Early electroencephalogram does not reliably differentiate outcomes in post-hypoxic myoclonus

Linda J Dalic, Gerard Fennessy, Mark Edmonds, Patrick Carney, Helen Opdam and John Archer

Myoclonic seizures are brief, sudden, involuntary muscle jerks. When they appear hours to weeks after successful cardiopulmonary resuscitation, they are termed post-hypoxic myoclonus (PHM). Incidence estimates of PHM in resuscitated patients range from 19% to 37%.[1] Seizures are focal, multifocal or generalised, and the origin can be either cortical or subcortical.[2] Onset of PHM in comatose patients within 24 hours of arrest has a reported mortality rate between 85% and 100%.[3] Myoclonic status epilepticus, denoting PHM lasting > 30 minutes, is usually universally fatal,[4] although case reports documenting survival do exist in patients who have received targeted temperature management (TTM).[5]

Prognostication in patients with PHM remains challenging. Withdrawal of care in the acute setting is usually fatal, and, thus, electroencephalograms (EEGs), somatosensory evoked potentials (SSEP), imaging and clinical assessment are relied upon to assist prognostication. In particular, following clinical neurological examination, EEG is recommended to evaluate patients with PHM,[6] and is the most commonly used method to predict prognosis after cardiac arrest.[7] However, the interpretation of EEGs has historically depended on the subjective judgement of the examiner, resulting in high inter-rater variability, which is problematic in two ways. First, the interpretation of EEG must have high reliability, if it is to have credibility in deciding whether or not to continue active care in patients. Second, the uniform classification of EEG in the critical care setting has limited the possibilities to compare the results of previous studies, leading to a delay in understanding how these patterns contribute to patient outcome.

Recent work by the American Clinical Neurophysiology Society has sought to standardise EEG interpretation in this setting,[8] with promising inter-rater agreement.[9] Further work by the TTM trial identified three categories of EEG patterns (highly malignant, malignant and benign) to predict patient outcomes[10] (Table 1). These patterns have shown correlation with other prognostic predictors[11] following cardiac arrest and high specificity (not sensitivity) for outcome, particularly in the highly malignant group.[12] Using these categories, we assessed the utility of early EEG in patients with PHM.

ABSTRACT

Objective: Prognostication in patients with post-hypoxic brain injury remains difficult; yet, clinicians are commonly asked to guide decisions regarding withdrawal of life support. We aimed to assess whether electroencephalogram (EEG) is a useful tool in predicting neurological outcome in patients with post-hypoxic myoclonus (PHM).

Design and setting: This study was conducted as part of an internal hospital audit assessing therapeutic hypothermia in patients with hypoxic cardiac arrest.

Participants: We identified 20 patients with PHM and evaluated their initial routine EEG.

Main outcome measures: Three blinded neurologists independently assessed EEGs and scored them using the standardised critical care EEG terminology from the American Clinical Neurophysiology Society (2012 version) and the EEG patterns identified by the Target Temperature Management (TTM) trial group. Glasgow Outcome Scale (GOS) scores were used to assess neurological outcome at 30 and 90 days. Mortality rates at these time points were also documented.

Results: We found that the majority of patients (18/20) with PHM had an initial EEG that was "highly malignant" or "malignant", but outcomes at 30 and 90 days were not universally fatal. Six patients were alive at 30 days, and five at 90 days. Of the latter, two patients had moderate disability (GOS score 4) and one improved from a GOS score of 3 to 5, with only low disability. Two patients with "benign" EEGs had unchanged GOS scores of 3 at 30 and 90 days, indicating severe disability.

Conclusion: This study shows that PHM is associated with a poor but not universally fatal prognosis. Early EEG does not reliably distinguish between good and poor outcomes.

Crit Care Resusc 2019; 21 (1): 45-52

Methods

Population

All patients with hypoxic cardiac arrest admitted to a single tertiary hospital intensive care unit (ICU) (Austin Health, Melbourne, Australia) between 1 January 2010

Table 1. Identified electroencephalogram (EEG) patterns in patients and predicted patient outcomes in the critical care setting*

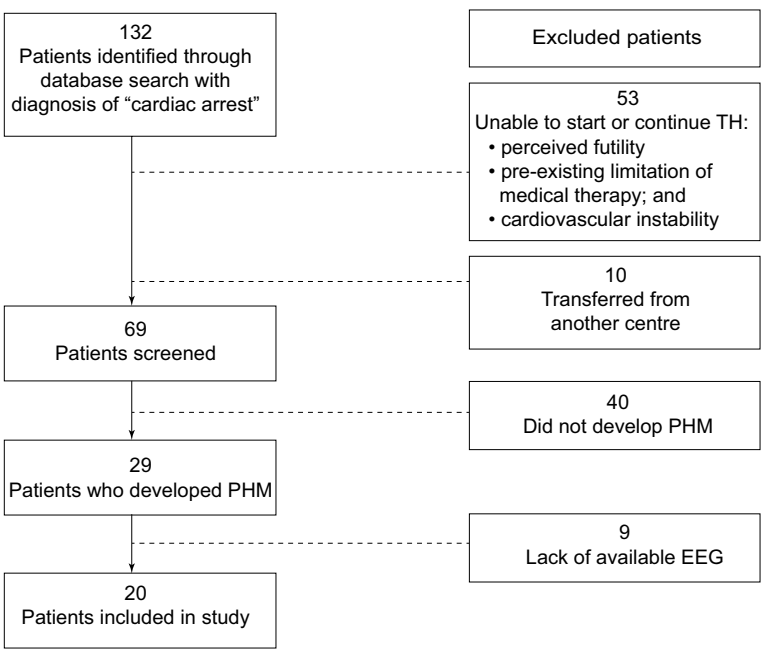
Category	Features	Predicted outcome
Highly malignant EEG	▪ Suppressed background without discharges ▪ Suppressed background with continuous periodic discharges ▪ Burst suppression background with suppression periods (> 50% recording)	Always associated with poor outcome
Malignant EEG	▪ Periodic or rhythmic patterns ▪ Abundant periodic discharges (> 50% recording) ▪ Abundant rhythmic spike and wave (> 50% recording) ▪ Electrographic seizure (at least one) ▪ Background EEG ▪ Discontinuous background with suppression periods > 10% ▪ Low voltage background ▪ Reversed anterior–posterior gradient ▪ Reactivity ▪ Absence of background reactivity or only stimulus-induced discharges ▪ SIRPIDs for both sound and pain stimuli	Nearly always associated with poor outcome
Benign EEG	▪ Absence of all malignant features stated above	Good outcome

SIRPIDs = stimulus-induced rhythmic, periodic or ictal discharges. * Adapted from Westhall et al.[10]

and 31 December 2011 were eligible for inclusion to an audit assessing therapeutic hypothermia with temperature targeted to 32–34°C (Figure 1). Patients were excluded if they had been transferred from another hospital or if they did not begin or complete therapeutic hypothermia. Sixty-nine patients were identified, and 29 developed PHM. Data on demographics, clinical examination findings and outcomes were prospectively collected.

Of the 29 patients with PHM identified, 20 adult patients (> 18 years old) were included (Figure 1). The remaining nine patients were excluded due to lack of EEG availability. All 20 patients developed PHM within 72 hours of arrest. Medical records were retrospectively checked for pre-existing causes of myoclonus, with no further patients excluded on this basis. Further clinical characteristics are described in Table 2 and Table 3.

Figure 1. Screening of patients for inclusion into the study*



EEG = electroencephalogram. PHM = post-hypoxic myoclonus. TH = therapeutic hypothermia. * All patients initially identified (*n* = 132) through searching of hospital database for admissions between 1 January 2010 and 31 December 2011.

Myoclonus

Myoclonus occurrence was recorded at the time. Patients were included if

myoclonus onset was ≤ 48 hours after arrest. Descriptions were divided into "continuous" or "intermittent" and "'whole-body" or "multifocal". Based on description and neurological review, myoclonus was characterised as "mild" (occasional jerking and/or lasting <1 hour, one limb or body area, and not interfering with care), "moderate" (frequent and continuing for > 1 hour, multifocal or generalised, but not requiring intervention, such as paralysis or interfering with care; ie, difficulty ventilating) or "severe" (persistent jerking continuing for > 2 hours, multifocal or generalised, or interfering with care).

Outcome

Neurological outcome was assessed using the Glasgow Outcome Scale (GOS) at 30 and 90 days (score 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = low disability). Thirty- and 90-day mortality rates were also recorded, including surviving the ICU and hospital settings. Treatment withdrawal was recorded for 14 patients. The reasons included previously expressed wishes and/or advice from family.

Table 2. Clinical characteristics of 20 patients with post-hypoxic myoclonus following hypoxic cardiac arrest

Characteristic	Value
Total number of patients	20
Age (years), median (IQR)	58 (47.5–72.8)
Gender, male (%)	15 (75%)
Arrest	
In-hospital	3 (15%)
Out-of-hospital	17 (85%)
Time (min) to ROSC, median (IQR)	27 (18–33.3)
Time (h) of myoclonus post-arrest, median (IQR)	23.5 (9.6–35.8)
Myoclonus severity	
Mild	2 (10%)
Moderate	1 (5%)
Severe	17 (85%)
Myoclonus type	
Multifocal	16 (80%)
Whole-body	4 (20%)
Intermittent	6 (30%)
Continuous	14 (70%)
Survived ICU	7 (35%)
Survived hospital	6 (30%)
Treatment withdrawn	14 (70%)
Mortality	
Alive at 30 days	6 (30%)
Alive at 90 days	5 (25%)

ICU = intensive care unit. IQR = interquartile range. ROSC = return of spontaneous circulation.

Electroencephalogram

EEG recordings were performed using the international 10–20 system, lasting 20–60 minutes. When multiple EEGs were performed, the first one was used. Mean duration between return of spontaneous circulation and EEG was 3.05 days (standard deviation [SD], 2.9). The initial EEG was recorded with ceased or reduced anaesthesia to visualise myoclonic jerks and their association with EEG discharges (if present). In the second half of the recording, a short-acting muscle relaxant or paralysing agent was used to block muscle artefacts, allowing a clearer view of cerebral activity.

All EEGs were assessed independently in a randomised order by three neurologists, blinded to patient identifiers, clinical characteristics and outcome. EEGs were scored according to the American Clinical Neurophysiology Society standardised critical care EEG terminology[8] and the EEG patterns identified by the TTM trial group.[10] Free-text descriptions of the EEG were also reported. Based on classifications and descriptions, the following categories were adopted: "highly malignant", "malignant" and "benign" (Table 1), as they are reported to correlate with outcome. When disagreement in interpretation between reviewers arose, the majority decision was used.

Results

Clinical characteristics

The median age was 58 years (interquartile range [IQR], 47.5–72.8), and 85% of participants had an out-of-hospital arrest. The median time to return of spontaneous circulation after arrest was 27 minutes (IQR, 18–33.3).

Myoclonus onset was 1–48 hours after arrest, with a median of 23.5 hours (IQR, 9.6–35.8). Most patients (17/20) had severe myoclonus; one patient had moderate and two patients had mild myoclonus (Table 3). Eighty per cent of patients had multifocal myoclonus, compared with 20% with whole-body myoclonus. Myoclonus was continuous (ie, myoclonic status epilepticus) in the majority of patients (14/20), and intermittent in the remainder. Further prognostic markers (clinical, neuroimaging and SSEP) for each patient are listed in Table 3.

Electroencephalogram and outcome

The majority of patients (18/20) had highly malignant or malignant initial EEGs. The distribution of these EEG patterns according to the GOS score at 30 and 90 days can be seen in Figure 2 and Figure 3.

Table 3. Prognostic features of 20 patients with post-hypoxic myoclonus following hypoxic cardiac arrest

		Myoclonus				Prognostic markers						
Patient no.	EEG	Severity	Description	Onset (hours after arrest)	Time to EEG (days)	Gag	Corneal reflex	VOR	Reactive pupil	SSEP	Computed tomography	Withdraw life support?
1	Malignant	Severe	▪ Whole-body ▪ Continuous	5	4	Yes	No	No	No	na	Diffuse loss of grey/ white differentiation	Yes
2	Highly malignant	Severe	▪ Multifocal: upper limb, eyes, chin ▪ Continuous	11	1	No	No	Yes	Yes	na	na	Yes
3	Malignant	Severe	▪ Multifocal: eyelids and feet, then upper limb and lower limb ▪ Intermittent	6	2	No	No	No	No	na	na	Yes
4	Malignant	Severe	▪ Multifocal: jaw twitching, then face, neck and chest ▪ Intermittent	12	2	No	No	No	Yes	Absent bilateral cortical potentials	na	Yes
5	Highly malignant	Severe	▪ Multifocal: upper limb and lower limb ▪ Intermittent	4	1	No	nr	nr	Yes	na	Normal (Day 0)	Yes
6	Highly malig-nant	Severe	▪ Multifocal: upper torso, feet ▪ Continuous	24	2	Yes	nr	nr	Yes	na	Normal (Day 0)	Yes
7	Highly malig-nant	Severe	▪ Multifocal: upper limb, lower limb, face ▪ Continuous	32	1	Yes	No	Yes	Yes	Low amplitude	Normal (Day 0)	Yes
8	Highly malignant	Severe	▪ Multifocal: shoulders, upper limb and lower limb (left > right), eyes ▪ Continuous	48	2	Yes	nr	nr	Yes	na	Normal (Day 2)	Yes
9	Malignant	Severe	▪ Multifocal: upper limb (left then right arm/ shoulder) mouth, tongue ▪ Continuous	10	2	No	Unable due to eye myoclonus	nr	No	na	na	Yes

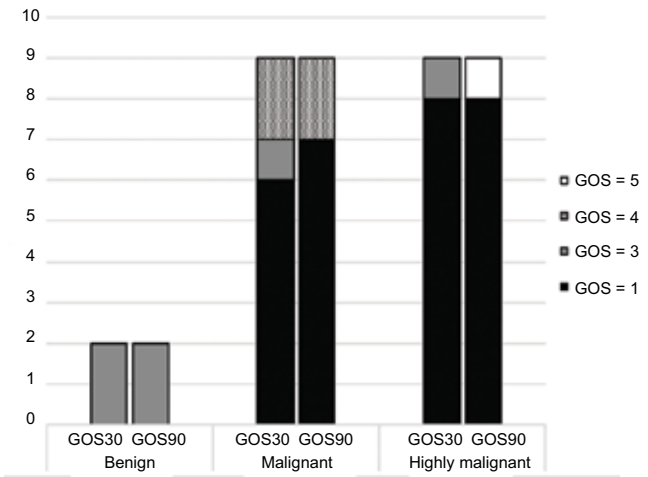
(*continued*)

Table 3. Prognostic features of 20 patients with post-hypoxic myoclonus following hypoxic cardiac arrest *(continued)*

		Myoclonus				Prognostic markers						
Patient no.	**EEG**	**Severity**	**Description**	**Onset (hours after arrest)**	**Time to EEG (days)**	**Gag**	**Corneal reflex**	**VOR**	**Reactive pupil**	**SSEP**	**Computed tomography**	**Withdraw life support?**
10	Highly malignant	Severe	▪ Multifocal: upper limb (left then right), torso and face ▪ Continuous	35	1	nr	nr	Yes	Yes	Normal	na	Yes
11	Malignant	Severe	▪ Multifocal: upper limb, lower limb, face, mouth ▪ Continuous	1	3	No	nr	nr	Yes	Normal	Diffuse loss of grey/ white differentiation	Yes
12	Malignant	Mild	▪ Multifocal: right arm, torso ▪ Continuous	38	1	Yes	Yes	Yes	Yes	na	na	No
13	Benign	Severe	▪ Multifocal: upper limb, lower limb ▪ Intermittent	10	1	Yes	Yes	Yes	Yes	na	na	No
14	Benign	Mild	▪ Multifocal: lower limb ▪ Continuous	28	6	Yes	Yes	Yes	Yes	na	na	No
15	Malignant	Severe	▪ Multifocal: upper limb, lower limb, torso ▪ Continuous	48	1	Yes	nr	Yes	Yes	na	Normal (Day 0)	No
16	Malignant	Moderate	▪ Multifocal: upper limb, lower limb ▪ Intermittent (ceased after 24 h)	43	2	Yes	Yes	Yes	Yes	na	Normal (Day 5)	No
17	Malignant	Severe	▪ Whole-body ▪ Continuous	30	2	No	No	Yes	Yes	na	Water-shed infarct	Yes
18	Highly malignant	Severe	▪ Whole-body ▪ Continuous	23	3	No	No	Yes	Yes	na	Diffuse loss of grey/ white differentiation	Yes
19	Highly malignant	Severe	▪ Multifocal: face, chest, legs ▪ Continuous	8.5	1	No	nr	No	No	na	Normal (Day 0)	Yes
20	Highly malignant	Severe	▪ Whole-body ▪ Intermittent (stimulus increased)	61	2	Yes	Unable due to eye myoclonus	Yes	Yes	na	Normal (Day 0)	No

EEG = electroencephalogram. na = not applicable. nr = not recorded. SSEP = somatosensory evoked potentials. VOR = vestibulo-ocular reflex.

Figure 2. Distribution of electroencephalogram patterns with respect to Glasgow Outcome Scale (GOS) score (1–5) at 30 days (GOS30) and 90 days (GOS90)



Eight of nine patients with a highly malignant EEG did not survive. However, one patient had a GOS score of 3 at 30 days, which improved to 5 at 90 days, and they left hospital after 49 days. This patient had myoclonic status epilepticus with severe myoclonus that developed 42 hours after arrest. Following the initial EEG, the patient's condition improved, although intermittent myoclonic jerks were present at 90 days.

Of the nine patients with malignant EEGs, two had a GOS score of 4 at 30 days, indicating moderate disability. At 90 days, the GOS score remained at 4 in one patient. The other patient received palliative care, according to family wishes, due to prior hemiparetic stroke. One patient with a malignant EEG and a GOS score of 3 at 30 days that improved to a GOS score of 4 at 90 days had severe myoclonus and spent 94 days in hospital before being discharged to rehabilitation. Intermittent myoclonic jerks were reported by the patient 2 years after arrest.

At 30 days, two patients with initial benign EEGs had a GOS score of 3. Both patients survived and the GOS score at 90 days was unchanged. One patient continued to have intermittent action myoclonus 2 years after arrest, but was managing most activities of daily living, including cooking simple meals.

For patients identified as surviving at 90 days (patient no. 13, 14, 15, 16 and 20 in Table 3), more detailed descriptions of their EEGs are offered in Table 4.

Discussion

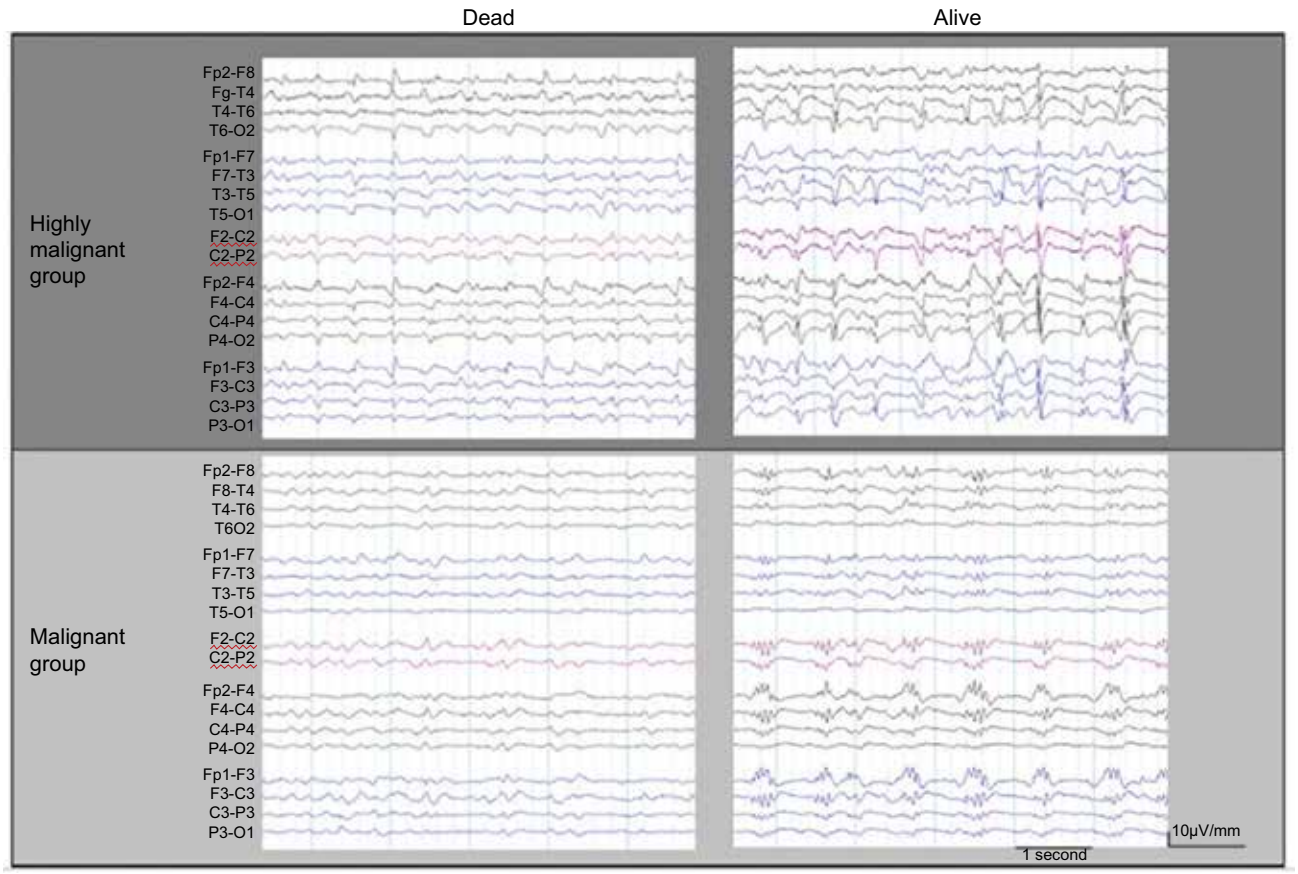
This study shows that patients with acute PHM mostly have poor outcomes, but that the condition is not universally fatal. Previous studies report mortality rates > 85%, whereas our 30-day mortality rate was 70%, increasing to 75% at 90 days. Furthermore, although EEG patterns were broadly consistent with prognosis, they did not reliably distinguish between good and bad outcomes, making decisions regarding life support difficult.[13] In addition, there is an ongoing potential for a self-fulfilling prognosis in this cohort; treatment withdrawal encompasses a number of factors, including comorbidities and aetiology of arrest, for example.

Studies assessing outcomes of patients with PHM have found that early generalised PHM has a poorer prognosis than later, focal myoclonus.[14,15] Our group comprised patients with both focal and generalised seizures, intermittent and sustained jerking. The median time to myoclonus was 23.5 hours (IQR, 9.6–35.8), but four patients who survived had onset of myoclonus 24–48 hours after arrest. The later onset of myoclonus may have accounted for our better observed outcomes. However, early use of sedation may have masked the exact seizure onset time, and, therefore, this observation must be interpreted with caution. Moreover, although

Table 4. Electroencephalogram features of surviving patients, according to American Clinical Neurophysiology Society (ACNS) criteria

	ACNS definition			
Patient no.	Discharge pattern	Background	Reactivity	Category
13	Lateralised/spike-wave	6 Hz posterior dominant rhythm	Reactive	Benign
14	None	7 Hz posterior dominant rhythm	Reactive	Benign
15	Generalised/spike-wave	Discontinuous	Non-reactive	Malignant
16	Generalised/periodic discharges	Discontinuous	Non-reactive	Malignant
20	Generalised/ periodic discharges	Suppression	Non-reactive	Highly malignant

Figure 3. Distribution of electroencephalogram patterns with respect to Glasgow Outcome Scale (1–5) at 30 days and 90 days



highly malignant EEG patterns have a high specificity for poor outcomes,[12] Elmer and colleagues[15] suggest that further classification into two distinct EEG phenotypes (ie, burst suppression and generalised periodic epileptiform discharges) is required for prognostication. Namely, patients with burst suppression on initial EEGs have a poor prognosis and, in this cohort, limitation of care rather than aggressive medical therapy should be considered. Division of the highly malignant EEG pattern into these two distinct entities may explain one of our patients in this group surviving at 90 days.

We found no early identifiable EEG marker to predict survival of patients with highly malignant or malignant patterns. Benign EEGs beyond 12 hours of seizure onset are associated with good outcomes;[16] however, we did not evaluate timing of the EEG with respect to seizure onset and rewarming in this study. This is important when considering the possible effect of temperature manipulation on the EEG rather than simply the timing alone.

Similarly, this study did not take into account subsequent EEGs in the days that followed. Although not specifically studied here, when prognosis is uncertain, we find that repeating EEGs after 24–48 hours can be helpful, with EEGs often diverging towards a more or less malignant pattern over time.

Additionally, clinical features such as low Glasgow Coma Score components, absent brainstem reflexes and other diagnostic tools (eg, magnetic resonance imaging and SSEP) can help inform neurological outcome. Along with the EEG, these components should form part of the evaluation of patients with PHM, and ultimately aid prognostication.

Conclusion

Our findings show that not all patients with PHM have dire outcomes. Future studies with larger numbers are required to better characterise EEG patterns of patients with PHM and of patients with cardiac arrest.

Competing interests

None declared.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Author details

Linda J Dalic[1,2]
Gerard Fennessy[3]
Mark Edmonds[1]
Patrick Carney[1,4]
Helen Opdam[5]
John Archer[1,2]

1 Department of Medicine, University of Melbourne, Melbourne, VIC, Australia.
2 Department of Neurology, Austin Health, Melbourne, VIC, Australia.
3 Department of Intensive Care, Western Health, Melbourne, VIC, Australia.
4 Department of Neurosciences, Eastern Health, Melbourne, VIC, Australia.
5 Department of Intensive Care, Austin Health, Melbourne, VIC, Australia.

***Correspondence*:** Linda.Dalic@austin.org.au

References

1 van Zijl JC, Beudel M, vd Hoeven HJ, et al. Electroencephalographic findings in posthypoxic myoclonus. *J Intensive Care Med* 2016; 31: 270-5.
2 Bouwes A, van Poppelen D, Koelman JH, et al. Acute posthypoxic myoclonus after cardiopulmonary resuscitation. *BMC Neurol* 2012; 12: 63.
3 Wijdicks EF, Hijdra A, Young GB, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; 67: 203-10.
4 Wijdicks EF, Young GB. Myoclonus status in comatose patients after cardiac arrest. *Lancet* 1994; 343: 1642-3.
5 Datta S, Hart GK, Opdam H, et al. Post-hypoxic myoclonic status: the prognosis is not always hopeless. *Crit Care Resusc* 2009; 11: 39-41.
6 Sandroni C, Cariou A, Cavallaro F, et al. Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. *Intensive Care Med* 2014; 40: 1816-31.
7 Friberg H, Cronberg T, Dunser MW, et al. Survey on current practices for neurological prognostication after cardiac arrest. *Resuscitation* 2015; 90: 158-62.
8 Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's standardized critical care EEG terminology: 2012 version. *J Clin Neurophysiol* 2013; 30: 1-27.
9 Westhall E, Rosén I, Rossetti AO, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. *Clin Neurophysiol* 2015; 126: 2397-404.
10 Westhall E, Rosén I, Rossetti AO, et al. Electroencephalography (EEG) for neurological prognostication after cardiac arrest and targeted temperature management; rationale and study design. *BMC Neurol* 2014; 14: 159.
11 Beuchat I, Solari D, Novy J, et al. Standardized EEG interpretation in patients after cardiac arrest: Correlation with other prognostic predictors. *Resuscitation* 2018; 126: 143-6.
12 Backman S, Cronberg T, Friberg H, et al. Highly malignant routine EEG predicts poor prognosis after cardiac arrest in the Target Temperature Management trial. *Resuscitation* 2018; 131: 24-8.
13 Wijdicks EF, Parisi JE, Sharbrough FW. Prognostic value of myoclonus status in comatose survivors of cardiac arrest. *Ann Neurol* 1994; 35: 239-43.
14 Gupta HV, Caviness JN. Post-hypoxic myoclonus: current concepts, neurophysiology, and treatment. *Tremor Other Hyperkinet Mov (N Y)* 2016; 6: 409.
15 Elmer J, Rittenberger JC, Faro J, et al. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann Neurol* 2016; 80: 175-84.
16 Hofmeijer J, Beernink TM, Bosch FH, et al. Early EEG contributes to multimodal outcome prediction of postanoxic coma. *Neurology* 2015; 85: 137-43.