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TELSTAR Investigators; Nutma, Sjoukje; Ruijter, Barry J.; Beishuizen, Albertus; Tromp, Selma C.; Scholten, Erik; Horn, Janneke; van den Bergh, Walter M.; van Kranen-Mastenbroek, Vivianne HJM; Thomeer, Elsbeth C.

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Clinical paper

Myoclonus in comatose patients with electrographic status epilepticus after cardiac arrest: Corresponding EEG patterns, effects of treatment and outcomes

Sjoukje Nutma[a,b,1,], Barry J Ruijter[b], Albertus Beishuizen[a], Selma C Tromp[c], Erik Scholten[d], Janneke Horn[e], Walter M van den Bergh[f], Vivianne HJM van Kranen-Mastenbroek[h], Elsbeth C Thomeer[g], Walid Moudrous[g], Marcel Aries[h], Michel JAM van Putten[a,b], Jeannette Hofmeijer[b,i], TELSTAR Investigators[2]*

Abstract

Objective: To clarify the significance of any form of myoclonus in comatose patients after cardiac arrest with rhythmic and periodic EEG patterns (RPPs) by analyzing associations between myoclonus and EEG pattern, response to anti-seizure medication and neurological outcome.

Design: Post hoc analysis of the prospective randomized Treatment of ELectroencephalographic STatus Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial.

Setting: Eleven ICUs in the Netherlands and Belgium.

Patients: One hundred and fifty-seven adult comatose post-cardiac arrest patients with RPPs on continuous EEG monitoring.

Interventions: Anti-seizure medication vs no anti-seizure medication in addition to standard care.

Measurements and Main Results: Of 157 patients, 98 (63%) had myoclonus at inclusion. Myoclonus was not associated with one specific RPP type. However, myoclonus was associated with a smaller probability of a continuous EEG background pattern (48% in patients with vs 75% without myoclonus, odds ratio (OR) 0.31; 95% confidence interval (CI) 0.16–0.64) and earlier onset of RPPs (24% vs 9% within 24 hours after cardiac arrest, OR 3.86;95% CI 1.64–9.11). Myoclonus was associated with poor outcome at three months, but not invariably so (poor neurological outcome in 96% vs 82%, p = 0.004). Anti-seizure medication did not improve outcome, regardless of myoclonus presence (6% good outcome in the intervention group vs 2% in the control group, OR 0.33; 95% CI 0.03–3.32).

Conclusions: Myoclonus in comatose patients after cardiac arrest with RPPs is associated with poor outcome and discontinuous or suppressed EEG. However, presence of myoclonus does not interact with the effects of anti-seizure medication and cannot predict a poor outcome without false positives.

Keywords: Hypoxic-ischemic encephalopathy, Post cardiac arrest syndrome, Myoclonus, Neuroprotection, Resuscitation, Anti-seizure medication, EEG

Introduction

Myoclonus in hypoxic-ischemic brain injury is characterized by involuntary, irregular, brief, muscular jerks in the face, trunk or extremities. It is observed in approximately 20% of comatose patients after cardiac arrest.[1] Generally, myoclonus is associated with severe hypoxic-ischemic encephalopathy and a poor outcome, especially when appearing within 24–48 hours after the cardiac arrest.[2] However, several authors have reported on myoclonus in patients that

* Corresponding author at: Medisch Spectrum Twente, Koningsplein 1, 7512 KZ, Enschede, the Netherlands.
E-mail address: s.nutma@mst.nl (S. Nutma).

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[2] The members of the TELSTAR Investigators are listed in Appendix 1 at the end of the article.

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ultimately had a good recovery, indicating that the presence of even early myoclonus may not be a definite sign of poor neurological outcome.[3]

Hypoxic-ischemic myoclonus has been linked to both cortical and subcortical brain damage. Myoclonus arising from cortical areas are found to be associated with specific EEG abnormalities, while myoclonus arising from deeper areas usually do not have a cortical correlate. Approximately 35–55% of patients with myoclonus after cardiac arrest show rhythmic and periodic EEG patterns (RPPs),[4–5] which may indicate a (partly) cortical origin. Several studies have tried to phenotype the EEG patterns of patients with posthypoxic myoclonus in relation to neurological outcome.[6–7] The observed patterns appeared heterogeneous with a slight predominance of burst suppression.[2] Clear epileptiform discharges have been reported in only a minority of patients but information on very early EEG was often lacking.[2] Low survival rates have been reported for myoclonus patients with a burst-suppression EEG.[6] However, characteristics of patients with early myoclonus and a possible good neurological outcome are largely unclear. The recent Treatment of ELectroencephalographic STatus Epilepticus After Cardiopulmonary Resuscitation (TELSTAR) trial showed no significant treatment effect of anti-seizure medication on outcome of patients with RPPs after cardiac arrest.[8] It is unknown whether the presence of myoclonus interacts with effects of this treatment. With the present post hoc analysis of the TELSTAR trial, we aimed to elucidate the significance of early myoclonus in comatose patients after cardiac arrest with RPPs by analyzing the associations between myoclonus and EEG patterns, response to anti-seizure medication and neurological outcomes. We hypothesized that myoclonus would not interact with effects of anti-seizure medication and was associated with a poor outcome.

Methods

Design

This is a post hoc analysis of the prospective randomized TELSTAR trial, conducted in eleven intensive care units in the Netherlands and Belgium. In short, in the TELSTAR trial, stepwise treatment to suppress all RPPs plus standard care was compared with standard care alone in comatose patients after cardiac arrest with RPPs on continuous EEG monitoring. Patients were included between May 2014 and January 2021.[8] The Medical Ethical Committee Twente and the institutional boards of all participating centres approved the trial protocol. Written informed consent was obtained from legal representatives of patients before randomization or, from January 10, 2017, in a deferred manner. Written informed consent for follow-up was obtained from surviving patients and/or legal representatives.

Study population

Consecutive, adult comatose patients after resuscitation for cardiac arrest of any cause, who had continuous EEG monitoring started less than 24 hours after return of spontaneous circulation, and RPPs on their EEG, were included. The classification of the RPP EEG patterns was in line with the international criteria that were used at the time the TELSTAR trial started.[9] The following were considered as RPPs: periodic discharges, rhythmic delta activity, and spike-and-wave or sharp-and-wave, at a rate of $\geq$0.5 Hz, irrespective of the spatiotemporal evolution, accompanying clinical phenomena, or effects of anti-seizure drugs. For continuous RPPs, the minimum duration requirement was thirty minutes. Intermittent RPPs of five minutes and longer, recurring at least twice, with intervals shorter than sixty minutes could also be included. For this post hoc analysis the population was divided in patients with and without myoclonus. Myoclonus was diagnosed at randomization by the treating intensive care physicians when jerks were present in the face/eyelids or trunk/limbs.

Patient characteristics

The following prospectively collected patient characteristics were used for this analysis: age, sex, out-of or in-hospital cardiac arrest (OHCA and IHCA respectively), aetiology of cardiac arrest, initial cardiac rhythm, witnessed arrest or not, delay of cardiopulmonary resuscitation (CPR), duration of CPR, history of epilepsy, onset of myoclonus, myoclonus characteristics, treatment details, EEG patterns, treatment allocation, presence of myoclonus, and location of myoclonus (face/eyelids and/or trunk/limbs). Presence and location of early myoclonus, regardless of their generalized or (multi)focal nature, were prospectively collected by the treating physicians at the time of randomization.

Treatment

Treatment in the intervention group consisted of a stepwise treatment strategy with the intention of completely suppressing RPPs during at least 48 hours in addition to standard care. Step 1 was a first anti-seizure drug plus a first sedative agent, step 2 was a second anti-seizure drug plus a second sedative agent, and step 3 was a barbiturate. Because no anti-seizure or sedative medication has been proven superior to another in improving outcomes after status epilepticus after cardiac arrest, treating physicians were allowed to follow local protocols, provided that these were in line with the overall stepwise approach. If RPPs returned after 48 hours, with the use of at least two anti-seizure medications, the decision to prolong treatment was left to the discretion of the treating physicians. Treatment was started within three hours after detection of RPPs. The control group had standard care, which was left to the discretion of the treating physicians, but generally followed European guidelines and included targeted temperature management.[10] In the control group, physicians were allowed to prescribe sedative medication, if needed for ventilation or to suppress clinically manifest myoclonus, irrespective of the EEG. Use of anti-seizure drugs was discouraged. Further treatment details and over all effects of treatment have been published previously.[8]

Withdrawal of life sustaining treatment

In both groups, decisions regarding limitation or withdrawal of treatment were based on Dutch guidelines, that were based on the European guidelines at the time we started the trial.[11] Briefly, withdrawal of treatment could be considered during normothermia and off-sedation. Criteria for withdrawal were bilateral absence of pupillary light reflexes and bilateral absence of somatosensory evoked potentials (SSEPs). EEG patterns within 72 h and clinical myoclonus were not taken into account.

Outcome

The primary outcome was neurologic outcome at three months according to the Cerebral Performance Categories (CPC). Outcome was dichotomized as ‘good’ (CPC 1–2) or ‘poor’ (CPC 3–5).[12] These scores were obtained by a standardized telephone interview con-

ducted by an investigator who was masked to treatment allocation and EEG pattern.

EEG registration and analysis

As part of standard care in the participating ICUs, continuous EEG monitoring was started within 24 hours after cardiac arrest and lasted at least three days or until discharge from the ICU or until RPPs were extinguished. The standard international 10–20 system of electrode placement was used in nine hospitals, a limited montage with ten electrodes in two hospitals. EEG recordings were checked every-three hours by a neurologist, clinical neurophysiologist, or clinical neurophysiology technician. The diagnosis of RPP EEG patterns was made by the attending neurologist or clinical neurophysiologist.

All EEGs were re-evaluated by two of four readers (BR, HK, MvP, JH). They classified the EEG pattern at inclusion as electrographic seizures (discharges at $\geq$ 2.5 Hz), evolving patterns (0.5 to 2.5 Hz), generalized periodic discharges (0.5 to 2.5 Hz), or other periodic patterns (0.5 to 2.5 Hz), with continuous, discontinuous, or suppressed background activity. They classified the treatment effect on the index EEG activity as complete (>90% of the recording), partial (50–90%), or no suppression of RPPs (<50%).

Statistical analysis

Patient characteristics are presented in a descriptive way. To study between-group differences, univariate analyses via T-tests and the Wilcoxon Rank-Sum test were performed. To identify the crude relationship between myoclonus and CPC-score, treatment effect, and EEG pattern (EEG pattern at inclusion, continuity of the EEG background activity, and onset time of RPPs), the Pearson $\chi 2$ or Fisher exact test was used and accompanied odds ratios were presented. P values below 0.05 were considered statistically significant. In addition, univariate logistic regression analysis was performed to calculate the treatment effect within the myoclonus, non-myoclonus and the whole group. The association of neurological outcome with the specific type of RPPs, background pattern, and onset time of RPPs in patients with and without myoclonus was only displayed in a descriptive and graphic way but not included in multivariate analyses. SPSS 24 (IBM Corp., Armonk, NY) was used for analyses.

Results

Patient characteristics

In the TELSTAR trial, 172 patients with RPPs were included and followed up. Of these, 157 had available data on myoclonus. Of these 157 patients, 98 (63%) had myoclonus upon randomization, which ranged from 8.5 to 117 hours (median of 35 hours and 10 minutes) after cardiac arrest. Nineteen patients (20%) had myoclonus in the trunk/limbs, 29 (31%) in the face/eyelids, and 46 (49%) in both face/eyelids and trunk/limbs. Table 1 shows the characteristics of patients with and without myoclonus. With myoclonus, cardiac arrest was less often witnessed (60% vs 78%) and associated with a longer delay to CPR (5 minutes vs 3 minutes).

EEG characteristics

EEG characteristics of patients with and without myoclonus are presented in Fig. 1. Myoclonus was associated with a discontinuous or suppressed EEG background pattern (52% in patients with vs 25% in patients without myoclonus; odds ratio (OR) 3.23, 95% confidence interval (CI) 1.56–6.25). In patients with myoclonus compared to those without, the onset of RPPs occurred more often in the first 24 hours after cardiac arrest (24% vs 9%, OR 3.86, 95% CI 1.64–9.11). However, there was no statistically significant association between myoclonus and a specific RPP category and no specific EEG feature was invariably associated with presence or absence of myoclonus.

Outcome

The proportion of patients with good neurological outcome at three months after cardiac arrest was lower in patients with than without myoclonus (4.1% vs 18.6%, OR 0.22 95%CI 0.07–0.66). The distribution of survivors over the various EEG categories was approximately equal for patients with and without myoclonus (Fig. 2); no statistical testing was performed because of the limited group size per category. When RPPs occurred on a discontinuous or suppressed EEG background, no patient survived, regardless of the presence of myoclonus. One patient with myoclonus and RPPs in the first 24 hours after cardiac arrest survived; the EEG showed a continuous background pattern at the time of myoclonus detection, with rhythmic activity of varying frequency (mostly rhythmic delta activity), without signs of GPDs.

Anti-seizure medication effect

There was no statistically significant difference in the proportion of patients with a good outcome at three months between the intervention and control group, neither for the whole group, nor for subgroups with or without myoclonus. Also, there was no statistically significant interaction between presence of myoclonus and treatment effect (Fig. 3).

Discussion

In this post hoc analysis of the prospective randomized TELSTAR trial, myoclonus was strongly associated with poor neurological outcome in comatose cardiac arrest patients with RPPs, but not invariably so. Presence of myoclonus did not interact with effects of treatment with anti-seizure medication. While we previously showed that effects of anti-seizure medication are likely related to the EEG pattern,[8] we now show that these effects are not related to the presence of myoclonus.

In patients with myoclonus, RPPs occurred more often in the first 24 hours after cardiac arrest and less often on continuous EEG background activity, suggesting more severe encephalopathy. However, myoclonus was not associated with one specific RPP pattern. Regarding the lack of association between myoclonus and EEG findings we cannot exclude effects of sedative medication. However, since myoclonus was diagnosed at the time of randomization, effects of study medication are unlikely.

Although myoclonus was associated with a poor neurological outcome in our series, one patient with myoclonus with RPPs within the first 24 hours had a good outcome. This particular patient was allocated to the intervention group and showed a continuous EEG when the myoclonus was reported. This is in line with previous reports on outcome prediction of comatose cardiac arrest patients, that report strong associations between myoclonus and a poor outcome, but not invariably so.[6,13–15] Apparently, myoclonus is a clinical manifestation of severe hypoxic brain damage, but the underlying EEG pattern (together with the other markers of neurological outcome) is needed for reliable prediction of poor outcome. Especially patients

Table 1 – Patient characteristics.

Characteristic	Myoclonus (n = 98)	No myoclonus (n = 59)
Intervention group no./total no. (%)	50/98 (51)	32/59 (54)
Demographic characteristics		
Median age (IQR) - yr	66 (59–73)	65 (54–74)
Male sex - no./total no. (%)	71/98 (72)	39/59 (66)
Characteristics of cardiac arrest		
Location of cardiac arrest - no./total no. (%)		
Out of hospital	94/98 (96)	54/59 (92)
In hospital	4/98 (4)	5/59 (8)
Presumed cause of cardiac arrest - no./total no. (%)		
Cardiac	78/98 (80)	48/59 (81)
Other	12/98 (12)	6/59 (10)
Unknown	8/98 (8)	5/59 (9)
Bystander-witnessed cardiac arrest - no./total no. (%)	59/98 (60)	46/59 (78)
First monitored rhythm - no./total no. (%)		
Shockable	57/98 (58)	43/59 (73)
Nonshockable	41/98 (42)	16/59 (27)
Median time from cardiac arrest (IQR) - min		
To start of basic life support	5 (3–10)	3 (0–5)
To return of spontaneous circulation	18 (10–30)	16 (12–28)
History of epilepsy	3 (3%)	0 (0%)
Good outcome (CPC 1–2) at 3 months	4/98 (4.1%)	11/59 (18.6%)

IQR = interquartile range; min = minutes; no. = number; yr = years.

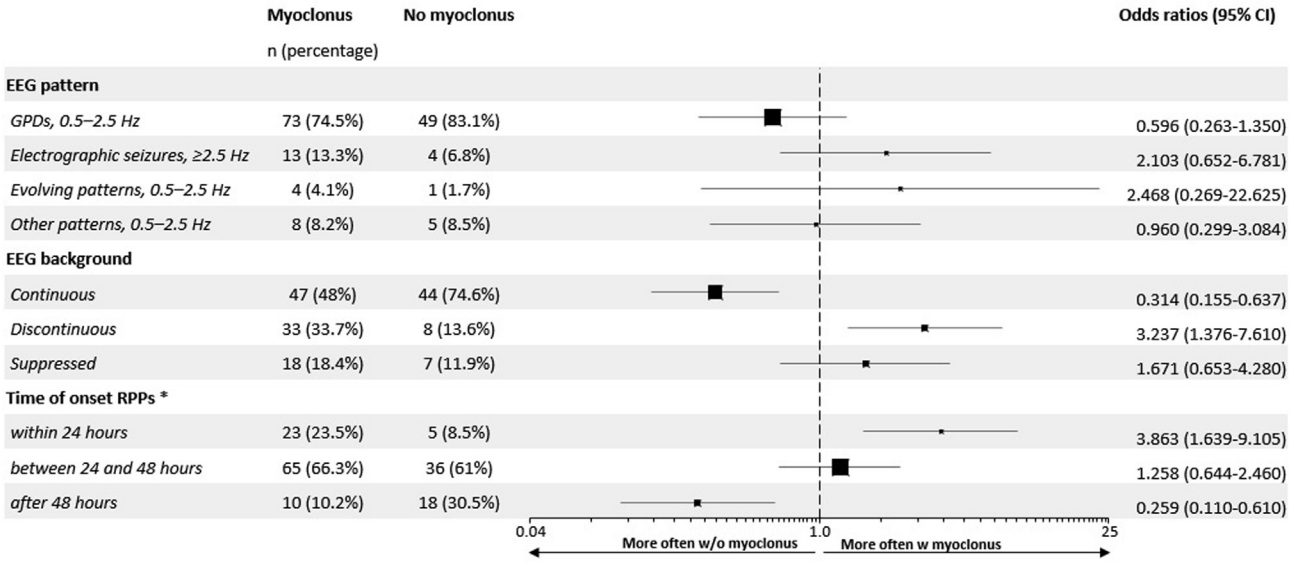

Fig. 1 – EEG characteristics of patients with and without myoclonus. Dotted line indicates an odds ratio of 1. Closed squares indicate the OR and whiskers represent the 95% confidence intervals. GPDs = generalized periodic discharges. *Time of onset of RRPs is expressed in hours after resuscitation.

with myoclonus and a continuous EEG background pattern may survive.[6]

Several underlying mechanisms have been proposed for myoclonus after cardiac arrest. The tentative origin could be cortical, subcortical, or mixed.[16] In most patients, myoclonus probably reflects a disturbed excitation-inhibition balance resulting from selective synaptic damage.[17] The only test to indisputably prove a cortical origin is a combined recording of EEG and EMG, since this can prove the time relationship between EEG activity and myoclonus, but studies on those measurements in this patient group are lacking.

Strengths of this analysis include the prospective data collection, continuous EEG, and blinded outcome measurement. Limitations include the following. First, we studied only patients with RPPs. Our findings can obviously not be extrapolated to patients with myoclonus without RPPs, including those with burst suppression with identical bursts. Second, data on myoclonus were collected by treating physicians. We cannot exclude that (subtle) myoclonus was not always detected. Third, although we presume ongoing myoclonus in most patients, clinically this is not always the case, we did not discriminate between sporadic myoclonic jerks

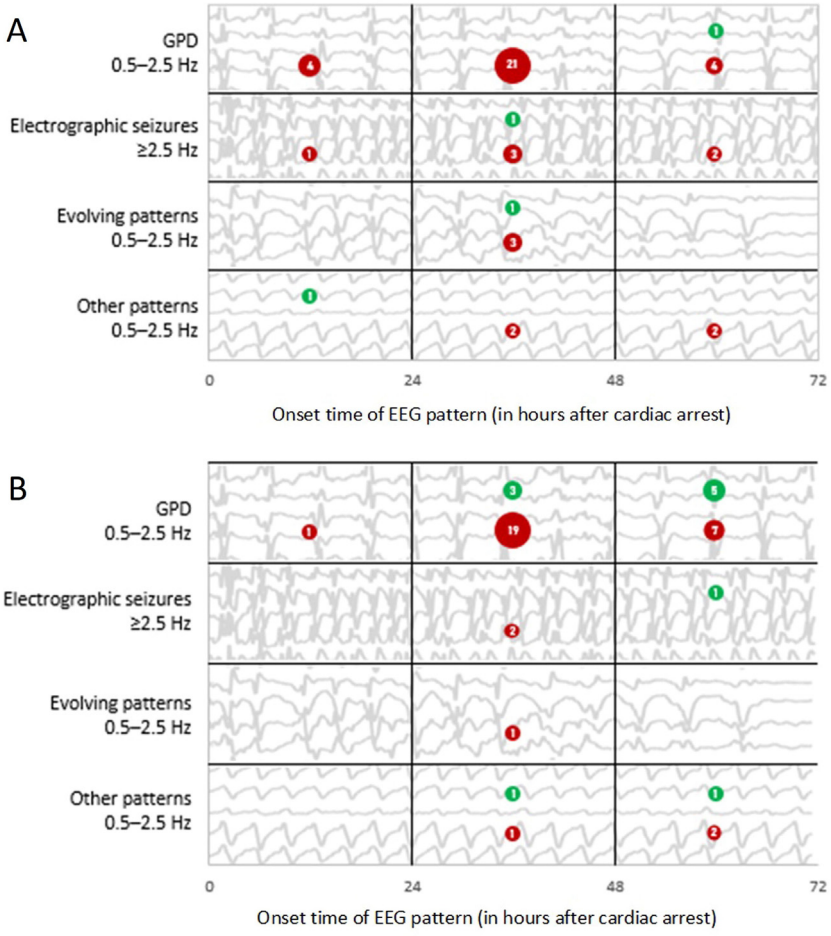

Fig. 2 – Outcome of patients with (A) and without (B) myoclonus in relation to EEG pattern, given a continuous background. Green bubbles indicate patients with good outcome, red bubbles patients with poor outcome. The size of the bubbles scales with the number of patients, as shown in white numbers. Since no patient with a discontinuous or suppressed EEG background pattern survived, only patients with a continuous EEG background pattern were taken into account in this figure. GPD: generalized periodic discharges.

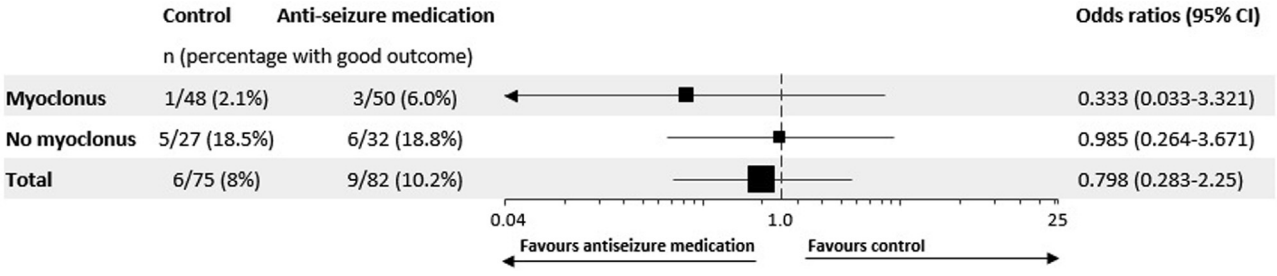

Fig. 3 – Good outcome with and without anti-seizure medication in patients with myoclonus vs no myoclonus. Good outcome indicates CPC 1 or 2 at three months after cardiac arrest. Dotted line indicates an odds ratio of 1. Closed squares indicate the OR and whiskers represent the 95% confidence intervals. 'Total' indicates all patients, regardless of presence of myoclonus.

or a status myoclonus. Also, we did not collect data on the exact time when myoclonus was first observed. However, we collected data on myoclonus at the time of randomization, which ranged from 8.5 to 117 hours after cardiac arrest,[8] which is relatively early and argues against late, more benign Lance-Adams, myoclonus. Fourth, although we show that there is no treatment effect of anti-seizure medication in myoclonus patients, we do acknowledge that both groups had few surviving patients and a possible treatment effect in a larger population is not ruled out. Finally, as in practically all studies in this patient category, we cannot exclude self-fulfilling prophecies resulting from decisions on withdrawal of life sustaining treatment.

Conclusion

In comatose cardiac arrest patients with RPPs, myoclonus is associated with poor outcome and with discontinuous or suppressed EEG. However, myoclonus does not preclude a good outcome and is not related to a specific RPP type. Presence of myoclonus does not alter effects of treatment with anti-seizure medication.

CRediT authorship contribution statement

Sjoukje Nutma: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Barry J Ruijter:** Data curation, Writing – review & editing. **Albertus Beishuizen:** Writing – review & editing. **Selma C Tromp:** Writing – review & editing. **Erik Scholten:** Writing – review & editing. **Janneke Horn:** Writing – review & editing. **Walter M van den Bergh:** Writing – review & editing. **Vivianne HJM van Kranen-Mastenbroek:** Writing – review & editing. **Elsbeth C Thomeer:** Writing – review & editing. **Walid Moudrous:** Writing – review & editing. **Marcel Aries:** Writing – review & editing. **Michel JAM van Putten:** Writing – review & editing. **Jeannette Hofmeijer:** Data curation, Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision.

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Appendix 1

TELSTAR Investigators

P. Noordzij, MD PhD[1], H. Moeniralam, MD PhD[1], A. Seeber, MD PhD[2], M. Datema, MD PhD[2], A.F. van Rootselaar, MD PhD[3], M.M. Admiraal MD PhD[4], D.C. Velseboer, MD PhD[4], J.H. Koelman MD PhD[3], J.W.J. Elting, MD PhD[5], G. Drost, MD PhD[5], N. Foudraine MD PhD[6], F. Kornips MD[7], R. Rouhl, MD PhD[8], D.M.W. Hilkman, MD PhD[8], W. van Mook, MD PhD[9], M. Vlooswijk, MD PhD[8], F. Nijhuis, MD PhD[10], S. Booij, MD PhD[10], H. Bernsen, MD PhD[10], A. Hoedemaekers, MD PhD[11], J. Doorduin, MD PhD[11], F. Taccone, MD PhD[12], N. Gaspard, MD PhD[13], S.C. Tromp, MD PhD[14]

1. Department of Critical Care, Antonius hospital, Nieuwegein, The Netherlands
2. Department of Neurology, Antonius hospital, Nieuwegein, The Netherlands
3. Department of Neurology, Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands
4. Department of Critical Care, Amsterdam University Medical Center, location AMC, Amsterdam, The Netherlands
5. Department of Neurology, University Medical Center Groningen, Groningen, the Netherlands
6. Department of Critical Care, VieCuri Medical Center, Venlo, the Netherlands
7. Department of Neurology, VieCuri Medical Center, Venlo, the Netherlands
8. Department of Neurology, Maastricht University Medical Center, Maastricht, The Netherlands
9. Department of Critical Care, Maastricht University Medical Center, Maastricht, The Netherlands
10. Department of Neurology, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands
11. Department of Neurology, Radboud University Medical Center, Nijmegen, The Netherlands
12. Department of Critical Care, Université Libre de Bruxelles, Brussels, Belgium
13. Department of Neurology, Université Libre de Bruxelles, Brussels, Belgium
14. Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

Author details

TELSTAR Investigators[2] *[a]Departments of Neurology and Clinical Neurophysiology, Medical Spectrum Twente, Enschede, the Netherlands [b]Department of Clinical Neurophysiology, Technical Medical Center, University of Twente, Enschede, the Netherlands [c]Departments of Neurology and Clinical Neurophysiology, Leiden University Medical Center, Leiden, the Netherlands [d]Department of Critical Care, St Antonius Hospital, Nieuwegein, the Netherlands [e]Department of Critical Care, Amsterdam University Medical Center, Location AMC, Amsterdam, the Netherlands [f]Department of Critical Care, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands [h]Department of Critical Care, Maastricht University Medical Center, Maastricht, the Netherlands [g]Department of Neurology and Clinical Neurophysiology, Maasstad Hospital, Rotterdam, the Netherlands [i]Department of Neurology, Rijnstate Hospital, Arnhem, the Netherlands*

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