1. Demographics and Clinical Characteristics of Cardiac Arrest Survivors Comparing Those With or Without Myoclonus

Demographics and Clinical Factors	All Patients (*n* = 2,532)	Patients Without Myoclonus (*n* = 2,061)	Patients With Myoclonus (*n* = 471)	*p*
Age (mean, SD)	62.3 ± 15.3	62.4 ± 15.2	61.8 ± 15.9	0.43
Female (*n*, %)	771/2,527 (31)	634/2,057 (31)	137/470 (29)	0.48
Rhythm ventricular tachycardia/ventricular fibrillation (*n*, %)	1,388/2,395 (58)	1,164/1,944 (60)	224/451 (50)	< 0.001
Witnessed (*n*, %)	2,112/2,518 (84)	1,752/2,048 (86)	360/470 (77)	< 0.001
Bystander cardiopulmonary resuscitation (*n*, %)	1,505/2,434 (62)	1,245/1,974 (63)	260/460 (57)	0.009
No-flow time (mean, SD)	7.29 ± 7.12	6.99 ± 7.06	8.60 ± 7.23	< 0.001
Total ischemic time (mean, SD)	23.0 ± 17.4	22.3 ± 17.7	25.6 ± 15.5	< 0.001
In-hospital arrest (*n*, %)	643/2,531 (25)	567/2,060 (27)	76/471 (16)	< 0.001
Admission Glasgow Coma Scale motor subscore (median, interquartile range)	1 (1–3)	1 (1–3)	1 (1–1)	< 0.001

TABLE 2. Demographics and Clinical Characteristics of Cardiac Arrest Survivors With Myoclonus, Comparing Those With Myoclonus and Good Versus Poor Neurologic Outcome at Hospital Discharge

Demographics and Clinical Factors	All Patients With Myoclonus (*n* = 471)	Patients With Myoclonus and Poor Outcome (*n* = 427)	Patients With Myoclonus and Good Outcome (*n* = 44)	*p*
Age (mean, SD)	61.8 ± 15.9	62.7 ± 15.7	53.7 ± 15.3	< 0.001
Female (*n*, %)	137/470 (29)	124/426 (29)	13/44 (30)	0.95
Rhythm ventricular tachycardia/ventricular fibrillation (*n*, %)	224/451 (50)	190/409 (47)	34/42 (81)	< 0.001
Witnessed (*n*, %)	360/470 (77)	360/426 (75)	40/44 (91)	0.02
Bystander cardiopulmonary resuscitation (*n*, %)	260/460 (57)	234/419 (56)	26/41 (63)	0.35
No-flow time (mean, SD)	8.60 ± 7.23	8.76 ± 7.33	7.07 ± 6.13	0.15
Total ischemic time (mean, SD)	25.6 ± 15.5	26.4 ± 15.6	18.9 ± 12.7	0.003
In-hospital arrest (*n*, %)	76/471 (16)	68/427 (16)	8/44 (18)	0.70
Admission Glasgow Coma Scale motor subscore (median, interquartile range)	1 (1–1)	1 (1–1)	1 (1–1.5)	0.003
Hypothermia therapy (*n*, %)	444/471 (94.3)	402/427 (94.1)	42/44 (95.5)	1
Neuromuscular blockade (*n*, %)	276/374 (73.8)	247/343 (72.0)	29/31 (93.5)	0.016

of TTM, modern ICU care, higher rates of bystander CPR, and shorter no-flow intervals. This registry cohort included 57% of patients with an initial heart rhythm of ventricular tachycardia or ventricular fibrillation, which is higher than most epidemiological samples of cardiac arrest survivors—therefore, the patients in our registry may represent a less severely injured cohort than that seen in many centers, where rates of myoclonus may be higher than 19%. Another explanation is that the severity of brain injury is unchanged, but routine utilization of neuromuscular blockade and/or sedation to control shivering in patients undergoing TTM masks myoclonic activity (36).

Several recent reports have called for delayed prognostication and increased conservatism in outcome prediction after cardiac arrest (37–39). The longer duration of care in our cohort of patients with myoclonus with good outcomes raises the question of whether prolonged supportive measures might have led to more good outcomes. We conjecture that the negative implications of status myoclonus (12, 31) may have driven early discontinuation of life support in some patients that would have made a good functional recovery. This series shows with certainty that status myoclonus patients who have good outcomes required prolonged ICU care and a longer hospital course than

TABLE 3. Electroencephalographic Findings of Cardiac Arrest Survivors With Myoclonus

Epileptiform Activity and Anticonvulsants	All Patients With Myoclonus ($n = 471$) (%)	Myoclonus and Poor Outcome ($n = 427$) (%)	Myoclonus and Good Outcome ($n = 44$) (%)	p
Any electroencephalography	374/471 (79)	343/417 (82)	31/44 (71)	0.06
Severe background attenuation	75/374 (20)	73/343 (21)	2/31 (6)	0.08
Burst suppression	153/374 (41)	149/343 (43)	4/31 (13)	0.002
Continuous background	91/374 (24)	74/343 (22)	17/31 (55)	< 0.001
Nonreactive background	41/374 (11)	41/343 (12)	0/31 (0)	0.08
Any epileptiform activity	205/374 (55)	200/343 (58)	5/31 (16)	< 0.001
Periodic epileptiform discharges	104/374 (28)	101/343 (29)	3/31 (10)	0.03
Electrographic seizures	56/374 (15)	55/343 (16)	1/31 (3)	0.09
Electrographic status epilepticus	102/374 (27)	100/343 (29)	2/31 (6)	0.01
Anticonvulsants	301/369 (82)	276/338 (82)	25/31 (81)	0.9

TABLE 4. Outcomes of Cardiac Arrest Survivors With Myoclonus

Directives and Outcomes	All Patients With Myoclonus ($n = 471$)	Patients With Myoclonus and Poor Outcome ($n = 427$)	Patients With Myoclonus and Good Outcome ($n = 44$)	p
Do-not-resuscitate order (n, %)	335/470 (71)	332/426 (78)	3/44 (7)	< 0.001
Withdrawal support-futility (n, %)	293/471 (62)	293/427 (69)	0	< 0.001
ICU LOS (median, IQR)	5 (3–8)	5 (3–8)	8 (5–11)	< 0.001
Hospital LOS (median, IQR)	11 (7–19)	9 (6–17)	14.5 (9–22)	0.01

LOS = length of stay, IQR = interquartile range.

TABLE 5. Characteristics of Cardiac Arrest Survivors With Myoclonus and Epileptiform Activity That Survived With a Good Outcome

Age, Gender	Total Ischemic Time	Epileptiform Activity	Targeted Temperature Management Dosing	Antiepileptic Drugs	ICU LOS	Hospital LOS	Best ICU CPC	Discharge CPC
80, Male	30	PEDs, status epilepticus	33°C × 24 hr	Yes	8	60	4	2
41, Male	22	PEDs	33°C × 24 hr	Yes	15	72	3	2
54, Female	Unknown	Seizures	33°C × 24 hr	Yes	6	19	3	2
48, Male	7	PEDs	33°C × 24 hr	Yes	12	13	1	1
42, Female	35	Status epilepticus	33°C × 24 hr	Yes	18	23	2	1

LOS = length of stay, CPC = Cerebral Performance Category, PEDs = periodic epileptiform discharges.

other survivors. Waiting the "minimum" time for awakening and recovery in patients with myoclonus prior to discontinuation of life support is likely to result in lost opportunities for good outcome. It also highlights the need for multimodal prognostication after cardiac arrest (37, 40, 41), including measures such as somatosensory-evoked potentials and serum or imaging biomarkers.

Only 79% of patients with myoclonus after cardiac arrest underwent any (intermittent or continuous) EEG monitoring. This may relate to either inconsistent use or availability of EEG monitoring, or perhaps to the unclear definition of status myoclonus, which does not require EEG (6, 15). Because status myoclonus has previously been described as early and severe myoclonus, some centers make no attempt to determine whether this is an epileptic on nonepileptic phenomenon. Myoclonus after cardiac arrest may coincide with cortical epileptiform discharges, which we see are associated with markedly different outcomes; we believe that EEG in such patients

TABLE 6. Outcomes of Registry Patients With Epileptiform Activity on Electroencephalography

Epileptiform Activity, Muscle Relaxants, and Anticonvulsants	All Patients (%)	Good Outcome (%)	Poor Outcome (%)	*p*
Severe background attenuation	226/2,532 (8.9)	31/986 (3.1)	195/1,546 (12.6)	< 0.001
Burst suppression	293/2,535 (11.6)	26/986 (2.6)	267/1,546 (17.3)	< 0.001
Continuous background	425/2,532 (16.8)	178/986 (18.1)	247/1,546 (16.0)	0.17
Periodic epileptiform discharges	164/2,532 (6.5)	8/986 (0.8)	156/1,546 (10.1)	< 0.001
Electrographic seizures	77/2,532 (3.0)	4/986 (0.4)	73/1,546 (4.7)	< 0.001
Electrographic status	139/2,532 (5.5)	4/986 (0.4)	135/1,546 (8.7)	< 0.001
Nonreactive background	113/2,532 (4.5)	3/986 (0.3)	110/1,546 (7.1)	< 0.001
Antiepileptic drugs	525/2,507 (20.9)	75/977 (7.7)	450/1,530 (29.4)	< 0.001
Neuromuscular blockade	1,361/2,229 (61.1)	555/858 (64.7)	806/1,371 (58.8)	0.006
Clinical convulsions	132/2,532 (5.2)	22/986 (2.2)	110/1,546 (7.1)	< 0.001

is important and useful. It may be used to identify the underlying EEG background rhythm, detect and guide the treatment of seizures, gather prognostic information, and help define the regions and severity of brain injury. Determining the precise electrophysiological and imaging correlates of status myoclonus may help distinguish a cortical pattern of injury from deeper injury involving basal ganglia or brain stem. Such patterns of injury are being studied using neuroimaging and neurophysiological techniques (17, 42, 43), but a careful prospective study correlating the neuroimaging patterns of brain injury to EEG findings, clinical myoclonus, and outcomes with aggressive treatment has not been performed. Such research is critically needed to better describe variations in the brain injuries incurred during and after cardiac arrest, their clinical correlates, and their prognostic significance.

This study has several weaknesses and limitations. Like all retrospective research, it depends on accurate data entry and consistent interpretations of clinical scenarios by data collectors. Although INTCAR uses standardized definitions for data entry, complex data points may still be differently interpreted. This especially pertains to EEG interpretation, which may suffer from high interobserver variability even among like-minded practitioners (44). Specifically, not using a standardized template and complex definitions for EEG interpretation, such as the American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology (45), or detailed definitions of what constitutes a convulsion are important weaknesses of these data. Furthermore, like all registries, there are missing data points of interest, such as the presence of absence of brainstem reflexes at the time of hospital or ICU admission, which is an important early indicator of brain injury severity (17, 46). Second, we are not able to distinguish between status myoclonus (which may be a sign of poor prognosis) and myoclonic jerks (which are not). Third, patients treated with continuous neuromuscular blockade may not have manifestations of myoclonus. Untreated myoclonus after cardiac arrest is rarely subtle, however, often manifesting most dramatically after the rewarming period, when neuromuscular blockade is not used, so we think this was unlikely to confound our results significantly. The strength of the study includes the size and comprehensive nature of our data, spanning Europe and the United States, with generalizable conclusions describing real-world practices and trends.

CONCLUSIONS

Nine percent of cardiac arrest survivors treated with TTM and exhibiting the physical examination finding of myoclonus after cardiac arrest had good functional outcomes. When the myoclonus was not associated with epileptiform activity on EEG, 15% had a good outcome. Death with myoclonus often occurred early and primarily after withdrawal of life support, but it is uncertain whether prolonged care would yield a higher percentage of good outcomes. EEG should be performed in patients with myoclonus after cardiac arrest, and the physical examination finding of myoclonus of itself should not be interpreted as a sign of futility. High-quality prospective studies that clarify the pathophysiology of myoclonus after cardiac arrest, aggressively support patients, and reliably identify patients with survivable injuries are urgently needed.

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APPENDIX 1. Participating Sites and Their Patient Contributions

1. Landspitali University Hospital—Reykjavik, Iceland (120)
2. Asklepios Kliniken—Langen, Germany (23)
3. Östersund Hospital—Östersund, Sweden (20)
4. Örebro, University Hospital—Örebro Municipality, Sweden (22)
5. Skåne University Hospital—Lunds Universitet, Lund, Sweden (111)
6. Kungälv Hospital—Kungälv, Sweden (18)
7. Kristianstad Central Hospital—Kristianstad, Sweden (33)
8. Blekingesjukhuset—Karlskrona, Sweden (37)
9. Karlstad Central Hospital—Karlstad, Sweden (18)
10. Kalmar hospital—Kalmar, Sweden (11)
11. Evangelisches Krankehnhaus—Wien, Austria (11)
12. Halmstad Regional Hospital—Halmstad, Sweden (31)
13. Falu hospital—Falun, Sweden (29)
14. Danderyd Hospital—Danderyd, Sweden (20)
15. Uppsala University Hospital—Uppsala, Sweden (166)
16. Ulleval University Hospital—Ullevål University Hospital, Oslo, Norway (204)
17. Stavanger University Hospital—Stavanger, Norway (102)
18. Centre Hospitalier de Luxembourg—Luxembourg, Luxembourg (89)
19. Rigshospitalets Heart Center—Copenhagen, Denmark (61)
20. Gentofte Hospital—Gentofte Hospital, Hellerup, Denmark (25)
21. Cardiocenter, General Teaching Hospital—Prague, Czech Republic (151)
22. St. John's Mercy Medical Center—St. Louis, MO (110)
23. Ochsner Baptist Medical Center—New Orleans, LA (40)
24. Sarver Heart Center—University of Arizona, Tucson, AZ (36)
25. Vanderbilt University Medical Center—Nashville, TN (188)
26. Lehigh Valley Health Network—Allentown, PA (171)
27. Minneapolis Heart Institute—Minneapolis, MN (276)
28. Central Maine Medical Center—Lewiston, ME (11)
29. Eastern Maine Medical Center—Bangor, ME (119)
30. Maine Medical Center—Tufts University, Portland, ME (226)
31. Kärnsjukhuset, Sweden (13)
32. Sjukhuset i Lidköping—Lidköping, Sweden (10)
33. Columbia University, New York, NY (13)
34. Swedish Medical Center, Englewood, CO (24)