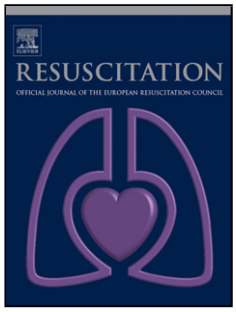

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Late heartbeat-evoked potentials are associated with survival after cardiac arrest

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Abstract

RATIONALE: Cardiac arrest (CA) is a serious condition characterized by high mortality rates, even after initial successful resuscitation, mainly due to neurological damage. Whether brain-heart communication is associated with outcome after CA is unknown. Heartbeat-evoked brain potentials (HEPs) represent neurophysiological indicators of brain-heart communication. The aim of this study was to address the association between HEPs and survival after CA.

METHODS: HEPs were calculated from resting EEG/ECG in 55 CA patients 24 hours after resuscitation. All patients were treated with targeted temperature management and a standardized sedation protocol during assessment. We investigated the association between HEP amplitude (180-320 ms, 455-595 ms, 860-1000 ms) and 6-month survival.

RESULTS: Twenty-five of 55 patients (45%) were still alive at 6-month follow-up. Survivors showed a higher HEP amplitude at frontopolar and frontal electrodes in the late HEP interval than non-survivors. This effect remained significant after controlling for between-group differences in terms of age, Fentanyl dose, and time lag between resuscitation and EEG assessment. There were no group differences in heart rate or heart rate variability.

CONCLUSION: Brain-heart communication, as reflected by HEPs, is associated with survival after CA. Future studies should address the brain-heart axis in CA.

Abstract word count: 193

Keywords: brain-heart interaction, cardiac arrest, interoception, neurological outcome, prognostication, sedation, targeted temperature management, visceral-afferent signals

Word count: 2991

Introduction

Only about 50% of patients survive cardiac arrest (CA) [1], even if spontaneous circulation is successfully restored. The most frequent cause of death after resuscitation is neurological damage caused by hypoxia during CA, followed by myocardial dysfunction, systemic ischemia, or precipitating pathology [2, 3]. In addition to end-organ damage, the interaction between brain and heart may play an important role for cardiovascular function after CA. Cardiac interoception, the perception of afferent signals originating from the cardiovascular system, is considered to reflect brain-heart communication. Altered cardiac interoception in cardiovascular diseases, such as arterial hypertension [4], congenital heart disease [5], or ventricular dysfunction [6], suggests that adequate brain-heart communication is required to preserve cardiovascular health.

Resuscitated patients typically require life support in intensive care units, which carries heavy workload and significant cost to the health-care system. The high mortality rate after successful resuscitation, however, highlights the urgent need for reliable predictors of patients' survival chances [7-10]. Currently available predictors, however, lack specificity, and their clinical application is limited [7]. According to the European Resuscitation Guidelines "a means of predicting neurological outcome that can be applied to individual patients immediately after return to spontaneous circulation (ROSC) is required" [11].

Heartbeat-evoked brain potentials (HEPs) represent neurophysiological indicators of brain-heart interaction. HEPs assessed while individuals are asked to focus their attention on their heartbeats are related to accuracy in heartbeat perception [12]. Importantly, HEPs assessed in a resting [6, 13-16] or sleeping state [17], are interpreted as indicators of the cortical representation of afferent signals originating from the cardiovascular system. HEPs require intact afferent signal transmission [18]. In patients with ventricular dysfunction, HEP

amplitudes correlate with stress-induced changes in cardiac output, suggesting that cardiac (dys-)function is also reflected in HEP amplitudes [6].

Blood outflow following cardiac contraction stimulates receptors in the vascular system, such as arterial baroreceptors. Afferent signals from these receptors are transmitted via cranial nerves and integrated into brainstem-located reflex circuits to ensure homeostasis [19]. Brainstem centers project onto the parabrachial nucleus and the locus coeruleus, from where hypothalamic and thalamic nuclei are reached [20]. Cortical structures that process visceral-afferent neural signals include the anterior cingulate, the frontal, the somatosensory and the right insular cortex [20, 21]. A dipole localization study [22] demonstrated that HEP amplitudes originate from exactly those four cortical areas.

Altered HEP amplitudes may result from disturbances in the periphery (e.g., cardiac dysfunction, autonomic nerves) [6, 18] or altered representations of afferent cardiac signals in the brain [13, 15, 23]. Altered afferent signals at brainstem level may result in aberrant efferent output of these reflexes (e.g., sympathetic hyper-arousal). If limited to the cortical level, it is still plausible that the inappropriate cortical regulation of lower brainstem signal transmission via the central autonomic network [24] causes disturbance in cardiovascular homeostasis [6], which could also contribute to cardiovascular ill-health.

The aim of the current study was to examine the potential association between brain-heart communication and outcome after CA. We investigated if HEP amplitudes are associated with 6-months survival in CA patients, a common timespan for outcome determination [25].

Methods

Participants

In this retrospective study, we included 57 patients from a prospective local registry of CA patients admitted between October 2010 and December 2015 for which electroencephalogram/electrocardiogram (EEG/ECG) data were available for HEP determination (Figure 1). Patients were older than 18 years, unconscious (Glasgow coma score $\leq$ 8) and received targeted temperature management at either 33°C or 36°C with sedation and neuromuscular blockade, and anti-epileptic medication if required, according to our protocol [9] (Table 1). This procedure allows suitable sedation with minimal electromyogram (EMG) artifacts on the EEG signal. After 24 hours, patients were rewarmed to 36°C at a maximum rate of 0.5°C/h and sedation was tapered. According to the national committee for ethics in research (CNER 2008/05) requirements, patients' relatives were asked for informed consent and patients regaining consciousness were also re-consented *a posteriori*. Decisions to withdraw life support or to limit care were never taken by considering HEPs, heart rate (HR) or heart rate variability (HRV). After tapering of sedation, only the absence of awakening after complete cessation of sedation, signs of brain death or early myoclonus or status epilepticus in combination with bilaterally absent N20 peak on somatosensory evoked potentials or imaging findings compatible with irreversible brain damage were taken into account [9].

Neurological evaluation

Neurological outcome was defined by the cerebral performance category (CPC) score at 6 months after CA [26]. CPC score 1 or 2 indicates no or minor neurological sequelae, 3 and 4 indicates severe neurological sequelae or coma, and 5 indicates death. Evaluation of the neurological status via phone calls or by face-to-face interviews, using the CPC scale was performed by physicians unaware of HEP or ECG data or treatment details. We defined

'survivors' (CPC score of 1-4 after 6 months: 25 patients [4 female], 53.0 [15.7] years) and 'non-survivors' (CPC score of 5: 30 patients [9 female], 67.1 [12.1] years). Cause of death in non-survivors was determined by clinical evaluation: neurological damage (22 patients), death of cardiac origin (6) and multiple organ failure (2).

Electroencephalographic assessment

EEG/ECG assessment was carried out for approximately 15 minutes. EEG was recorded continuously using 14 Ag-/AgCl subdermal passive electrodes (13×0.40 mm) and a BrainRT amplifier system. The electrodes – Fp(1,2), F(3,4), C(3,4), P(3,4), T(3,4), O(1,2) and A(1,2) – were mounted according to the 10–20 system, and referenced to linked mastoids. The signals were digitized at 250 Hz (hardware filters: 1-70 Hz; software filter: 1-35 Hz).

Analysis of Heartbeat-Evoked Potentials (HEPs)

Only cardiac cycles with a normal QRS complex (resulting from SA node depolarization) were included in HEP analyses. EEG data were averaged, relative to the detected R-waves in epochs ranging from 200 ms before the R-wave to 1000 ms after the R-wave and baseline-corrected (-200 to 0 ms). We focused on a time window of 455-595 ms after the R-wave ('normal' HEP interval; see Figure 2) [6, 13-16], during which the electro-cardiac field is considered minimal [27]. HEP amplitudes of T3 and C3, as well as of C4 and T4 were collapsed to create an equally sized 5 × 2 electrode field on the scalp. Due to technical malfunction of channel C4 for all participants, data in cell 'central/right' was only based on T4. To test whether group differences between survivors and non-survivors are specific to HEPs or may be a general effect on event-related brain potentials, we also derived mean activity in two HEP control intervals of the same duration: an early HEP interval (180-320 ms), during which the cortical processing of afferent cardiac signals and the electrocardiac field may overlap [27], and a late HEP interval (860-1000 ms), which is temporally located after the cortical processing of cardiac

signals in un-medicated patients [6]. The polarity of the HEP in the early and late interval is negative (more negativity implies stronger signal representation; Figure 2), but positive in the 'normal' HEP interval [14, 28].

Cardiovascular Data Analysis

Electrodes for ECG measurement were placed according to a standard lead II configuration. The ECG signal was high-pass filtered (0.1 Hz). Interbeat intervals were calculated from the ECG, with a normal cycle RR-interval time series as output signal, of which mean HR data was derived. As time domain measures of HRV are more robust against corrected QRS complexes than frequency domain measures, we used the root mean square of successive differences (RMSSD) as an indicator of central parasympathetic tone, and the standard deviation of normal-to-normal RR intervals (SDNN) as a correlate of total HRV power (sympathetic and parasympathetic) across all spectral frequency bands [29].

Outcome Measures

The primary endpoint of this study was HEP amplitude (as an indicator of brain-heart communication). To examine the role of cardiovascular activation for possible differences in brain-heart-communication, secondary endpoints were HR and HRV as indicators of autonomic cardiovascular activation.

Statistical Analysis

Group differences between survivors and non-survivors with regard to age, BMI, dose of medication, mean HR and HRV, were analyzed using t-tests for independent samples. In case of violation of equality of variances (Levene test), corrected *df*s and *p*-values are reported. To evaluate HEP amplitudes, we employed a 2×3×5×2 mixed design ANOVA with the between-subjects factor 'group' (survivors; non-survivors) and the repeated-measurement factors 'HEP interval' (early/180-320 ms; normal/455-595 ms; late/860-1000 ms), 'electrode site'

(frontopolar; frontal; central; parietal; occipital), and 'hemisphere' (right; left). Using the same factors, an analysis of covariance (ANCOVA) was calculated with the covariates 'age', 'Fentanyl dose' and 'time lag between ROSC and EEG assessment'. Post-hoc analyses were performed using t-tests for dependent samples. Huyhn-Feldt corrected *p*-values are reported for effects including repeated measurements and more than two conditions,

Results

Patients

Analyses included EEG and ECG data of 57 patients with CA and subsequent resuscitation. Data of 2 participants had to be excluded due to poor EEG quality, resulting in 55 complete data sets. The mean time lag between ROSC and the EEG/ECG assessment was 23.9 (SD=10.7) hours. Survivors were significantly younger (mean [SD]: 53.0 [15.7] years) than non-survivors (67.1 [12.1] years; $p<0.001$; Table 1). The two groups received comparable medication.

Heartbeat-Evoked Potentials

The total number of heartbeats during the acquisition period varied with participants' actual HR, but did not differ across groups (see Table 2). HEP amplitudes were more positive over the right hemisphere (-0.01 [SEM=0.08] µV) than over the left hemisphere (-0.24 [0.09] µV), as suggested by a significant main effect for 'laterality' ($F[1,53]=6.44$; $p=0.014$; $\eta^2=0.11$). Furthermore, we found greater HEP positivity in the 'normal' (455-595 ms: -0.04 [0.10] µV) and the late HEP interval (860-1000 ms: -0.03 [0.06] µV) than in the early HEP interval (180-320 ms: -0.30 [0.11] µV; all ps<0.05), as suggested by a significant main effect for 'interval' ($F[2,106]=3.99$; $p=0.029$; $\eta^2=0.07$). We observed higher HEP amplitudes in 'survivors' as compared to 'non-survivors' in the late HEP interval only at frontopolar ($p = 0.007$) and frontal electrodes ($p = 0.048$; see Figure 3), as indicated by a significant 3-way interaction 'interval' × 'electrode' × 'group' ($F[8,424]=2.71$; $p=0.027$; $\eta^2=0.05$).

Age, Fentanyl dose and time lag between ROSC and EEG assessment were entered as covariates into the ANCOVA model, showing that non-survivors were older than survivors. In addition, patients receiving a lower dose of Fentanyl or who had a longer time lag between ROSC and EEG assessment were also at higher risk of death, although these two latter effects only approached statistical significance (Table 1). While the main effects for 'laterality' and

'interval' were not significant in this ANCOVA, the interaction 'interval' × 'electrode' × 'group' remained significant (F[8,400]=2.30; p=0.05; η^2=0.04). None of the remaining effects was significant.

To test if body temperature accounted for group differences, we repeated the original ANOVA, distinguishing between survivors and non-survivors maintained at 33°C vs. 36°C. There were no differences in HEP amplitudes between patients maintained at 33°C and those maintained at 36°C.

Cardiovascular Data

Ten survivors and seven non-survivors showed ectopic beats or cardiac arrhythmia that were interpolated (sum of both intervals, divided by two) before HRV calculation, whereas four survivors and nine non-survivors had serious arrhythmia, which resulted in an exclusion from HRV analysis. We did not observe significant differences between survivors and non-survivors with regard to mean HR (Table 2). The resulting 21 survivors (3 women) and 21 non-survivors (6 women; comparison of sex distribution in both groups: χ^2[df=1]=1.27; p=0.26) did not differ in RMSSD or SDNN.

Discussion

This is the first study to investigate the association between brain-heart communication, as represented by HEPs, and survival after CA. We hypothesized larger HEP amplitudes, indicating a stronger cortical representation of afferent cardiac signals, in survivors than in non-survivors. This was confirmed in that we found higher HEP amplitudes in survivors, however, not in the expected 'normal' HEP interval, but in the late HEP interval. Survivors were also significantly younger than non-survivors, and showed a trend to receiving more Fentanyl. When controlling for these variables, the difference in late HEP amplitudes between groups remained significant. These results suggest, therefore, that brain-heart communication, as reflected by HEPs, may serve as predictor of mortality after successful resuscitation in CA patients. As temperature management did not have any effect on HEPs, we conclude that level of target temperature does not play a key role in brain-heart communication after CA.

These effects, however, are limited to late HEPs at frontopolar and frontal electrodes. As summarized by Schandry and co-workers [28], HEPs at frontal electrodes represent cortical representations of visceral-afferent signals, whereas components at central electrodes are associated with afferent somatosensory signals. In line with previous research, we found higher amplitudes over the right hemisphere, which may be due to the primarily contralateral projections of visceral-afferents from the thorax to the brain [12, 18].

Afferent signals from the cardiovascular system are integrated into reflex circuitries controlling efferent sympathetic and parasympathetic cardiac output, such as the arterial baroreflex circuit. Due to the reciprocal nature of signal transmission, the exact origin of the alterations in HEPs remains unclear. Aberrant cortical representations of visceral-afferent signals could be due to altered peripheral cardiac (e.g., sympathetic) activation or neurological damage in one of the neural structures responsible for the processing of visceral-afferent signals. As there were no differences in HR between groups it is unlikely that HEP differences

are due to cardiovascular autonomic activation or morbidity. We would argue, therefore, that damage in neural structures involved in mediating visceral-afferent signal transmission is more plausible. To investigate possible brain damage, however, neuro-imaging studies or high density EEG assessments, which allow for a dipole localization of HEPs, are necessary. Although there was no indication for differences in sympathetic or parasympathetic tone between survivors and non-survivors, it is still possible that reduced cortical representation of afferent cardiac signals in non-survivors contributed to impaired adaptation of the cardiovascular system that could also promote cardiac mortality [6]. As we assessed HEPs in sedated, unconscious patients, it remains for future research to clarify if conscious processing of cardiac sensations (as indicated by HEPs assessed while performing a heartbeat perception task) is also associated with cardiac mortality.

It remains unclear why the group difference in HEPs was limited to the late HEP interval, but not visible in the 'normal' HEP interval between 455-595 ms after the R-wave. The CNS processing of afferent baroreceptor signals, which represent one important source of afferent cardiac signals reflected by HEPs, are likely to occur between 400 and 800 ms after the cardiac R-wave [6]. This timeframe, however, is based on healthy, un-medicated individuals. In contrast, individuals from the current sample were sedated including benzodiazepine (Midazolam), anesthetics (Propofol) and opiates (Fentanyl, Sufentanil, Piritramide). Sedation with benzodiazepines [30, 31], opiates [32, 33], and Propofol [34, 35] can substantially prolong the latency of event-related potentials (ERPs) for auditory and somatosensory stimulation by 10 ms for early (ERP components Pa, Nb) [32] and 140 ms for late ERPs (P2) [33]. As HEPs can be considered a particularly late ERP, a more pronounced prolongation would be plausible. There is also a prolongation of ERP latency in hypothermia [36, 37] and neurological damage following CA [38, 39]. Although the interaction of sedation, hypothermia and neurological damage on HEPs remains unknown and should, therefore, be systematically addressed in future

studies (e.g., by including a control group with sedation only, but without hypothermia or neurological damage), it is likely that these factors contribute to the prolonged processing of visceral-afferent neural signals. This may ultimately result in group differences, observable only in the late HEP interval of 860-1000 ms, which exceeds the 'normal' time frame by 60 to 200 ms of processing of afferent cardiac signals of 400-800 ms.

In summary, these findings suggest that HEPs during the late interval could serve as a prognostic factor for mortality after CA. As compared to serum-based indicators, such as microRNAs [7], enzymes [8] or proteins [40], EEG-based indicators may be more cost-effective and could be available with a minimal time lag, e.g., if they are provided by an automatic device. The bispectral index (BIS) was previously introduced as predictor of neurological outcome in similar patients [9]. As BIS and HEP indicators are both related to activity at frontal electrodes, future research should consider if frontal lobe functioning is particularly indicative of outcome after CA. Given that HEPs are ERPs, their calculation may be more robust against artifacts and an interruption of EEG assessment as compared to BIS, as no spectral analysis is required.

Limitations

Due to the limited sample size and the single center design of this study, we suggest a replication of this investigation in a large-scale multi-center study. Furthermore, replication studies are needed to reduce the probability of erroneous findings. Although the majority of survivors (22 of 25) had a CPC of 1, it cannot be ruled out that patients with a CPC of 2-4 may have different HEP patterns, which could not be systematically tested in the current study, as only 3 patients in the current study had a CPC between 2 and 4. Autopsy results would have provided the most reliable cause of death. Due to the retrospective design of this study, conclusions on causal relationships between heart-brain-interaction and survival after CA have to be drawn with caution. For the same reason, the major inclusion criterion of this study was the availability and quality of EEG/ECG data. It cannot be ruled out, therefore, that a selection

bias (e.g., patients with most severe damage died before EEG data assessment) may have had an effect on the present results. As this study did not include a control group with sedation, but without neurological damage or hypothermia, the reason for HEP differences occurring in the late interval remains unclear.

Conclusion

This is the first study to demonstrate that the cortical representation of visceral-afferent signals, as reflected by HEPs, is associated with mortality after CA. As survivors and non-survivors had similar heart rates and heart rate variability, sympathetic activation is unlikely to account for this effect. Differences between survivors and non-survivors remained significant when controlling for age, medication, and time lag between ROSC and EEG assessment. HEPs may represent novel indicators of prognosis after CA.

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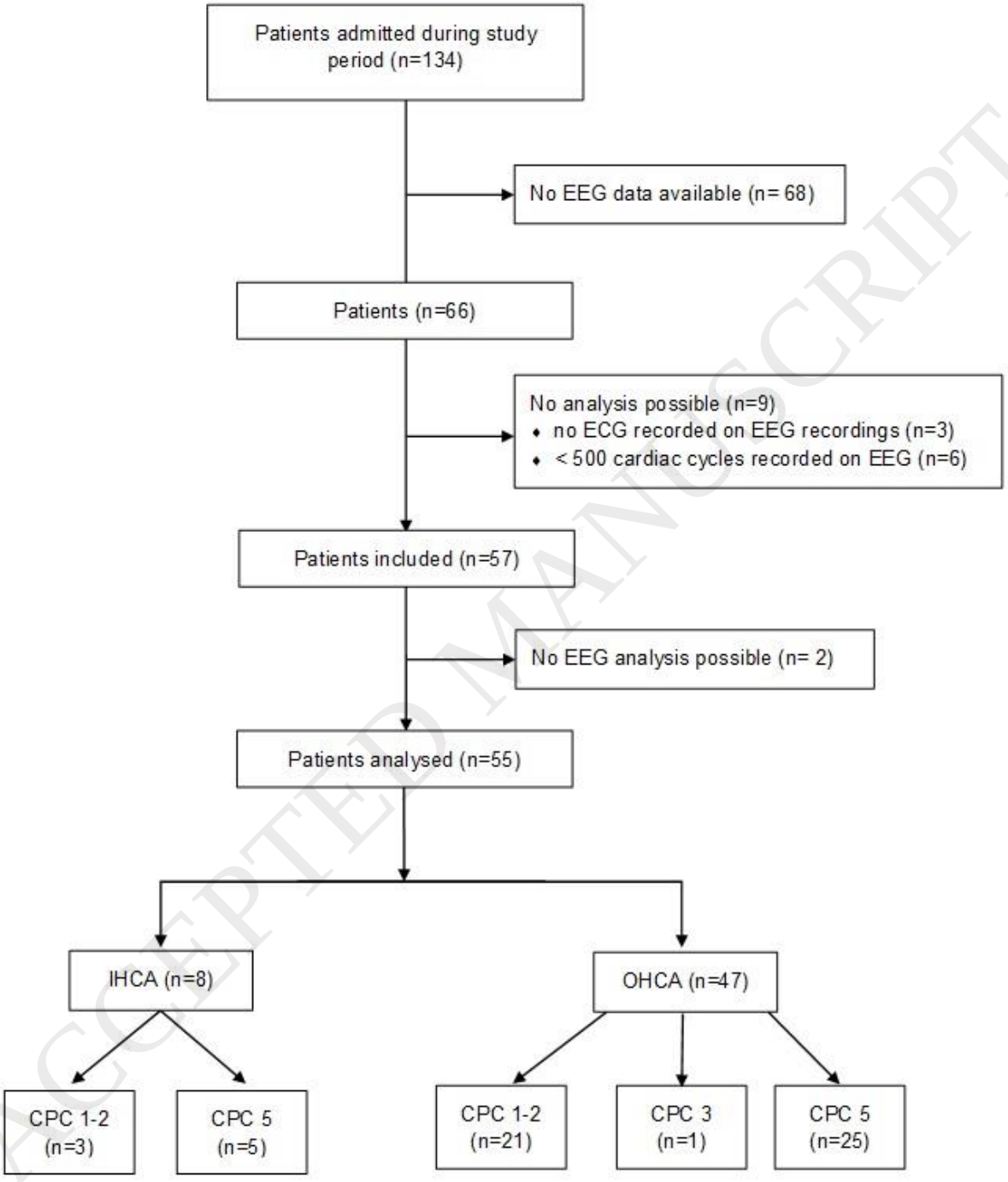
Conflicts of interests

All authors declare that they have no conflict of interest.

Figure 1 Caption

Flow-chart of study participants.



Legend: EEG = electroencephalogram; ECG = electrocardiogram; IHCA = in hospital cardiac arrest; OHCA = out of hospital cardiac arrest; CPC = cerebral performance category

Figure 2 Caption

Example scheme of heartbeat-evoked potentials (HEPs) in healthy individuals. Scheme (b) shows the average ECG, while scheme (a) depicts the average EEG activity at electrode Fz, both averaged over all cardiac cycles within 5 minutes. The reference point at 0 ms for both schemes is the R-wave in the ECG. Note the similarities between the ECG and EEG during the R-wave and T-wave in the ECG, which is due to the cardiac field artifact. Due to this artifact, activity in the 'early' HEP interval from 180-320 ms (I) should be interpreted with caution. Activity related to the cortical representation of afferent signals related to a heartbeat can be typically observed in the 'normal' HEP interval (II) from 455-595 ms in healthy, conscious individuals. The 'late' HEP interval (III) from 860-1000 ms exceeds the typical period of heartbeat-related afferent signals in healthy individuals, but may still include cardio-afferent signals in sedated CA patients. The polarity of the HEP in intervals (I) and (III) is negative (more negativity reflects stronger signal representation), but positive in interval (II).

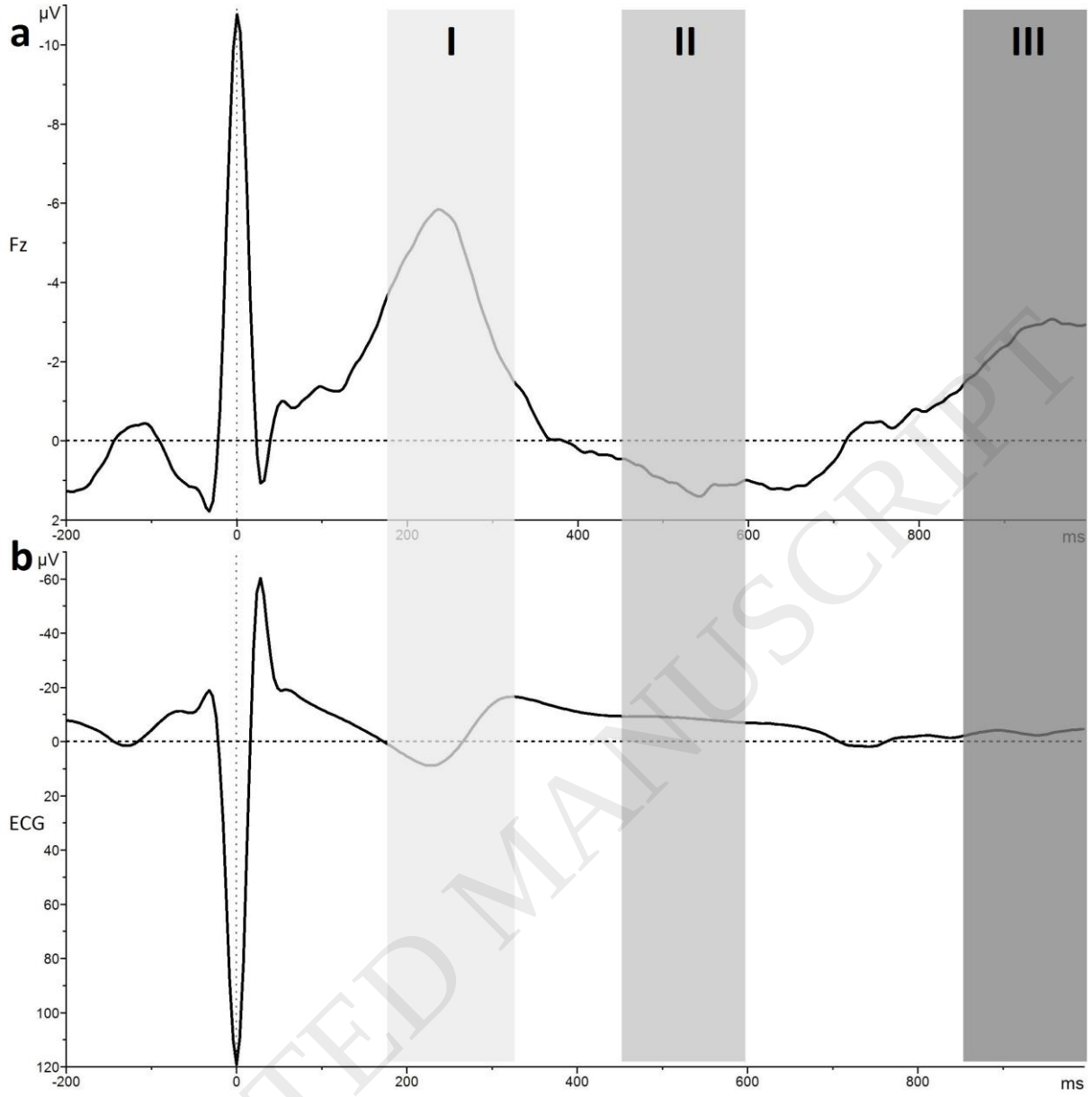
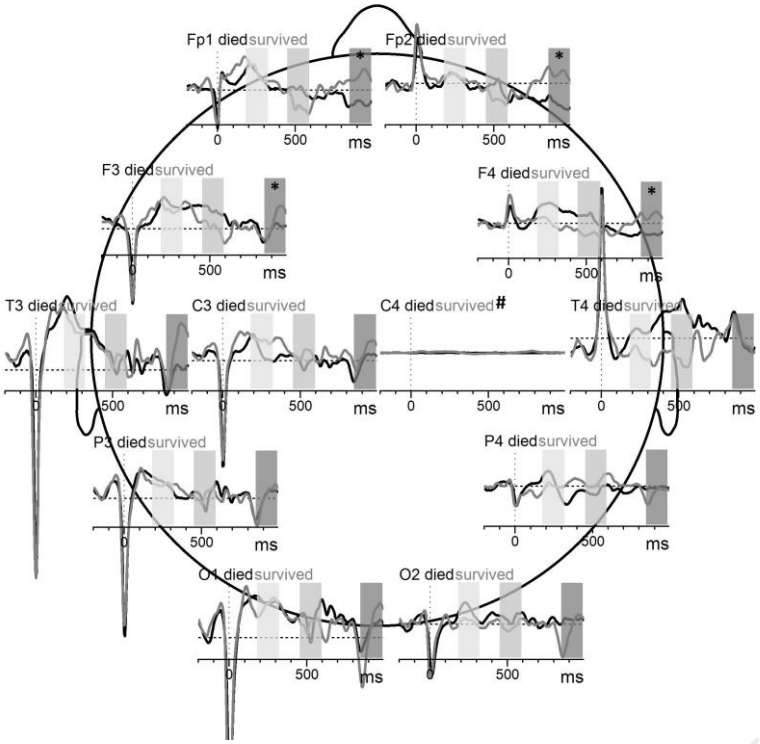


Figure 3 Caption

HEPs in survivors and non-survivors at an early (light gray, 180-320 ms), normal (medium gray, 455-595 ms) and late time interval (dark gray, 860-1000 ms) relative to R-waves. At frontopolar and frontal electrodes, HEP amplitudes were higher in survivors than in non-survivors (*). Please note that due to technical malfunction data at C4 was lost and not included in the analysis (#).



Tables:

Table 1. Patient characteristics

			Non-survivors			**Survivors**				
			n=30			**n=25**				
Variable	Unit		M	(SD)		M	(SD)	*T*/χ^2	df	*p*
Sex	m/f		21/9			21/4		1.48	1	0.22
Target temperature	33°C/36°C		15/15			12/13		0.02	1	0.88
Age	years		67.1	(12.1)		53.0	(15.7)	3.76	53	<0.001
BMI	kg/m²		29.0	(6.2)		27.5	(6.3)	0.91	53	0.37
Propofol	mg/kg/h		0.19	(0.50)		0.30	(0.73)	-0.66	53	0.51
Midazolam	mg/kg/h		0.15	(0.19)		0.21	(0.12)	-1.27	53	0.21
Diazepam	mg		0.67	(3.65)		0	(0)	0.91	53	0.36
Sufentanil	µg/kg/h		0.02	(0.09)		0.05	(0.08)	-1.11	53	0.27
Fentanyl	µg/kg/h		0.04	(0.15)		0.40	(0.98)	-1.80	25.00[1]	0.085
Piritramide	mg/kg/h		0.07	(0.19)		0.02	(0.02)	1.39	53	0.17
Dobutamine	µg/kg/h		76.3	(159.3)		54.7	(94.4)	0.60	53	0.55
Noradrenaline	µg/kg/h		17.2	(58.9)		3.9	(4.8)	1.13	53	0.26
Adrenaline	µg/kg/h		4.9	(22.5)		2.1	(7.3)	0.60	53	0.55
Bisoprolol	mg		0.08	(0.46)		0.10	(0.50)	-0.13	53	0.90
Sotalolol	mg		0	(0)		3.2	(16)	-1.00	24.00[1]	0.33
Time lag ROSC[2]/EEG	hours		26.1	(13.1)		21.2	(6.0)	1.84	42.04[1]	0.073

[1]in case of violation of assumption of equal variances, degrees of freedom were corrected accordingly

[2]return of spontaneous circulation

Table 2. Indices of cardiovascular autonomic activation

.											
			Non-survivors			**Survivors**					
			n=30			**n=25**					
Variable	Unit		M	(SD)		M	(SD)		*T*	df	*p*
Number of heartbeats in acquisition period			1043	(579)		1087	(384)		-0.32	53	0.75
Mean HR[1]	bpm		80.0	(21.4)		77.4	(16.0)		0.51	53	0.61
RMSSD[1]	ms		17.5	(18.6)		17.5	(39.4)		-0.01	40[2]	0.99
SDNN[1]	ms		19.8	(17.6)		27.6	(44.9)		-0.75	40[2]	0.46

[1]HR = heart rate; RMSSD = root mean square of successive differences; SDNN = standard deviation of NN intervals

[2]exclusion of participants with cardiac arrhythmia resulted in 21 survivors vs. 21 non-survivors