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Clinical paper

Heart rate variability for neuro-prognostication after CA: Insight from the Parisian registry



Sarah Benghanem^{a,b,c,*}, Tarek Sharshar^{b,c,d}, Martine Gavaret^{b,c,e}, Florence Dumas^{b,f}, Jean-Luc Diehl^{b,g}, Nicolas Brechot^{b,g}, Fabien Picard^{b,h}, Diego Candia-Riveraⁱ, Minh-Pierre Le^a, Frederic Pène^{a,b}, Alain Cariou^{a,b,1}, Bertrand Hermann^{b,c,g,1}

Abstract

Background: Hypoxic ischemic brain injury (HIBI) induced by cardiac arrest (CA) seems to predominate in cortical areas and to a lesser extent in the brainstem. These regions play key roles in modulating the activity of the autonomic nervous system (ANS), that can be assessed through analyses of heart rate variability (HRV). The objective was to evaluate the prognostic value of various HRV parameters to predict neurological outcome after CA.

Methods: Retrospective monocentric study assessing the prognostic value of HRV markers and their association with HIBI severity. Patients admitted for CA who underwent EEG for persistent coma after CA were included. HRV markers were computed from 5 min signal of the ECG lead of the EEG recording. HRV indices were calculated in the time-, frequency-, and non-linear domains. Frequency-domain analyses differentiated very low frequency (VLF 0.003–0.04 Hz), low frequency (LF 0.04–0.15 Hz), high frequency (HF 0.15–0.4 Hz), and LF/HF ratio. HRV indices were compared to other prognostic markers: pupillary light reflex, EEG, N20 on somatosensory evoked potentials (SSEP) and biomarkers (neuron specific enolase-NSE). Neurological outcome at 3 months was defined as unfavorable in case of best CPC 3–4–5.

Results: Between 2007 and 2021, 199 patients were included. Patients were predominantly male (64%), with a median age of 60 [48.9–71.7] years. 76% were out-of-hospital CA, and 30% had an initial shockable rhythm. Neurological outcome was unfavorable in 73%. Compared to poor outcome, patients with a good outcome had higher VLF (0.21 vs 0.09 ms²/Hz, $p < 0.01$), LF (0.07 vs 0.04 ms²/Hz, $p = 0.003$), and higher LF/HF ratio (2.01 vs 1.01, $p = 0.008$). Several non-linear domain indices were also higher in the good outcome group, such as SD2 (15.1 vs 10.2, $p = 0.016$) and DFA $\alpha 1$ (1.03 vs 0.78, $p = 0.002$). These indices also differed depending on the severity of EEG pattern and abolition of pupillary light reflex. These time-frequency and non-linear domains HRV parameters were predictive of poor neurological outcome, with high specificity despite a low sensitivity.

Conclusion: In comatose patients after CA, some HRV markers appear to be associated with unfavorable outcome, EEG severity and PLR abolition, although the sensitivity of these HRV markers remains limited.

Keywords: Cardiac arrest, Prognostication, Heart rate variability, ECG, Autonomic nervous system

Abbreviations: ANS, autonomic nervous system, CA, Cardiac Arrest, CMSE, composite multiscale entropy, CPC, Cerebral Performance Category, CSI, CardioSympathetic Index, CVI, CardioVagal Index, DFA, detrended fluctuation analysis, DFA $\alpha 1$, detrended fluctuation analysis over short time, DFA $\alpha 2$, detrended fluctuation analysis over long time., ECG, electrocardiogram, EEG, Electroencephalogram, ERC, European Resuscitation Council, ESICM, European Society of Intensive Care Medicine, ESM, Electronic Supplementary Material, GCS, Glasgow Coma Scale, HIBI, hypoxic ischemic brain injury, HF, high frequency, HR, heart rate, HRV, heart rate variability, IBI, inter-beat intervals, ICU, Intensive-Care-Unit, IQR, Interquartile-Range, LF, low frequency, NSE, Neuron-Specific Enolase, PLR, pupillary light reflexes, pNN50, percentage of the number of successive differences larger than a 50 ms, RASS, Richmond-Agitation-Sedation-Scale, RCMSE, refined composite multiscale entropy, RMSSD, Root Mean Square of Successive Differences, ROSC, Return of Spontaneous Circulation, SD1, standard deviation of the Poincaré plot orthogonal to the identity line, SD2, standard deviation of the Poincaré plot along the identity line, SDNN, standard deviation of the NN (R-R) intervals, SSEP, Somatosensory Evoked Potentials, TTM, Targeted Temperature Management, VLF, Very low frequency, WLST, Withdrawal-of-Life-Sustaining-Treatments

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Introduction

A vast majority of patients resuscitated from cardiac arrest (CA) are comatose after return of spontaneous circulation (ROSC). Despite the improvement of post-CA care, most of them will die following withdrawal of life-sustaining treatment (WLST) for suspected irreversible and severe hypoxic-ischemic brain injury (HIBI).¹ Early and accurate identification of prognosis is one of the most challenging issues in this situation. European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) guidelines recommend using a prognostication algorithm for prediction of poor outcome.^{2,3} The recommended strategy is to apply a multimodal prognostication approach using at least two concordant markers among clinical examination (bilateral pupillary and corneal reflexes abolition, early status myoclonus), neurophysiological investigations (electroencephalogram (EEG); somatosensory evoked potentials (SSEPs)), biological (Neuron specific enolase, NSE), and neuroradiological (CT scan or MRI) tools. This prognostication algorithm is highly specific of poor neurological outcome, despite a low to moderate sensitivity. Indeed, the prognostic of patients remain indeterminate in 50 to 68% of cases despite the use of this algorithm, highlighting the need of new prognostic tools.^{2,4}

A recent post-mortem analysis suggested that severe lesions of HIBI are predominantly observed in the neocortical areas, the insula and hippocampus, and to a lesser extent in the brainstem.⁵ Nevertheless, all these regions are essential for the control of vital functions and the acute response to stress as they are key regions of the integration and modulation of the autonomic nervous system (ANS) activity.⁶ Composed by the sympathetic (e.g., noradrenergic) and parasympathetic (e.g., cholinergic) systems, ANS has a major role in regulating body homeostasis and allostasis, but its functioning can be altered in various situations of cerebral aggression. Thus, many critical illnesses are characterized by ANS dysregulation and/or dysfunction.^{7–9} ANS activity can be assessed through heart-rate variability (HRV) analyses with different time-, frequency- and non-linear-domain indices reflecting the modulation of sympathetic and parasympathetic activities. Time-domain indices of HRV (like SDNN, pNN50 or RMSSD) quantify the amount of variability of the interbeat interval (IBI), ie. the interval between successive heartbeats. Frequency-domain measurements estimate the frequency content of the IBI time series in three frequency bands, the very-low-frequency (VLF), influenced by the heart intrinsic nervous system, the low-frequency (LF), reflecting sympathetic and parasympathetic modulation, and the high-frequency (HF) band, mostly reflecting parasympathetic activity. Hence LF/HF ratio is influenced by the ratio between sympathetic and parasympathetic activities. Finally, non-linear measurements (i.e., SD1, SD2, DFA α 1 and α 2) allow to quantify the unpredictability of the IBI time series. The oscillations of healthy subjects are complex and non-linear. Despite this, the higher levels of resting vagally-mediated HRV are linked to performance of executive functions like attention and emotional processing by the prefrontal cortex.^{10,11}

Recently, HRV analyses evidenced ANS dysfunction at the early stage after CA, with interesting performances for poor outcome prediction.¹² Yet these results have not been consistently confirmed.^{13,14} The aim of the present study was to assess the

prognostic value of the different HRV parameters for prediction of poor neurological outcome. We also assessed the correlation between HRV parameters and other signs of brainstem dysfunction (i.e., pupillary light reflexes abolition and abnormal EEG patterns). Finally, we investigated the correlation between abnormal HRV parameters and HIBI severity assessed by different prognostic markers (i.e., EEG, SSEP and NSE levels).

Method

Population

All consecutive adult patients who were admitted in a comatose state (Glasgow coma scale [GCS] \leq 8) after resuscitation from CA between November 2007 and July 2021 in the intensive care unit (ICU) of Cochin University Hospital (Paris, France) were screened. For the present investigation, we included all CA patients with at least one EEG recording performed for prognostication purpose, with a concomitant ECG recording and available EEG/ECG data to carry out the HRV analysis. In our center, EEG for neuro-prognostication is ordered in all patients who remain comatose after CA in the absence of confounding factors. Patients investigated for brain death diagnosis, patients who died within 48 h post CA before a reliable neurological examination could be performed, or patients awake before EEG were excluded. Additionally, patients with atrial fibrillation during ECG were also excluded.

Data collection

We performed a retrospective analysis of prospectively collected data from our CA registry (PROCAT registry) which has been previously described [1,15](#). The following data were collected: patients' characteristics, betablocker use before admission, pre-hospital care and CA management data using Utstein style, in-hospital management including Targeted Temperature Management (TTM) use, post-resuscitation shock and sedation during EEG/ECG. Finally, we also reported ICU mortality. This study followed the STROBE guidelines.¹⁶

Ethics

Data collection was approved by the Ethics Committee of the French Intensive Care Society (#CESRLF_12-384 and 20–41) and conducted according to French health authorities' regulations (French Data Protection Authority #MR004_2209691), who waived the need for informed consent. Patients' next of kin were informed that data were collected for clinical research purposes.

ICU management

Post-CA care was protocolized as previously described and presented in Electronic [Supplementary Material \(ESM1\)](#). Practices did not change throughout the study period^{2,3,17} and comprised TTM for 24 h (use of external cooling device to reach a temperature of 33–36 °C adapted to hemodynamic tolerance starting immediately upon ICU admission in the absence of contra-indication) and a short-acting drugs sedation regimen (propofol and remifentanyl) based on the Richmond Agitation-Sedation Scale (RASS), titrated to obtain a RASS of -5 (no response to voice or physical stimulation) and interrupted after rewarming.

Neurological prognostication process and withdrawal of life-sustaining therapies decisions

In case of persistent coma 72 h after CA and without confounding factors, a multimodal prognostication protocol was used based on the ESICM recommendations.²⁹ In the event of unfavorable developments, the WLSTs were discussed collectively, in accordance with the recommendations available at each period of the study^{2,18,19} (**Supplementary Figure 1**).

EEG and other prognostic markers assessment

EEG recordings with 13 to 19 channels were acquired over 20 to 30 min with a Natus Deltamed recording system (Natus, Middleton, USA), with a 256 Hz sampling frequency. Standard qualitative EEG were interpreted according to standardized criteria of the American Clinical Neurophysiology Society²⁰ by one board-certified expert neurophysiologist blinded to the clinical outcome, ECG and others prognostic markers. Each EEG was retrospectively classified into one of the mutually exclusive categories defined by ACNS and Westhall et al^{21,22} namely highly malignant pattern (suppressed background or burst-suppression, with or without superimposed periodic pattern), malignant pattern (presence of at least one of the following: abundant periodic discharges or rhythmic spike-waves, electroencephalographic seizure, discontinuous or low-amplitude background, absence of reactivity) or benign pattern (continuous and reactive EEG, without malignant features).^{20,23} In the present analysis, we used the first EEG/ECG performed during the ICU stay.

We also collected indicators of neurological status (i.e., pupillary reflexes, N20 on SSEP recording and NSE level at 24, 48 and 72 h after CA). NSE levels were analyzed at 72 h after CA, or 48 h when missing. NSE level was dichotomized as $<$ or $>$ 60 $\mu\text{g/L}$, according to recent guidelines.² Description of SSEP interpretation and NSE level analysis were available in the **ESM 3 and 4**.

ECG preprocessing

ECG signal was retrieved from the ECG lead of the EEG recording. ECG was preprocessed following the three steps described above, in order to obtain 5-minutes time series of interbeat intervals (IBI) for each patient. 1) Artifact detection: periods with major artifacts were manually marked. The first continuous 5 min period without artifacts was then extracted. 2) QRS detection: ECG were band-pass filtered between 0.5 and 20 Hz. QRS were automatically detected with Elgendi²⁴ algorithm. Quality of the detection was then visually assessed and R peak localization was manually corrected if needed. 3) R-R interval correction: ectopic beats were manually marked and corrected with linear interpolation. Patients with atrial fibrillation were discarded from the analysis as were patients with less than 5 min of consecutive data without artifacts or with failed R-peak detection.

HRV markers computation

Several indices of HRV were computed from the IBI time series following standards of measurements^{10,11,25}:

- 1) In the time-domain: we computed measures of heart rate (HR) [mean, minimum, maximum and standard deviation of the NN (R-R) intervals (SDNN)] and indices derived from the successive differences of R-R interval [Root Mean Square of Successive Differences (RMSSD) and percentage of the number of successive differences larger than a 50 ms (pNN50)].

- 2) In the frequency-domain: power spectral density in the very low frequency (VLF, 0.003–0.04 Hz), low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.4 Hz) bands was computed using the Welch method with a 64 s Hamming time window and 50% overlap from the IBI timeseries resampled to 4 Hz and interpolated using a cubic spline interpolation. Power in these frequency band was then expressed as the absolute power, as normalized power and as the ratio between LF and HF (LF/HF), roughly estimating the ratio between sympathetic and parasympathetic modulations.
- 3) In the non-linear domain: Using the Poincaré plot, we computed the standard deviation of the Poincaré plot orthogonal to the identity line (SD1), the standard deviation of the Poincaré plot along the identity line (SD2), the time-varying SD2, the CardioSympathetic Index (CSI) and, the time-varying SD1, the CardioVagal Index (CVI). We also computed measures of entropy [approximate entropy, sample entropy and refined composite multiscale entropy (RCMSE)] and detrended fluctuation analysis (DFA) over short time (DFA $\alpha 1$) and long time (DFA2).

ECG preprocessing and HRV analyses were performed in python using MNE-python, systole and neurokit2 packages.

Outcome assessment

The primary outcome was the “best” neurological status at 3 months using the best cerebral performance categories (CPC) score observed during that period, dichotomized in good (CPC 1 or 2) or poor (CPC 3–4–5) outcome^{2,26} (**ESM5**). We used the best CPC to avoid considering patients who recovered consciousness after CA and subsequently died from non-neurological causes as poor neurological outcome.²⁶

The secondary outcomes were the associations of HRV parameters with pupillary light reflexes (PLR), EEG patterns (highly malignant, malignant and benign EEG), SSEPs N20 results and NSE levels at day 3 after CA.

Statistical analysis

Continuous data were expressed as median and interquartile range [IQR]. Comparisons between groups were performed with Mann-Whitney Wilcoxon test (two groups) or Kruskal Wallis test (more than two groups). Qualitative data were expressed as number and percentage and compared across group using the Chi-squared test or Fisher test as appropriate. We performed statistical analyses to produce ROC curves of the standard prognostic variables (PLR, EEG, N20 SSEP and NSE) and HRV parameters predicting a poor outcome at 3 months. Optimal thresholds were assessed according to the Youden’s index. As HRV parameters are quantitative metrics, we also reported sensitivities for a fixed false positive rate of 5%, a threshold defining a robust prognostic marker for poor outcome prediction according to European guidelines.^{2,27} In order to understand the added value of HRV for prognosis, three other models were built.

- 1) First, a clinical model including Utstein variables known to be associated with prognosis (age, out- or in-hospital CA, shockable rhythm, witnessed CA, no-flow and low-flow times, and total dose of adrenaline received during cardiopulmonary resuscitation),²⁸

- 2) Second, a model with HRV parameters was used. Selection of HRV metrics was performed using a stepwise bidirectional binary logistic regression model initially including all HRV variables with univariate p -value < 0.2 .
- 3) Third, a model combining Utstein and HRV parameters was used. Added value of HRV parameters over clinical Utstein variables was assessed by comparing AUC and computing Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI).

Each model was computed on complete-case data. Confidence intervals were computed using a 95% interval and using 2000 bootstrap replicate. Significance level was set at 0.05. Statistical analyses were performed using R version 4.2 (2022 The R Foundation for Statistical Computing).

Results

Patients

From November 2007 to July 2021, in our single tertiary center ICU, 240 patients were comatose after CA and had at least one EEG/ECG performed during their ICU stay, with an EEG/ECG raw data available. Among them, 41 patients were excluded, 27 because of atrial fibrillation and 14 because of insufficient data quality (less than 5 min of consecutive data or poor QRS detection) ([Supplementary Figure 2](#)). The remaining 199 patients were included in the analysis.

Baseline characteristics are described in [Table 1](#). Patients were mostly male (64%), with a median age of 60.0 IQR [48.9–71.7] years. Seventy-six percent of patients suffered from out-of-hospital CA and 30% had an initial shockable rhythm. Median time of no-flow and low-flow were 2.5 IQR [0–6] minutes and 18 IQR [10–25] minutes, respectively. TTM was used in 87% of patients. An unfavorable outcome was observed in 146/199 (73%) patients at 3 months, among which 141 (71%) patients died. Compared to good outcome group, patients with a poor outcome were older (65.6 vs 57.8, $p = 0.039$), with a longer duration of low-flow (19 vs 15 min, $p = 0.008$).

Neuro-prognostication markers

EEG and SSEP recordings were obtained in 199 patients (100%) and 120 patients (60%) respectively, at a median delay of 3 IQR [3,4,29] days and 4 IQR [3–5] days after CA (i.e., without hypothermia). EEG pattern was highly malignant in 44/199 (22%), malignant in 102/199 (51%) and benign in 53/199 (27%) of cases. N20 SSEP were bilaterally absent in 36/120 (30%) patients. Median NSE levels at days 2 and 3 were available in 72 and 66 patients with median values of 66 IQR [35–201] $\mu\text{g/L}$ and 100 IQR [36–338] $\mu\text{g/L}$ respectively. PLR abolition (49 vs 17%, $p = 0.026$), EEG patterns (highly malignant 30 vs 0%; malignant 62 vs 21%; benign 7.5 vs 32% $p < 0.001$), bilateral N20 abolition (36 vs 0%, $p < 0.001$), and NSE level at 48 h (131.5 vs 31 $\mu\text{mol/L}$, $p < 0.001$) and 72 h (168 vs 28 $\mu\text{mol/L}$ $p < 0.001$) significantly differed between poor and good outcomes groups ([Table 1](#)).

HRV parameters according to neurological outcome

Regarding time-domain HRV indices, mean, minimal and maximal heart rate were not different between poor and good outcome patients. However, compared to patients with poor outcome, patients

with good outcome presented a higher SDNN (11.4 vs 8.4 ms, $p = 0.024$) ([Table 2](#)).

Frequency-domain HRV markers differed between patients with good and poor outcome with higher total power (0.39 vs 0.18 ms^2/Hz , $p = 0.008$) including a higher VLF (0.21 vs 0.09 ms^2/Hz , $p < 0.01$), LF (0.07 vs 0.04 ms^2/Hz , $p = 0.003$) and LF/HF ratio (2.01 vs 1.01, $p = 0.008$) respectively. We found no significant difference of HF between good and poor outcome groups (0.05 vs 0.02, $p = 0.1$). Yet, in proportion of the total power, HF was lower in the good outcome patients (12.0% vs 22.7%, $p = 0.042$) ([Table 2](#)).

Several non-linear domain HRV markers were also higher in the good outcome group, namely SD2 (15.1 vs 10.2, $p = 0.016$), CSI (2.62 vs 1.83, $p = 0.005$), CVI (1.87 vs 1.71, $p = 0.044$) RCMSE (1.44 vs 1.32, $p = 0.013$) and DFA $\alpha 1$ (1.03 vs 0.78, $p = 0.002$). Others HRV parameters did not differ between the two groups ([Table 2](#)).

HRV parameters according to potentials confounders

50/199 (25%) patients were initially comatose without sedation but finally sedated during EEG/ECG recording. Moreover, 46/199 (23%) were treated with betablockers before ICU admission. Neurological outcome did not differ according to these two potential confounding factors. Moreover, the different HRV parameters associated with the neurological outcome were neither associated with sedation nor with beta-blocker ([Supplementary Tables 1 and 2](#)).

HRV parameters according to EEG patterns

We then assessed if the different HRV parameters scaled with HIBI severity, as reflected by the EEG classification (i.e., benign, malignant and highly malignant EEG). VLF decreased according to EEG severity with higher median values from benign to malignant and highly malignant (0.19 ms^2/Hz , 0.11 ms^2/Hz and 0.04 ms^2/Hz respectively, $p = 0.001$), as well as LF and LF/HF (LF: 0.07, 0.05 and 0.03 ms^2/Hz , $p = 0.004$; LF/HF: 2.03, 1.14 and 0.75, $p = 0.007$). Same was true for SD2 ($p = 0.048$), RCMSE ($p = 0.001$), DFA $\alpha 1$ and $\alpha 2$ markers ($p < 0.001$ and $p = 0.006$), while SD1/SD2 increased with increasing EEG severity ($p = 0.035$). ([Fig. 1 and Supplementary Table 3](#)). *Post-hoc* two-by-two comparisons showed that these differences were mainly driven by significant differences between highly malignant patterns and both malignant and benign patterns, while only a trend was observed for the comparison between malignant and benign EEG ([Fig. 1](#)).

HRV parameters according to other prognostication tools: pupillary light reflex abolition, SSEP and NSE

In order to better understand the determinants of autonomic dysfunction after CA, we also assessed the association between HRV parameters and other neuroprognostication tools. Brainstem dysfunction, reflected by standard pupillary light reflex (PLR) abolition was associated with significantly lower VLF ($p = 0.033$), LF ($p = 0.047$), LF/HF ($p = 0.010$) and SD2 ($p = 0.043$) and higher normalized HF ($p = 0.039$) as compared to preserved PLR ([Fig. 2, Supplementary Table 4](#)). These different markers were those associated with 3-month neurological outcome.

By contrast, none of the HRV parameters differed according to SSEP results (bilateral abolition of N20 vs uni- or bilateral preservation, [Supplementary Table 5](#)) and only the approximate entropy

Table 1 – Patient's characteristics and prognostic makers according to neurological outcome at 3 months. In case of missing data, we specified the number of patients for whom the variable was available (n). Continuous data are expressed in median [interquartile range] and quantitative data as number (percentage). CA: cardiac arrest; ICU: intensive care unit; ECG: electrocardiogram; EEG: electroencephalogram; NSE: Neuron-Specific Enolase; SSEP: Somatosensory Evoked Potentials; PLR: pupillary light reflexes; TTM: Targeted temperature management; N20: negative component 20 ms after stimulus onset on SSEP.

Patient's characteristics	Total N = 199	Good outcome N = 53 (27%)	Bad outcome N = 146 (73%)	p-value
Baseline characteristics				
Female sex	71 (36)	17 (32)	54 (37)	0.5
Age (years)	60.6 [48.9–71.7]	57.8 [44.4–65.4]	65.6 [50.6–73.4]	0.039
Betablocker before CA (n = 195)	46 (24)	11 (21)	35 (25)	0.6
CA location				0.8
In-hospital	47 (24)	12 (23)	35 (24)	
Out-of-hospital	152 (76)	41 (77)	111 (76)	
Initial rhythm (n = 187)				0.035
Asystole	104 (56)	20 (38)	84 (58)	
Pulseless electrical activity	15 (8)	5 (9.4)	10 (6.8)	
Ventricular tachycardia/fibrillation	68 (36)	26 (49)	42 (29)	
Witnessed CA (n = 191)	132 (69)	35 (69)	97 (69)	>0.9
No-flow (min) (n = 184)	2.5 [0–6]	2 [0–5]	3 [0–7]	0.3
Low-flow (min) (n = 190)	18 [10–25]	15 [7.5–21.0]	19 [12.0–26.5]	0.008
Adrenaline total dose (n = 189)	2 [1,3,4,29]	2 [0–3]	2 [1,3,4,29]	0.046
TTM (n = 194)	168 (87)	48 (91)	120 (85)	0.3
Post-resuscitation shock (n = 122)	72 (59)	25 (66)	47 (56)	0.3
Prognostic markers				
PLR (n = 192)				
Delay between PLR and ICU admission	3 [3,4,29]	2 [1,3,29]	3 [3,4,29]	0.026
Bilaterally abolished	77 (40)	9 (17)	68 (49)	<0.001
EEG				
Delay between EEG and ICU admission (days)	3 ^{2–4}	2 [1,3,29]	3 [3,4,29]	0.026
EEG patterns				
Highly malignant	44 (22)	0 (0)	44 (30)	<0.001
Malignant	102 (51)	11 (21)	91 (62)	
Benign	53 (27)	42 (79)	11 (7.5)	
Sedation during EEG/ECG	50 (25)	17 (32)	33 (23)	0.2
SSEP (n = 120)				
Delay between SSEP and ICU admission	3 [3,4,29]	3 [3,4,29]	3 [3,4,29]	0.13
Bilaterally absent N20	36 (30)	0 (0)	36 (36)	<0.001
NSE				
Levels at 48 h (µmol/L) (n = 72)	66 [35–201]	31.0 [20.75–48.0]	131.5 [54.25–240.5]	<0.001
Levels at 72 h (µmol/L) (n = 68)	101 [36–338]	28 [18–41.0]	168 [67–364.5]	<0.001

was higher in patients with NSE level < 60 µg/L at either 48 or 72 h after CA ([Supplementary Tables 6 and 7](#)).

Prognostic value of HRV parameters and others neuroprognostication tools

In order to assess the prognostic values of HRV parameters to predict poor outcome, we first performed ROC curves of individual HRV parameters along the ones of standard neuroprognostication tools (PLR, EEG, SSEP and NSE). AUCs were generally moderate. Highest AUCs were achieved for VLF (AUC 0.65 CI95 [0.56–0.74]) and DFA $\alpha 1$ (AUC 0.65 CI95 [0.56–0.73]), that is AUCs close to bilaterally absent PLR, highly malignant EEG or N20 SSEP, but with much less specificity (i.e., higher false-positive rates) ([Supplementary Figure 3 and Supplementary Table 8](#)). As all HRV parameters are quantitative metrics, we also computed sensitivities for thresholds corresponding to 5% false-positive rate as recommended in the recent European guidelines. Sensitivities dropped below 25%

with large 95% confidence intervals showing that HRV parameters are not reliable markers of poor neurological outcome ([Fig. 3.A](#)). Performances of HRV parameters were not improved if we focused only on patients with malignant or benign EEG or on patients with “uncertain prognosis” after multimodal prognostication algorithm (no highly malignant EEG, no bilaterally absent N20, NSE levels < 60 µg/L at both day 2 and 3 after CA) ([Supplementary Figure 4](#)).

A combination of HRV parameters (SDNN, LF, SD2, SD1/SD2, CVI, DFA $\alpha 2$ and RCMSE, selected based on bilateral stepwise regression) had only a slightly better AUC 0.69 CI95 [0.61–0.77]. This AUC was similar to the one of combined Utstein preadmission criteria (age, out-of- or in-hospital CA, witnessed CA, shockable rhythm, durations of no-flow and low-flow and total adrenaline dose received prior to ROSC) usually associated with outcome (AUC 0.71 CI95 [0.63–0.79], $p = 0.795$). However, the addition of HRV parameters to Utstein variables significantly improved the AUC (0.79 CI95 [0.72–0.86], $p = 0.016$) with significant NRI (0.61 CI95

Table 2 – HRV parameters according to neurological outcome at 3 months. Data are expressed in median [interquartile range]. HR: heart rate; SDNN: standard deviation; RMSSD: Root Mean Square of Successive Differences; pNN50: percentage of the number of successive differences larger than a 50 ms. VLF: very Low frequency; LF: low frequency; HF: high frequency; CSI: CardioSympathetic Index; CVI: CardioVagal Index; SD1: standard deviation of the Poincaré plot orthogonal to the identity line; SD2: standard deviation of the Poincaré plot along the identity line; RCMSE: refined composite multiscale entropy; DFA a1: detrended fluctuation analysis over short time; DFA a2: detrended fluctuation analysis over long time.

HRV parameters	Best CPC 3 months		p-value
	Good outcome (CPC 1–2)N = 53	Poor outcome (CPC 3–5)N = 146	
Time-domain indices			
Mean HR (bpm)	88.5 [75.1–107.2]	93.0 [79.2–105.0]	0.417
Min HR (bpm)	83.0 [66.2–101.7]	88.5 [74.0–99.0]	0.224
Max HR (bpm)	95.4 [81.3–115.5]	99.1 [83.5–113.6]	0.482
SDNN (ms)	11.4 [6.9–20.9]	8.4 [5.4–14.7]	0.024
RMSSD (ms)	6.8 [5.2–11.7]	6.7 [5.2–10.9]	0.473
pNN50 (%)	0 [0–0.24]	0 [0–0.22]	0.983
Frequency-domain indices			
VLF (ms²/Hz)	0.21 [0.09–1.02]	0.09 [0.02–0.32]	0.001
LF (ms²/Hz)	0.07 [0.03–0.29]	0.04 [0.01–0.13]	0.003
HF (ms ² /Hz)	0.05 [0.02–0.15]	0.02 [0.01–0.07]	0.102
LF/HF ratio	2.01 [0.73–3.98]	1.01 [0.33–2.47]	0.008
VLF norm. (%)	56.9 [30.4–75.3]	48.7 [24.0–72.6]	0.267
LF norm. (%)	19.6 [13.1–34.2]	17.2 [8.2–29.9]	0.137
HF norm. (%)	12.0 [6.9–30.0]	22.7 [8.9–45.9]	0.042
Non-linear indices			
SD1 (ms)	4.8 [3.7–8.3]	4.7 [3.6–7.7]	0.475
SD2 (ms)	15.1 [8.0–28.4]	10.2 [6.0–18.5]	0.016
SD1/SD2	0.38 [0.29–0.66]	0.56 [0.39–0.84]	0.005
CSI	2.62 [1.56–3.43]	1.83 [1.17–2.58]	0.005
CVI	1.87 [1.54–2.38]	1.71 [1.40–2.17]	0.044
Approximate entropy	1.11 [0.98–1.19]	1.12 [0.97–1.21]	0.952
Sample entropy	1.32 [1.08–1.50]	1.26 [0.96–1.48]	0.228
RCMSE	1.44 [1.16–1.73]	1.32 [0.89–1.60]	0.013
DFA (α-1)	1.03 [0.74–1.21]	0.78 [0.44–1.05]	0.002
DFA (α-2)	1.15 [0.86–1.25]	1.00 [0.68–1.20]	0.059

[0.29–0.92], $p < 0.001$) and IDI (0.11 CI95 [0.06–0.16], $p < 0.001$) as compared to Utstein criteria alone (Fig. 3.B).

Discussion

In this cohort of patients comatose at 72 h after CA, we found that some HRV parameters differed between patients with a poor and a good outcome at 3 months. Especially, we highlighted that frequency-domain (i.e., VLF, LF powers and LF/HF ratio) and non-linear domain HRV parameters (SD2, SD1/SD2, CSI and CVI, RCMSE and DFA α -1) were associated with the neurological outcome.

These results are consistent with the few current available studies. Endoh et al assessed HRV during the first 24 h after CA, and found that VLF, LF, LF/HF index and DFA α 1 significantly differed between the good and poor outcome groups.¹² Their results also indicate that HRV analysis could be used for neuroprognostication, with a limited prognostic performance (AUC between 0.79 and 0.84 according to HRV markers). Another recent study investigated the predictive value of HRV captured by multiscale entropy (MSE), and found that this marker provides accurate outcome prediction when assessed during the first 24 h after CA.¹⁴ Here we also found differences of HRV complexity assessed by RCMSE with higher

complexity in patients with good outcome. However, our study suggests that the prognostic performances of HRV could be lower than the ones reported in the two previous studies. These conflicting results could be related to the timing of HRV analysis. Here, we assessed the prognostic value of HRV markers later. Indeed, we included patients still comatose 72 h after CA, in concordance with current guidelines for neuroprognostication.^{2,27} We specifically chose this population because the clinical relevance of neurological prognosis arises in this group. This likely resulted in the inclusion of more severe CA survivors. Poorer performances could also be explained by the HRV analyses techniques, which are not standardized across studies, because of lack of consensus on optimal length of recordings. Finally, we also defined the HRV markers values in order to obtain an excellent specificity, and a low false positive rate (i.e., lower than 5%). As a result, sensitivity is limited for most of these HRV parameters. Despite this, the combination of HRV parameters with Utstein clinical variables increased the AUC, to higher levels than most other neuroprognostication tools.

Our study also sheds new lights on the type and source of ANS dysfunction following CA. Although interpretation of HRV parameters should be cautious,¹¹ our results mainly points towards a decreased sympathetic modulation (i.e., decreased VLF, LF, CSI and SD2) with a corresponding increased parasympathetic to sympathetic ratio (i.e., decreased LF/HF and SD1/SD2, increased relative HF fre-

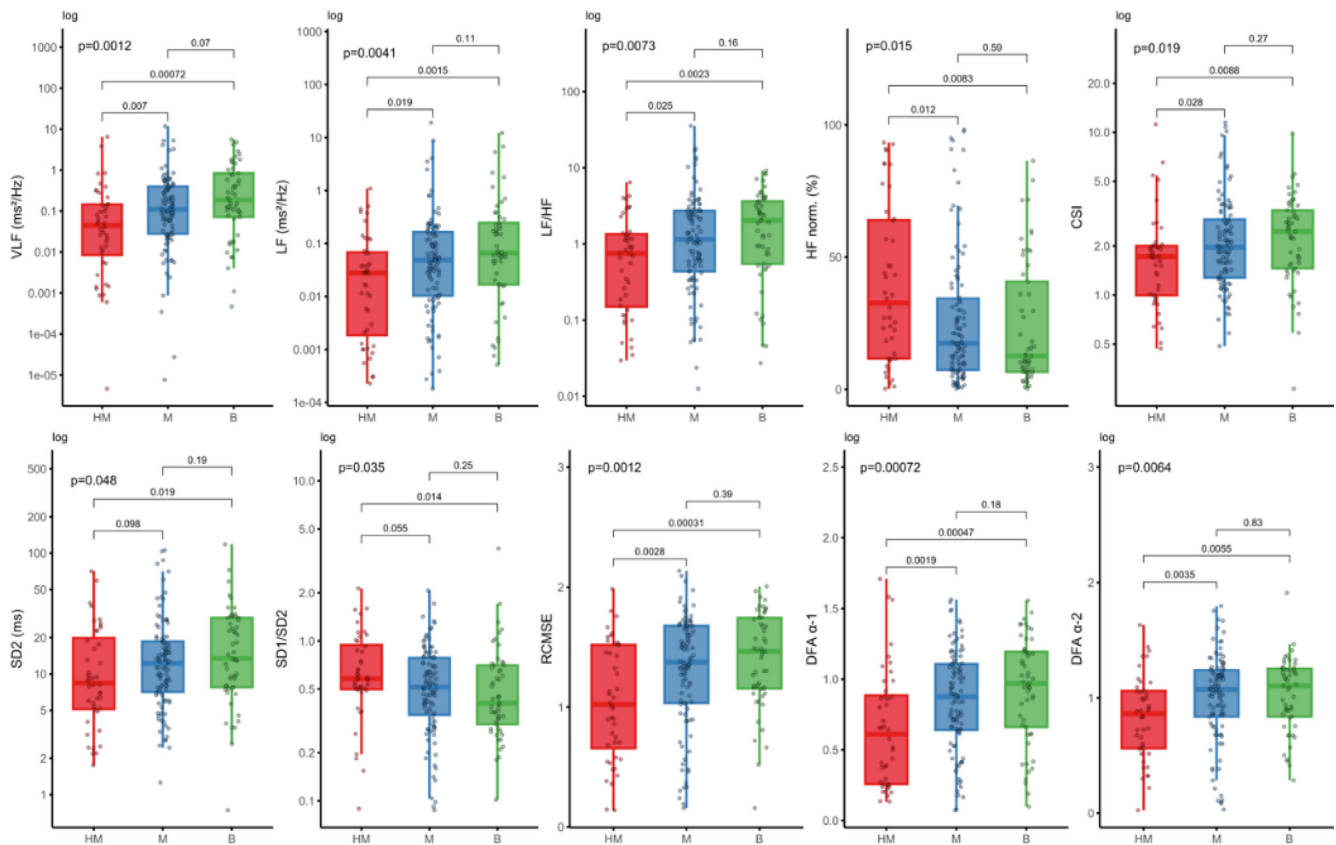


Fig. 1 – HRV parameters according to EEG patterns. We used a logarithmic scale for each HRV parameters. Boxplots represent the median and interquartile range with whiskers representing $1.5 * IQR$. HM: highly malignant; M: malignant; B: benign electroencephalogram. VLF: very Low frequency; LF: low frequency; HF: high frequency; CSI: CardioSympathetic Index; SD2: standard deviation of the Poincare plot along the identity line; RCMSE: refined composite multiscale entropy; DFA α 1: detrended fluctuation analysis over short time; DFA α 2: detrended fluctuation analysis over long time.

quency²⁹ in case of poor outcome). Moreover, our results are consistent with some others studies because VLF abnormalities, marker of the heart intrinsic nervous system,³⁰ has been previously associated with increased systemic inflammation³¹ and all-cause mortality in ICU patients.³² In this line, patients could be facing disruptions in associated pathways (e.g., locus coeruleus-noradrenaline), as changes in HR and slow fluctuations of HRV (LF, SD2) are signs of changes in the noradrenaline release rate.³³ More generally, these HRV alterations could also reflect the ANS dysfunction that has been described in different brain injury (CA, stroke, traumatic brain injury and subarachnoid hemorrhage)^{34–36} and non-brain injury patients as septic associated encephalopathy.^{37,38,39}

Regarding the anatomical regions underlying this ANS dysfunction, our study also brings interesting new elements. Indeed, we found that HRV markers reflecting sympathetic and parasympathetic tone modulation were associated with bilateral PLR abolition and also with HIBI severity reflected by EEG patterns. These results points towards a functional and/or structural dysfunction of the brainstem. Brainstem centers are major neuroanatomical structures for the control of both PLR (nuclei of the III oculo-motor nerve in the mid-brain) and ANS (notably parasympathetic nuclei in the medulla oblongata).⁶ A large post-mortem analysis suggested that brainstem lesions were mostly observed in the most severe patients, i.e., in highly malignant EEG patterns.⁵ Importantly, this study also evi-

denced that HIBI were predominantly observed in the neocortical areas, the insula and hippocampus, regions that are essential for the integration and modulation of the ANS activity.⁶ The difference of HRV parameters according to EEG patterns could thus reflect these cortical lesions. Yet we found no association between HRV markers and N20 SSEP responses or NSE level at 48/72 h after CA. In addition to a lack of power to detect differences, as SSEP and NSE were not available in the whole population, several hypotheses can be made to explain these results. About SSEP, the generators of the N20 are mainly located at the level of the primary somatosensory cortex.^{40,41} Thus, there could be limited correlation with the aforementioned anatomical structures that regulates ANS activity. Same is true for NSE levels which reflects the diffuse neuronal injury with no regional specificity. Moreover, we evaluated the association between HRV markers and dichotomized variables. For SSEP, we used “N20 response bilaterally absent” or “uni/bilaterally present” and not the N20 amplitude which could have refined the assessment of HIBI severity.⁴² We also dichotomized the NSE level as $>$ or $<$ $60\mu\text{G/L}$, according to the 2021 European Guidelines for neuroprognostication.^{2,27} Bilaterally absent N20 and NSE $>$ $60\mu\text{G/L}$ are recognized as robust markers of poor outcome, but bilaterally present N20 and NSE $<$ $60\mu\text{G/L}$ are not associated with good outcome.^{43,44} Thus, it may have hampered our ability to demonstrate a difference in HRV using these dichotomous criteria. Overall, these

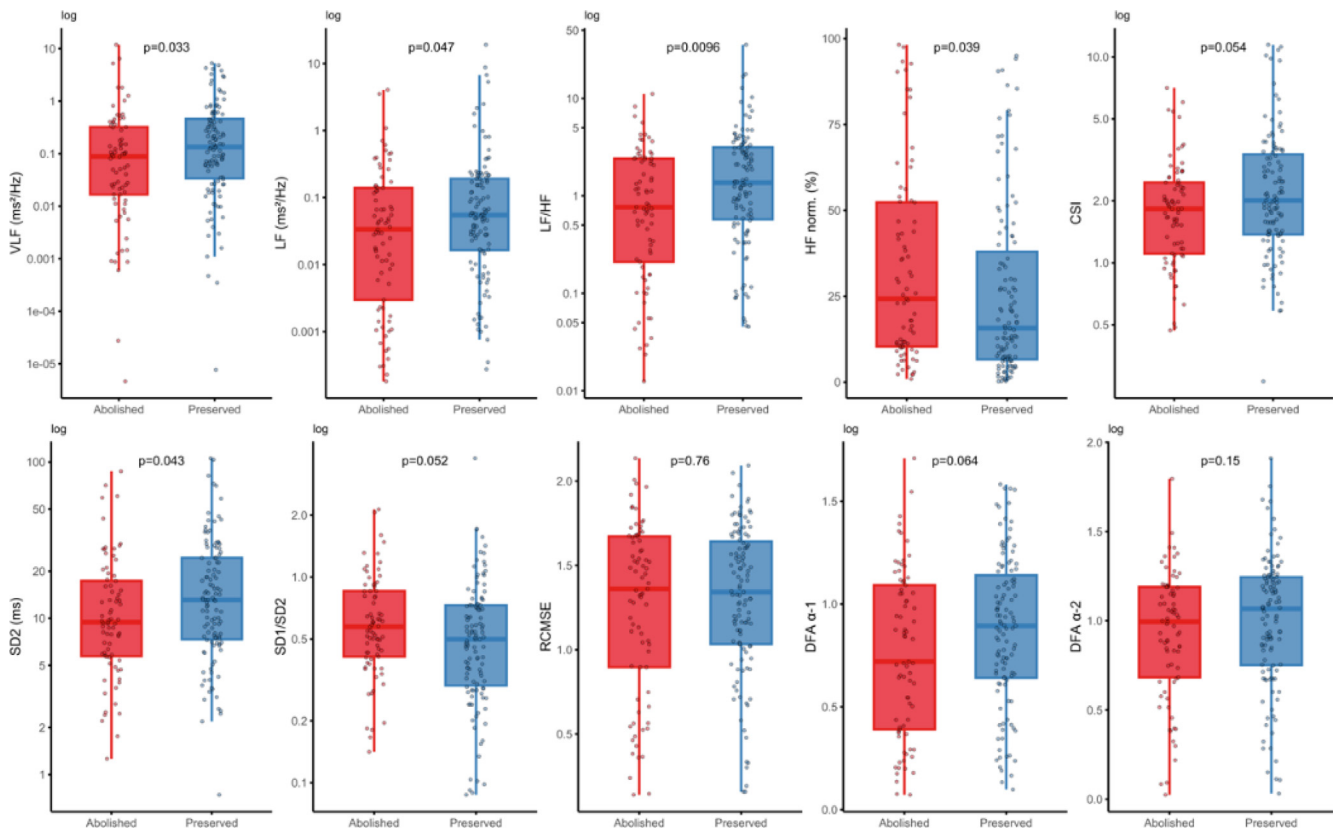


Fig. 2 – HRV parameters according PLR abolition. PLR was available in 192 (96.5%) of patients. We used a logarithmic scale for each HRV parameters. PLR was dichotomized as bilateral abolished or uni/bilaterally preserved. Boxplots represent the median and interquartile range with whiskers representing $1.5 \times$ IQR. HR: heart rate; SDNN: standard deviation; RMSSD: Root Mean Square of Successive Differences; pNN50: percentage of the number of successive differences larger than a 50 ms. VLF: very Low frequency; LF: low frequency; HF: high frequency; CSI: CardioSympathetic Index; CVI: CardioVagal Index; SD1: standard deviation of the Poincaré plot orthogonal to the identity line; SD2: standard deviation of the Poincaré plot along the identity line; RCMSE: refined composite multiscale entropy; DFA α 1: detrended fluctuation analysis over short time; DFA α 2: detrended fluctuation analysis over long time.

negative results could also indicate that HRV parameters better track changes of ANS activity related to brainstem impairment, hence their poor predictive performances. ANS dysfunction, and notably the dysfunction related to cortical lesions, might be better captured by the assessment of bilateral brain–heart interactions relying on both HRV and EEG power as we have recently described³⁶ and as it was shown in patients with disorders of consciousness.⁴⁵

Our study presents several strengths. In the largest sample of patients to date, we investigated ANS dysfunction after CA using a comprehensive set of HRV markers together with a multimodal approach (EEG, SSEP, NSE, and PLR) and long-term outcome assessment. Our original approach allowed us to characterize ANS dysfunction and to suggest a dose–effect association with HIBI severity as reflected by EEG patterns. We also demonstrated a clear relationship with patient’s neurological prognosis within a multimodal frame, as recommended by the latest guidelines. We included in- and out-of-hospital CA, suggesting that our results are widely generalizable, excluding patients that presented atrial fibrillation during ECG recording. We also use the best CPC, to avoid considering patients who recovered consciousness after CA and subsequently died from non-neurological causes, as poor neurological outcome.

Lastly, several potential confounding factors of HRV analysis such as sedation during EEG/ECG recording and betablockers use before ICU admission were assessed and were not found to influence our results.

Our study presents some limitations; This is a retrospective and single-center study, subject to biases inherent to this design. We thus cannot exclude the risk of self-fulfilling prophecy, although HRV parameters were not available for the physicians and thus not considered in the neuroprognostication algorithm. The study was also conducted over a relatively long period of time, but with relatively few changes in care practices over time. We excluded patients with atrial fibrillation (27/240 patients, 11%), which may limit the generalizability of our results to all CA patients. We only assessed PLR dichotomously and do not have quantitative automated pupillometry data. We also did not collect brain imaging data, allowing us to document lesions in the different ANS centers and modulating areas. Nevertheless, imaging data following CA highlight that HIBI is characterized by diffuse and extensive brain injury predominant in cortical and basal ganglia areas.²⁷ Moreover, neurophysiological tools are functional biomarkers of brain injury, while imaging are structural biomarkers of brain injury.⁴⁶ Thus, it is possible that the hypothesized

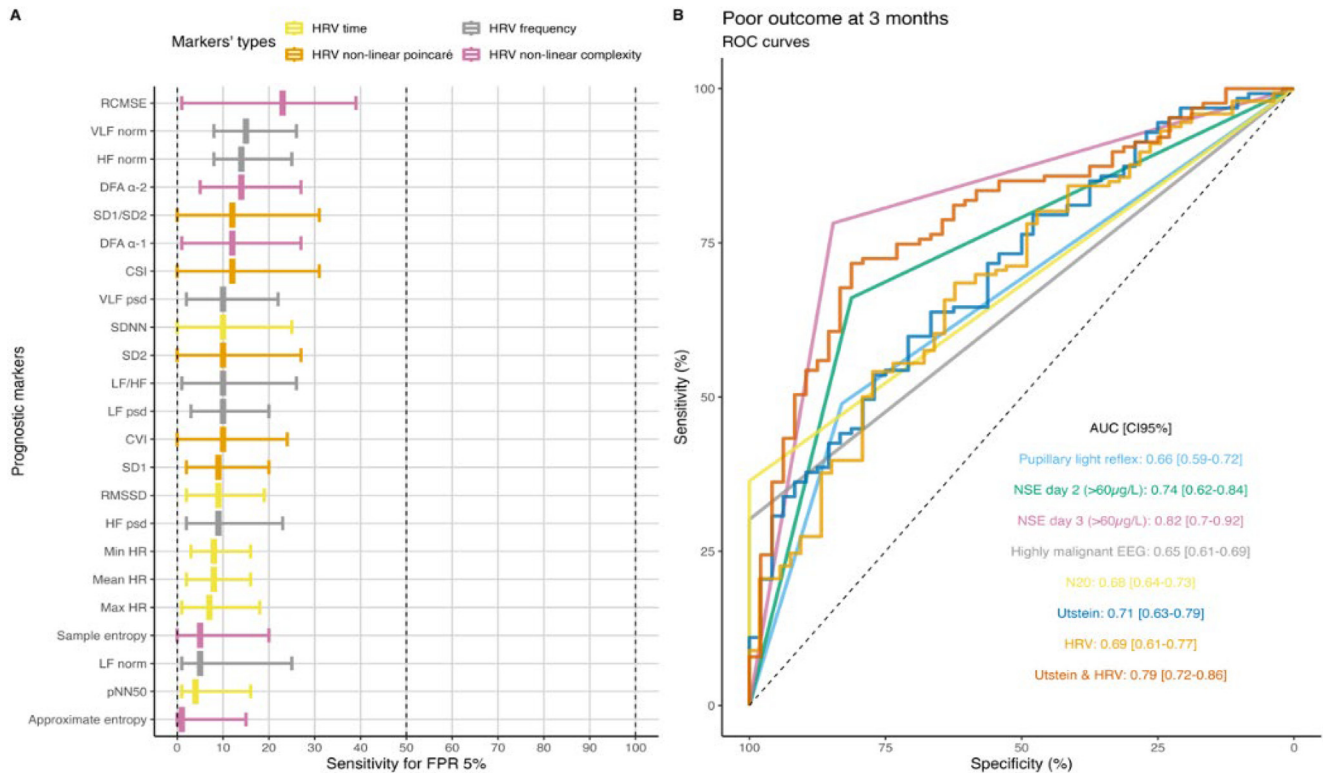


Fig. 3 – Prognostic performance of HRV parameters and others neuroprognostication tools. A. Sensitivity of each HRV indices for thresholds corresponding to a false-positive rate < 5%, as recommended in the recent European guidelines, with their 95% confidence interval (CI95%). B. AUC of each usual neuroprognostication markers and of a combination of different HRV parameters (i.e., SDNN, LF, SD2, SD1/SD2, CVI, DFA a2 and RCMSE) selected based on bilateral stepwise regression. In case of missing data, analyses were performed on complete-case data. AUC: area under curve; NSE: neurone-specific enolase, HRV: heart rate variability.

brainstem dysfunction is functional rather than structural. We did not assess the HRV parameters according to other potentials confounding factors, like vasopressors infusion during EEG/ECG recording. Despite this, EEG/ECG recordings were obtained at a median delay of 3 days, post-resuscitation shock being often resolved at this time.¹ Thus, these results are exploratory, and need to be confirmed in a larger prospective study.

Conclusion

In comatose patients after CA, certain time–frequency (VLF, LF and LF/HF ratio) and non-linear domain HRV parameters abnormalities are associated with poor neurological outcome at 3 months, abnormal PLR and EEG severity, arguing for an ANS dysfunction at the acute stage. Some of these HRV markers could be used for poor outcome prediction with a high specificity despite a low sensitivity, and seems to improve existing clinical prognostic markers.

Ethics approval and consent to participate

Data collection was approved by the Ethics Committee of the French Intensive Care Society (#CESRLF_12-384 and 20–41).

Availability of data and materials

Data could be available if request to corresponding author, to a reasonable extent.

CRediT authorship contribution statement

Sarah Benghanem: Writing – review & editing, Writing – original draft, Resources, Methodology, Data curation, Conceptualization. **Tarek Sharshar:** Writing – review & editing, Conceptualization. **Martine Gavaret:** Writing – review & editing, Validation, Data curation.

Florence Dumas: Data curation. **Jean-Luc Diehl:** Writing – review & editing. **Nicolas Brechot:** Writing – review & editing. **Fabien Picard:** Writing – review & editing, Data curation. **Diego Candia-Rivera:** Methodology, Formal analysis. **Minh-Pierre Le:** Writing – review & editing. **Frederic Pène:** Writing – review & editing, Validation, Supervision, Funding acquisition, Data curation, Conceptualization. **Bertrand Hermann:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.resuscitation.2024.110294>.

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