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Short paper

Cognition, emotional state, and quality of life of survivors after cardiac arrest with rhythmic and periodic EEG patterns

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Abstract

Aim: Rhythmic and periodic patterns (RPPs) on the electroencephalogram (EEG) in comatose patients after cardiac arrest have been associated with high case fatality rates. A good neurological outcome according to the Cerebral Performance Categories (CPC) has been reported in up to 10% of cases. Data on cognitive, emotional, and quality of life outcomes are lacking. We aimed to provide insight into these outcomes at one-year follow-up.

Methods: We assessed outcome of surviving comatose patients after cardiac arrest with RPPs included in the 'treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation' (TELSTAR) trial at one-year follow-up, including the CPC for functional neurological outcome, a cognitive assessment, the hospital anxiety and depression scale (HADS) for emotional outcomes, and the 36-item short-form health survey (SF-36) for quality of life. Cognitive impairment was defined as a score of more than 1.5 SD below the mean on $\geq$ 2 (sub)tests within a cognitive domain.

Results: Fourteen patients were included (median age 58 years, 21% female), of whom 13 had a cognitive impairment. Eleven of 14 were impaired in memory, 9/14 in executive functioning, and 7/14 in attention. The median scores on the HADS and SF-36 were all worse than expected. Based on the CPC alone, 8/14 had a good outcome (CPC 1–2).

Conclusion: Nearly all cardiac arrest survivors with RPPs during the comatose state have cognitive impairments at one-year follow-up. The incidence of anxiety and depression symptoms seem relatively high and quality of life relatively poor, despite 'good' outcomes according to the CPC.

Keywords: Cardiac arrest, Status epilepticus, Cognition, RPPs

Introduction

After cardiac arrest followed by successful resuscitation, 64–80% of patients arrive at the hospital in a comatose state because of diffuse postanoxic encephalopathy.[1,2] During this comatose state, brain activity can be measured with an electroencephalogram (EEG). Different EEG patterns reflect divergent extents of ischemic brain injury, and some are reliable predictors of functional outcome.[3–5]

Rhythmic and periodic patterns (RPPs), often referred to as electrographic seizures or status epilepticus, are reported in 10–33% of patients, with case fatality rates of 80–100%, despite treatment with anti-epileptic drugs.[6–8] Based on the few existing reports on long-term outcomes of survivors, 6–10% may have a good outcome according to the Cerebral Performance Categories (CPC 1 or 2),[8–10] but data on cognitive, emotional, and quality of life outcomes are lacking. Studies in cardiac arrest survivors using more sensitive instruments than the CPC found disturbances in the domains of

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cognition, emotion, and fatigue in approximately half of unselected survivors.[11,12] The incidence and severity of these problems may be higher in the subgroup of survivors with RPPs, since these reflect a more severe postanoxic encephalopathy, but data are so far lacking.[10]

Here, we aim to provide insight into the neurological, cognitive, emotional, and quality of life outcomes at one year after cardiac arrest in patients with RPPs in the comatose stage. Knowledge about these patients' long-term outcomes could guide treatment and appropriate care decisions.

Methods

Study design

A predefined analysis of prospectively collected one-year outcomes of patients included in the 'treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation' (TELSTAR) trial was performed.[8] TELSTAR was a multicenter randomized trial in comatose cardiac arrest patients with RPPs on continuous EEG lasting > 30 minutes. The intervention contrast was a step-wise strategy suppressing RPPs with anti-seizure medication for $\geq$ 48 h in addition to standard care versus standard care alone. The primary outcome was neurological recovery according to the CPC at 3 months. Secondary outcomes collected in 5/11 participating centers included cognitive outcome assessed with a cognitive assessment, emotional outcomes with the HADS, and quality of life with the SF-36 at twelve months. The TELSTAR trial was approved by the Medical Research Ethics Committee Twente in the Netherlands (NL46296.044.13). Methods and primary outcomes have been published previously.[13]

Participants

The trial population consisted of comatose adult patients after cardiac arrest and successful cardiopulmonary resuscitation, with RPPs on continuous EEG. RPPs comprised periodic discharges, rhythmic delta activity, and spike-and-wave or sharp-and-wave, at a rate of $\geq$ 0.5 Hz, during $\geq$ thirty minutes. One-year survivors that received a one-year follow-up cognitive assessment were included in the current analyses.

Procedure

Written informed consent was obtained from legal representatives. The patients or legal representatives were asked for separate informed consent for the one-year follow-up. At the one-year follow-up, information on cognitive functioning, depression and anxiety, and quality of life were obtained at the local hospital or at the patients' residence.

Measures

Cognitive assessment

Depending on the mental capacity of the patient, one of three predefined cognitive test batteries was administered (Supplementary materials, Table 1). The full test battery took 2.5 hours. We analyzed (sub)tests for three cognitive domains:[14]

- memory: 15-word learning test; complex figure of Rey; location learning test; visual association test.
- executive functioning: Digit span backward and sorting; trail making test-B; frontal assessment battery; semantic word fluency; letter fluency; cognitive screening test.
- attention: Stroop; trail making test-A; symbol substitution task.

Anxiety and depression

The Hospital Anxiety and Depression Scale (HADS) was used to assess feelings of depression and anxiety.[15] A higher score represents more complaints: 0–7 indicates no anxiety or depression, 8–10 indicates a possible anxiety disorder or depression, and a score of 11–21 indicates a probable anxiety disorder or depression.[16].

Quality of life

Quality of life was assessed by the 36-item short-form health survey (SF-36), containing 36 questions assessing eight subdomains of quality of life.[17] Items can be scored from 0-100 with higher scores indicating a better health state.

Neurological outcome

Neurological outcome was assessed with the CPC, a five-point scale that ranges from good cerebral performance (1) to death (5), at 12-months. The scores are often dichotomized in "good" (CPC 1–2) and "poor" (CPC 3–5) outcome.[18]

Statistical analysis

Data analyses were performed using SPSS Statistics 25.0.[19] Descriptive statistics were used to describe patient, cardiac arrest, and RPP characteristics. A patient was considered impaired in a cognitive domain if he/she had a score more than 1.5 SD below the mean of the norm group (general population, controlled for sex, age, and education) on $\geq$ 2 (sub)tests within the domain of memory, executive functioning, or attention.[20,21,22] The scores on the SF-36 and the HADS were compared to norm scores of the general population[23,24], scores of unselected cardiac arrest survivors one-year post-arrest from the Activity and Life After Survival of a Cardiac Arrest trial (ALASCA)[25], and other patient groups.[26,27] Medians and interquartile ranges (IQRs) were used because of the small sample size and non-normally distributed data. To test for potential selection bias, baseline characteristics of survivors included in this analysis were compared with those not included, using Mann-Whitney and Chi-squared tests, where appropriate. P-values < 0.05 were considered statistically significant.

Results

Patient characteristics

Fourteen of the 31 patients who survived to one-year from the total 172 patients in the TELSTAR trial had a cognitive assessment and were included in this analysis. Seventeen of the survivors were not included in this analysis, because they were included in the participating centers that did not collect data on cognitive or emotional outcome at one year (n = 5) or refused to take part in the follow-up (n = 12). Baseline characteristics of the sample (n = 14) compared to the other survivors (n = 17) did not differ in terms of age (median = 58 vs 59 years) or sex (21% vs 32% female). The proportion of patients with a favorable outcome (CPC 1 or 2) was slightly (but not significantly) higher in the current sample (57% (8/14) vs. 41% (7/17)). All but one patient had continuous EEG background activity

Table 1 – Patient characteristics.

Characteristic	Median (IQR) or n/N	Range
Total patients	14	
Age, years	58 (16)	41–75
Female sex	3/14	
Living at home	11/14	
CPC good outcome (score 1-2)	8/14	
CPR duration, min[a]	20 (10)	6–30
Witnessed cardiac arrest	9/14	
Days on ICU	15 (10)	3–58
Control group	9/14	
Electrographic characteristics		
Type of RPP		
- Periodic discharges	10/14	
- Evolving seizures	2/14	
- Rhythmic delta	2/14	
Background activity		
- Continuous	13/14	
- Discontinuous	1/14	
Duration of RPPs, hours	42 (46)	2–253

CPC = Cerebral Performance Categories; CPR = Cardiopulmonary resuscitation; ICU = Intensive care unit; RPP = Rhythmic and Periodic Pattern; IQR = Interquartile range.

[a] Data were missing for 5 subjects.

during RPPs (13/14). The most common RPP type was periodic discharges (10/14). More information about the sample and EEG characteristics can be found in Table 1.

Cognitive functioning as measured by cognitive assessment

Results on cognitive functioning are presented in Fig. 1. Eleven patients completed the full-length test battery, the remaining three a shortened version, because of incapacity to perform all tests. Eleven out of fourteen patients had memory impairment, 7/14 attention impairment, and 9/14 executive functioning impairment. Thirteen out of fourteen patients had cognitive impairment in at least one cognitive domain. More information about the scores on the cognitive tests can be found in the Supplementary materials (Figs. 1-3).

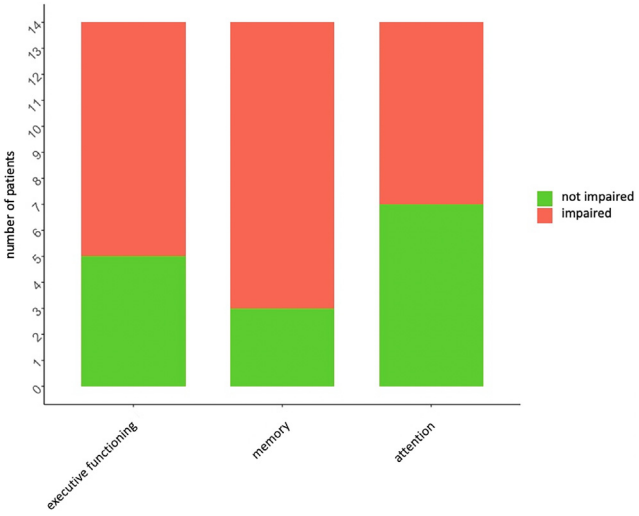

Fig. 1 – Stacked bar chart of the number of participants that were impaired on the three cognitive domains.

Anxiety and depression (HADS) and quality of life (SF-36)

According to the HADS, that was completed by eight participants, two had a possible depression, one a possible anxiety disorder ($8 \leq$ score ≤ 10), one a probable depression, and one a probable anxiety disorder (score ≥ 11). The median score of the five patients who completed the SF-36 was 53 on a scale ranging from 0 to 100 (scores = 38, 43, 53, 57, 84). In Table 2, the medians and IQRs of scores on the SF-36 subscales and the HADS are compared with those of the general population (age 55–64 years), an unselected cardiac arrest population at one-year follow-up, ICU survivors after SARS-CoV-2 pneumonia at one-year follow-up, and ST-elevation myocardial infarction (STEMI) patients at 18-month follow-up.[23–27] The patients in the current sample scored lower on most of the SF-36 subscales.

Discussion

This is the first study to describe the cognitive, emotional, and quality of life outcomes of one-year post cardiac arrest patients with RPPs during the comatose state. We found that 13/14 patients (93%) had a cognitive impairment.[20,21]

This subgroup with RPPs during coma seems more impaired than unselected one-year survivors of cardiac arrest. In the ALASCA trial, 13–43% of 141 patients remained cognitively impaired one-year post-arrest, in the current sample this is 93%.[21] This may reflect relatively severe postanoxic encephalopathy and a higher risk of poorer cognitive outcome in patients with RPPs during coma, although the sample was too small to draw strong conclusions.

Half of the assessed patients reported a concerning level of symptoms of depression or anxiety. This seems to be a higher proportion than in the general population, unselected one-year cardiac arrest survivors, and STEMI patients.[24,25] The quality of life also seems lower compared to the general population and other patient groups.[23,25]

Table 2 – Comparison of scores on SF-36 and HADS, expressed as median (Q1 - Q3), with the general population, unselected cardiac arrest patients, STEMI patients, and SARS-CoV-2 pneumonia survivors.

	Patients included in analysis[a]	Norm data general population[b]	Cardiac arrest patients 1-yr[c]	STEMI patients 18-mth[d]	ICU survivors after SARS-CoV-2 pneumonia 1-yr[e]
Physical health					
Physical functioning	50 (45–55)	85 (60–95)	80 (55–92.5)	-	75 (65–90)
Pain	78 (55–88)	72 (51–84)	87.8 (67.3–100)	-	62 (41–84)
General health	50 (50–70)	67 (50–82)	60 (45–80)	-	67 (52–82)
Physical role limitation	0 (0–0)	100 (50–100)	75 (0–100)	-	100 (25–100)
Mental health					
Emotional role limitation	67 (0–100)	100 (66.7–100)	100 (33.3–100)	-	100 (33.3–100)
Social functioning	63 (63–75)	100 (62.5–100)	87.5 (62.5–100)	-	75 (50–100)
Vitality	55 (45–65)	65 (45–80)	65 (45–80)	-	60 (45–75)
Mental health	76 (64–76)	80 (64–92)	80 (64–88)	-	76 (60–88)
HADS anxiety	6 (2.5–7.3)[f]	4 (2–7)	3 (1–6)	3 (1–7)	-
HADS depression	7 (3–8.5)[f]	3 (1–5)	2 (1–6)	2 (1–5)	-

STEMI = ST Elevation Myocardial Infarction, HADS = Hospital Anxiety Depression Scale (a higher score indicates more anxiety/depression complaints), SF-36 = 36-item short-form health survey (a higher score indicates a better health state).

[a] Data were available for 5 patients.

[b] Norm data of the general population (N = 269) regarding the SF-36 were derived from the "SF-36 Health Survey Manual and Interpretation Guide" (age 55 – 64).[23]; Norm data of the HADS are based on a general population (N = 363), men aged 55–59 years from Northwest England.[24]

[c] Norm data regarding the SF-36 and the HADS were derived from the ALASCA trial (N = 110) one year after cardiac arrest.[21]

[d] Data from the Targeted Temperature Management at 33 °C versus 36 °C (TTM) trial [26] (N = 119).

[e] Data of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia [27] (N = 65).

[f] Data were available for 8 patients.

The poor cognitive outcomes are somewhat surprising, since 8/14 patients had a "good outcome" according to the CPC. This confirms previous findings that using more sensitive instruments to test cognition and wellbeing is warranted.[11,12]

Strengths of this study include the prospective design. The most important limitation is the small sample size. There was a high case fatality rate of comatose patients with RPPs in TELSTAR. Due to the small sample size, it was not possible to perform statistical analyses, nor to draw strong conclusions from the data. Another limitation is the use of three different cognitive test batteries with different difficulties and workload, necessary for the wide range of mental capacity levels within the study population. The consequent reduction in standardization complicated our analysis. Three out of 14 patients were on anti-seizure medication at one year and had clinically manifest seizures. Although we believe that cognitive dysfunction was primarily caused by postanoxic encephalopathy in our cohort, we cannot exclude an association between anti-seizure medication and our cognitive outcomes.

Conclusions

To conclude, this small-scale analysis provides insights into one-year recovery after cardiac arrest of comatose patients with RPPs. All but one had cognitive impairment at one-year follow-up, often despite a 'good' outcome according to the CPC. The quality-of-life and depression and anxiety scores were worse than those of unselected cardiac arrest survivors, other patient populations, and the general population.

CRediT authorship contribution statement

Pauline C.W. van Gils: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Barry J. Ruijter:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **Rubia J.K. Bloo:** Investigation, Methodology, Writing – review & editing. **Michel J.A.M. van Putten:** Writing – review & editing. **Norbert A. Foudraine:** Investigation, Writing – review & editing. **Moniek S.E. van Hout:** Investigation, Writing – review & editing. **Selma C. Tromp:** Investigation, Writing – review & editing. **Walther N.K.A. van Mook:** Investigation, Writing – review & editing. **Rob P.W. Rouhl:** Investigation, Writing – review & editing. **Caroline M. van Heugten:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Jeannette Hofmeijer:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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REFERENCES

1. Gorjup V et al. Acute ST-elevation myocardial infarction after successful cardiopulmonary resuscitation. Resuscitation 2007;72 (3):379–85.
2. Thomassen A, Wernberg M. Prevalence and prognostic significance of coma after cardiac arrest outside intensive care and coronary units. Acta Anaesthesiologica Scandinavica 1979;23(2):143–8.
3. Ruijter BJ et al. Early electroencephalography for outcome prediction of postanoxic coma: a prospective cohort study. Ann Neurol 2019;86 (2):203–14.
4. Bongiovanni F et al. Standardized EEG analysis to reduce the uncertainty of outcome prognostication after cardiac arrest. Intensive Care Med 2020;46(5):963–72.
5. Westhall E et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016;86(16):1482–90.
6. Beretta S et al. Neurologic outcome of postanoxic refractory status epilepticus after aggressive treatment. Neurology 2018;91(23): e2153–62.
7. Rossetti AO et al. Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 2007;69(3):255–60.
8. Ruijter BJ et al. Treating rhythmic and periodic EEG patterns in comatose survivors of cardiac arrest. New Engl J Med 2022;386 (8):724–34.
9. Legriel S et al. Prognostic value of electrographic postanoxic status epilepticus in comatose cardiac-arrest survivors in the therapeutic hypothermia era. Resuscitation 2013;84(3):343–50.
10. Hofmeijer J, van Putten MJAM. EEG in postanoxic coma: prognostic and diagnostic value. Clin Neurophysiol 2016;127(4):2047–55.
11. Moulaert VR et al. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation 2009;80 (3):297–305.
12. Schaaf KPW et al. Anxiety, depression, and PTSD following cardiac arrest: a systematic review of the literature. Resuscitation 2013;84 (7):873–7.
13. Ruijter BJ et al. Treatment of electroencephalographic status epilepticus after cardiopulmonary resuscitation (TELSTAR): study protocol for a randomized controlled trial. Trials 2014;15(1):1–8.
14. Lezak MD et al. Neuropsychological assessment. USA: Oxford University Press; 2004.
15. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta psychiatrica scandinavica 1983;67(6):361–70.
16. Bjelland I et al. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. J Psychosomatic Res 2002;52 (2):69–77.
17. McHorney CA, Ware Jr JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 1993:247–63.
18. Grossestreuer AV, Abella BS, Sheak KR, Cinousis MJ, Perman SM, Leary M, Gaieski DF. Inter-rater reliability of post-arrest cerebral performance category (CPC) scores. Resuscitation 2016;109:21–4.
19. IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.
20. Litvan I et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement Disorder Society Task Force guidelines. Movement Disorders 2012;27(3):349–56.
21. Steinbusch CV et al. Cognitive impairments and subjective cognitive complaints after survival of cardiac arrest: a prospective longitudinal cohort study. Resuscitation 2017;120:132–7.
22. Ben Schmand, Peter Houx en Inge de Koning, Normen van psychologische tests voor gebruik in de klinische neuropsychologie, Published on the website of the section Neuropsychologie Nederlands Instituut van Psychologen; 2012.
23. Ware JE. SF-36 health survey: manual and interpretation guide. Health Institute; 1993.
24. Breeman S et al. Normative data for the hospital anxiety and depression scale. Quality Life Res 2015;24(2):391–8.
25. Moulaert VR et al. Long-term outcome after survival of a cardiac arrest: a prospective longitudinal cohort study. Neurorehabilitation Neural Repair 2017;31(6):530–9.
26. Lilja G, Nilsson G, Nielsen N, Friberg H, Hassager C, Koopmans M, Cronberg T. Anxiety and depression among out-of-hospital cardiac arrest survivors. Resuscitation 2015;97:68–75.
27. Eberst G, Claudé F, Laurent L, Meurisse A, Roux-Claudé P, Barnig C, Chirouze C. Result of one-year, prospective follow-up of intensive care unit survivors after SARS-CoV-2 pneumonia. Ann Intensive Care 2022;12(1):23.