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Heart rate complexity: An early prognostic marker of patient outcome after cardiac arrest

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HIGHLIGHTS

- Fifteen minutes ECG recording provides accurate patients' outcome prediction on the first day of coma.
- Heartrate complexity provides an easy-to-measure prognostic marker in comatose patients after cardiac arrest.
- Coma outcome prediction based on heartrate variability is non invasive prognostic marker suitable for clinical practice.

ABSTRACT

Objective: Early prognostication in comatose patients after cardiac arrest (CA) is difficult but essential to inform relatives and optimize treatment. Here we investigate the predictive value of heart-rate variability captured by multiscale entropy (MSE) for long-term outcomes in comatose patients during the first 24 hours after CA.
Methods: In this retrospective analysis of prospective multi-centric cohort, we analyzed MSE of the heart rate in 79 comatose patients after CA while undergoing targeted temperature management and sedation during the first day of coma. From the MSE, two complexity indices were derived by summing values over short and long time scales (CI_s and CI_l). We splitted the data in training and test datasets for analysing the predictive value for patient outcomes (defined as best cerebral performance category within 3 months) of CI_s and CI_l.
Results: Across the whole dataset, CI_l provided the best sensitivity, specificity, and accuracy (88%, 75%, and 82%, respectively). Positive and negative predictive power were 81% and 84%.
Conclusions: Characterizing the complexity of the ECG in patients after CA provides an accurate prediction of both favorable and unfavorable outcomes.
Significance: The analysis of heartrate variability by means of MSE provides accurate outcome prediction on the first day of coma.

1. Introduction

Cardiac arrest (CA) represents a major global health problem (Gräsner and Bossaert, 2013). The "chain-of-survival," including early recognition and bystander cardiopulmonary resuscitation, early defibrillation, advanced life support, and standardized post-resuscitation care, has increased the number of survivors after cardiac arrest, the majority of whom remain comatose due to hypoxic-ischemic brain injury (Perkins et al., 2015). The use of targeted temperature management (TTM), with a target temperature between 33 °C and 36 °C during 12–24 hours for comatose patients after CA, is recommended to improve chances of survival and neurological outcomes, and to reduce global ischemia and reperfusion injury processes (Bernard et al., 2002).

Early prognostication of patients after CA is essential to guide clinical care to, for instance, avoid inappropriate withdrawal of life-sustaining treatment in patients with a chance to recover. In current clinical practice, prognostication is based on repeated clinical

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and para-clinical examination (comprising electroencephalography, evoked potentials, and serum markers) over the first days of coma and especially after the end of TTM, which can affect prognostication accuracy (Cronberg et al., 2020). Even with all these tools and brain imaging combined, prognosis remains uncertain for the majority of these patients (Bongiovanni et al., 2020; Moseby-Knappe et al., 2020). Heart rate variability (HRV) has emerged as potential new prognostic marker for predicting patients' outcome after CA (Carney et al., 2005; Chen et al., 2009; Dougherty and Burr, 1992; Lombardi and Mortara, 1998; Tiainen et al., 2009).

HRV is a non-invasive method to assess the activity of the autonomic nervous system (ANS) (Berntson et al., 1997; Riganello, 2016) and central autonomic network (CAN) based on analysis in time, frequency, or non-linear domain of the Electrocardiography (ECG) tachogram (ie, the series of time-intervals between consecutive heart-beats). The CAN is an integrative model described by Benarroch (Benarroch, 2007) where the neural and heart functions are involved and functionally linked in affective, cognitive, and autonomic regulation. HRV reflects the activity of physiological factors modulating the heart rhythm (Shaffer and Ginsberg, 2017) and its adaptation to changing conditions (Carney and Freedland, 2009; Garan, 2009). As in healthy conditions, the heart rate time series have a complex spatial and temporal structure, the analysis based on metrics derived from information theory suits the non-linearity of the tachogram at multiple time scales well (Costa et al., 2005, (Costa et al., 2006)).

Previous studies on HRV in patients with cardiovascular diseases and patients after CA have suggested that high predictability of the tachogram sequence is typically linked to poor outcome prognosis (Costa et al., 2006, 2005; Ho et al., 2011; Silva et al., 2016). Most studies so far have been conducted during a later phase after CA (after the end of TTM). A recent study was performed during TTM (Endoh et al., 2019), however it was monocentric, performed on a subset of patients with initial GSC motor score of 1, and used a very short outcome assessment (2 weeks after CA). Moreover, the study required ECG duration of 8 hours and considered 20 different HRV-related measures.

Here we investigate on the first day of coma the prognostic value of multiscale entropy (MSE), a complexity index of HRV, for predicting favorable and unfavorable outcomes (FO/UO) in patients after CA during TTM. Following previous reports linking the complexity index to the severity of clinical condition in comatose patients (Endoh et al., 2019), we hypothesize lower values of CI in patients with UO. The availability of accurate early prediction of favorable outcome alleviate the stress of lengthy waiting periods for families and –in combination with other prognostic markers- provides justification for continuation of treatment. Compared to previous studies conducted during TTM (Endoh et al., 2019), our approach is based on a considerably shorter ECG signal recording time (15 minutes, instead of 8 hours) and considers a more reliable clinical endpoint, i.e. the best Cerebral Performance Categories (CPC) within 3 months after CA which characterizes a range of neurological and cognitive disabilities. In addition, we compare the predictive value of MSE with other available predictors results including the values of time to return of spontaneous circulation (ROSC), the results of the reactivity tests and those based on bilateral median nerve somatosensory evoked potentials (SSEP) evaluation.

2. Methods

2.1. Patients and outcome definition

Seventy-nine consecutive patients (21 female, age 68 ± 9; 58 male, age 60 ± 15) from a prospectively acquired multicentric register who were admitted to the intensive care units of the Lausanne University Hospital (36), Bern University Hospital (39), Sion Regional Hospital (3), and Fribourg Regional Hospital (1) following Cardiac Arrest (CA) between January and June 2016 were included (see Supplemental Material for a complete patient descriptions). In the first 24 hours after CA, the patients were sedated by continuous infusion and bolus injections of sedative agents; all except 4 underwent targeted temperature treatment at 33 °C (n = 15) or 36 °C (n = 60).

The neurological conditions were assessed by pupillary, oculocephalic and corneal reflexes, motor reactivity, and background reactivity based on bedside electroencephalographic (EEG) recordings (Tsetsou et al., 2015). Withdrawal of life sustaining therapy was performed in accordance with the European Society of Intensive Medicine guidelines (Nolan et al., 2015) after multimodal examinations including bilateral median nerve somatosensory evoked potentials (SSEP) evaluation in some patients.

The clinical outcome was defined based on the best CPC (Booth et al., 2004) assessed during hospitalization and at 3 months with a semistructured phone call. A favorable outcome corresponded with CPC scores of 1 or 2, or if the neurological assessment during hospitalization was considered equivalent to such a score. An unfavorable outcome corresponded to an assessment within 3 months that was, at best, equivalent to a CPC of 3, 4, or 5.

2.2. ECG acquisition and entropy computation

Fifteen minutes of electrocardiographic activity were recorded during TTM by means of electrodes applied on the chest at a sample rate of 1024 Hz. The tachogram (the series of consecutive intervals between heartbeats) was extracted from the electrocardiogram through a custom MATLAB script (https://ch.mathworks.com/matlabcentral/fileexchange/72-peakdetect-m/content/peakdetect.m) and visually inspected for possible missed heartbeats. Interpolation was used to correct eventual ectopic beats (Choi and Shin, 2018). The MSE (Costa et al., 2005) analysis was performed to quantify the complexity of the non-linearity and non-stationary properties of the signal over different time scales τ. The method involves the construction of coarse-grained interbeat-interval time series and the quantification of the degree of irregularity of each of these (Fig. 1). Interbeat intervals ('RR') refer here to the number of data points separating two 'R' peaks of the 'QRS' complex in the ECG. Different time series were then constructed by averaging the interbeat-interval /tachogram's data points within non-overlapping windows of increasing length τ (1–10). Finally, the Sample Entropy (SampEn)(Richman et al., 2004) was applied for each coarse-grained construct. The purpose of SampEn is to identify patterns in a time series and quantify their degree of predictability or regularity. The SampEn measure shows consistency over broad ranges of data length (N). The dimensional phase space m and the tolerance for accepting matches of two patterns r were set to $m = 2$ and $r = 0.2$. For the analysis we used the Kubios HRV Advanced Analysis software version 3.1 (Tarvainen et al., 2014).

The complexity index of the MSE is calculated as the area under the SampEn time scale curve and provides insights into the integrated complexity of a system over a range of time scales of interest. The summations of quantitative SampEn values over time scales 1 to 5 and over time scales 6 to 10 represent the complexity indices calculated in short (CI_s) and long time scales (CI_l), respectively. They are related to the parasympathetic and sympathetic nervous systems, respectively (Costa et al., 2005; Silva et al., 2016).

2.3. Statistical analysis

Complexity indices of patients with both FO and UO were compared based on the Mann-Whitney exact test. Effect size was calcu-

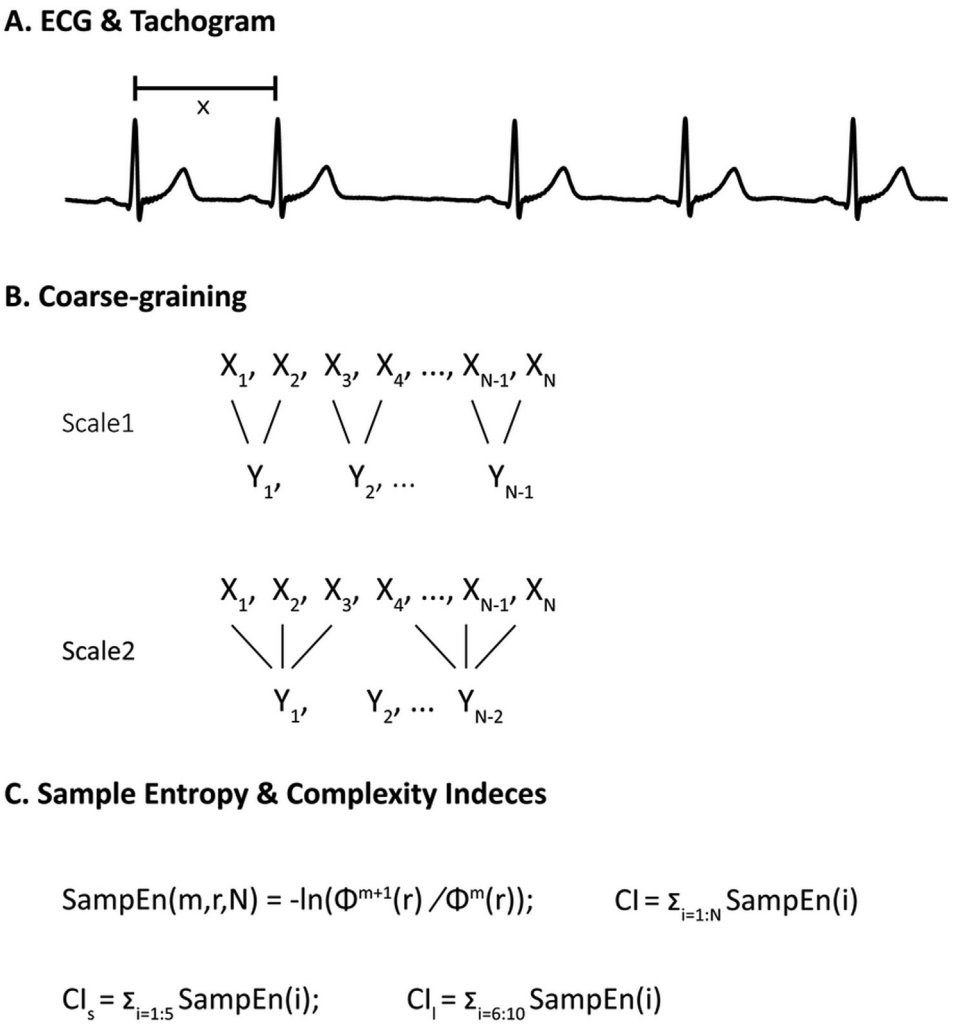

Fig. 1. Multiscale Entropy Schematic. **a)** From the ECG, the peak R of the ECG complex is indentified. The tachogram represents the series of RR intervals expressed in ms (x_1, x_2,x_3...). **b) Coarse-graining procedure**: From the original time series (a), new times series are constructed by averaging the data points. **c) Sample Entropy calculation:** For each time-series, the entropy is based on the ratio ϕ^{m+1}/ϕ^{m}. In a sequence of length N, considering a value of tolerance r, ϕ^{m} is the probability that two sequences are similar for m points, and ϕ^{m+1} is the probability that two sequences are similar for m + 1 points. Maximum regularity corresponds to $\phi^{m+1}/\phi^{m} = 1$ and a Sample Entropy of 0. For values of this ratio less than 1, the entropy increases. **Complexity Index:** summations of the quantitative values of the Sample Entropy of *N* coarse-grained scales. ECG: Electrocardiography; RR: number of data points separating two 'R' peaks of the 'QRS' complex in the ECG; CI_s: Complexity index in short time scales; CI_l: Complexity index in long time scales. ϕ^{m} : probability that two sequences will match for m samples.

lated as the absolute value of $Z/\sqrt{(N)}$ where Z is the Z-statistic of the statistical test, and N is the total number of subjects. The effect size results were considered as follows: r < 0.1, not significant; 0.1 ≤ r < 0.3, low; 0.3 ≤ r < 0.5, medium; r > 0.5, high. The prediction accuracy for patient outcomes was analysed based on the Receiver Operating Characteristic (ROC) curve (Mandrekar, 2010). For determining a threshold of MSE values we split the data in training and test datasets with random assignment. The complexity index threshold for predicting patient outcome was based on the highest accuracy of the training dataset and then used for evaluating the prediction results in the test dataset.

In addition, we computed the prediction accuracy of available clinical scores as binary variables based on the presence or absence of the SSEP and the presence or absence of evidence of a reactive EEG. Based on the values of time to return of spontaneous circulation (ROSC), we derived a ROC curve and evaluated the predictive performance of patient outcome similarly to the analysis performed on the complexity indices.

3. Results

Forty-three of the 79 patients had a favorable outcome (54.4%). The difference between patients with FO and UO was significantl for both CI_s (Mann-Whitney exact test: z = -3.514, p < 0.0001, r = 0.40) and CI_l (Mann-Whitney exact test: z = -5.325, p < 0.0001, r = 0.60).

Based on the whole dataset, both indices showed prognostic value with an area under the ROC curve of 0.85, 95% CI [0.75–0.94] for CI_l and 0.73, 95% CI [0.62–0.84] for CI_s. (Fig. 2). The highest accuracy in the training dataset (N = 40) was obtained with a threshold of CI_l = 4.93. Based on this value, we obtained an accuracy of 78%, corresponding to 18 correctly predicted FOs (out of 20 total) and 13 correctly predicted UOs (out of 20 total) (Fig. 3, left column). Using the same threshold in a separate test group (N = 39), prediction results generalized well with an accuracy of 87%, corresponding to 20 correctly predicted FOs (out of 23 total) and 14 correctly predicted UOs (out of 16) (Fig. 3, right column).

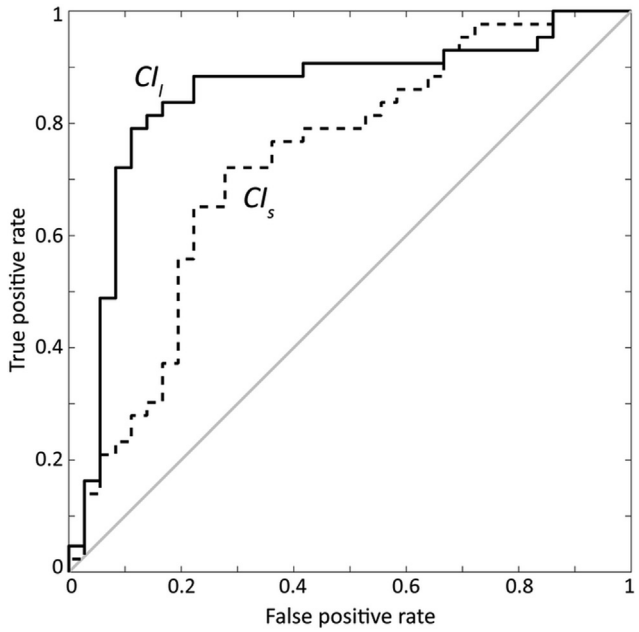

Fig. 2. Receiver Operating Characteristic (ROC) curve. The ROC curve represents the plot of sensitivity (abscissa) vs 1-specificity (ordinate). The diagonal (grey line) represent the random classification and divide the space into good classification results (above the diagonal) and bad results (below the diagonal). In the figure the ROC curve for CI_l (continuous line) and for CI_s, (dashed line). CI_s: Complexity index in short time scales; CI_l: Complexity index in long time scales.

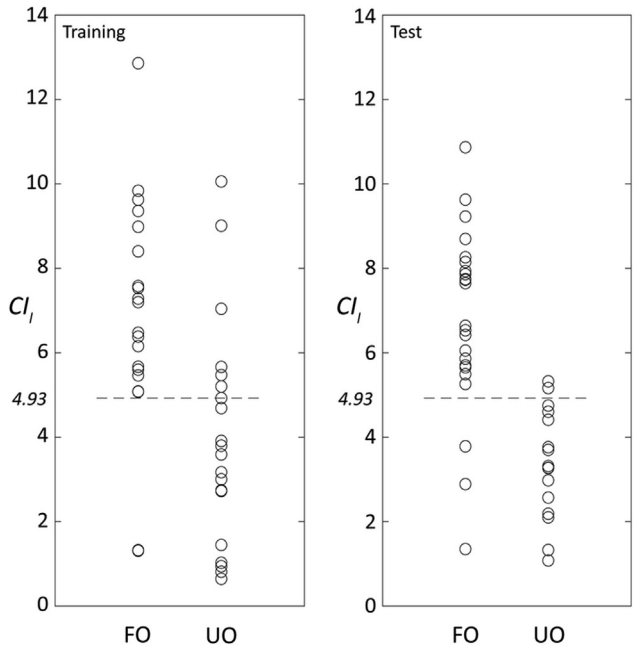

Fig. 3. CI_l and prediction results for favorable and unfavorable outcomes in the training and test datasets (left and right columns respectively). The dashed line is the CI_l value that provides the highest accuracy in the training dataset. FO: Favorable outcome; UO: Unfavorable outcome; CI_s: Complexity index in short time scales; CI_l: Complexity index in long time scales.

Table 1 summarizes the prediction results based on the training and test dataset where we refer to TP and TN the correctly predicted patients with favourable and unfavourable outcome respectively. In this context we refer to sensitivity as the ratio of correctly predicted patients with favourable outcome, and specificity as the ration of correctly predicted patients with unfavourable outcome (although please note that in many studies th UO is considered 'positive').

Additionally, we considered the prediction based on each of the available clinical scores (Table 1). The best prediction results were based on reactivity, available for n = 57 patients, with an accuracy of 88%; 29 of 33 patient FOs and 21 of 24 patient UOs were correctly predicted. The SSEP was only available for n = 31 patients. When binaring the results of the SSEP as present or absent we obtained correct prognostication in 77% of patients, indicating that both the presence and absence of SSEP are indicative of chances of having favourable and unfavourable outcome respectively. The prediction performance based on the time to ROSC was computed based on the same ROC analysis of the complexity indices by considering first the best ROSC threshold value in the training dataset. The highest accuracy was obtained for a ROSC threshold value of 20 minutes. Overall across training and test datasets, we obtained correct outcome prediction in 34 patients with favourable outcome and 23 patients with unfavourable outcome, i.e. an accuracy of 72% (Table 1).

4. Discussion

We investigated the HRV in comatose patients during the first 24 hours after cardiac arrest by quantifying the unpredictability of the heart rate over time. From 15-minute ECG recordings, we calculated the CI in two different aggregations of coarse-grained time scales: the CI_s (ie, the sum of SampEn for time scales 1 to 5) and CI_l (ie, the sum of SampEn for time scales 6 to 10) related, respectively, to the parasympathetic and sympathetic nervous systems (Costa et al., 2005; Silva et al., 2016). Both CI_s and CI_l were significantly different between FO patients and UO patients and allowed for discrimination between them. By chosing an appropriate threshold value of CI_l, we reached an 82% accuracy with a sensitivity and specificity of 88% and 75%, respectively (Table 1).

The HRV-based prediction is comparable to those based on EEG background reactivity (Table 1), though the comparison is partially confounded by the different number of patients for which the scores are available. The HRV-based prediction presents the advantage of being quantitative (and thus more objective) and does not require special equipment. Other methods for prediction of recovery (clinical examination, pupillometry, EEG, and imaging) produce similar accuracy, depending on timing of examination (Sandroni et al., 2020; Wagner et al., 2020), but frequently take place later in the course.

Although 24 hours after coma onset is too early for taking the decision of withdrawal of life support, especially based on one diagnostic test only, early HRV is reasonably accurate to predict a good recovery, which is in contrast to most other studies, which focus on unfavorable outcome. Similar to EEG reactivity, in the clinical situation where the family is uncertain of the patient's wish to continue invasive life support for an unpredictable prognosis, this piece of information can help clinicians and family to agree on a shared decision regarding therapeutic goals. Further, studies on neurological prognostication are often biased since comatose survivors of cardiac arrest dying form cardiac causes early in their course are usually classified in the unfavorable outcome group, even if they would have had a late awakening. Early HRV might help improving accuracy of multimodal prognostication by adding information of a potential good neurological recovery.

Our results are consistent with previous evidence of lower values of HRV in comatose patients with UO compared to those with the FO when the HRV was evaluated on 30-minute ECG recordings after return to normal temperature upon suspension of the TTM (Hopfe et al., 2009). In another recent study (Endoh et al., 2019), non-linear analysis of the HRV was performed on continuous 8-

Table 1
Summary of outcome predictions. Prediction results for FO based on the CI_l, the SSEP, the EEG reactivity, and the ROSC. The EEG reactivity and CI_l provide the highest prediction scores. TP/FP/FN/TN, true positive/false positive/false negative/true negative; PPV, positive predictive value; NPV, negative predictive value. Here 'positive' and 'negative' refers to favourable/unfavourable outcome. Sensitivity and specificity are defined as TP/(TP + FN) and TN/(TN + FP) respecitively.

Predictor	*TP/FP/FN/TN*	*PPV*	*NPV*	*Sensitivity*	*Specificity*	*Accuracy*
Complexity Index	38/9/5/27	0.81	0.84	0.88	0.75	0.82
SSEP	19/7/0/5	0.73	1	1	0.42	0.77
EEG reactivity	29/4/3/21	0.88	0.88	0.91	0.84	0.88
ROSC	34/13/9/23	0.72	0.72	0.79	0.64	0.72

hour ECG recordings in comatose patients after cardiac arrest treated with TTM. Several non-linear characteristics, including the MSE, showed significant differences between patients with favorable and unfavorable outcomes as defined at fourteen days after injury. Outcome prediction was based on a combination of detrend fluctuation analysis (ie, a quantification of the scaling properties of the tachogram) and a very low frequency metric (related to the power spectrum of the RR sequence up to 0.04 Hz) of the HRV and provided sensitivity and specificity of 61% and 100%, respectively, for the prediction of unfavorable poor outcome.

Our study reports for the first time, accurate prediction of both favorable and unfavorable outcomes using a single measurement and based on short-lasting ECG recording during the first day after cardiac arrest. Our results demonstrate higher predictive performance than those based on previously reported metrics (Endoh et al., 2019; (Hopfe et al., 2009) with the advantage of a significantly shorter ECG recording time (15 minutes vs 8 hours).

4.1. The neural underpinning of heart rate variability

The fluctuations observed in the HRV result from a complex bidirectional interaction between the brain-nervous system and the heart (Riganello, 2016). Loss in variability indicates a less flexible and rapid modulation in response to environmental changes due to neurological and non-neurological disease, generally involving the ANS. The brain–heart two-way interaction is conceptualized with the central autonomic network (CAN), an integrative model describing the neural and heart functions involved and functionally linked in affective, cognitive, and autonomic regulation (Riganello, 2016; Riganello et al., 2019; Thayer and Lane, 2009). In the CAN model, the ANS mediates the homeostatic regulation through the sympathetic and parasympathetic branches. The CAN includes the brainstem (periaqueductal grey matter, nucleus ambiguous, and ventromedial medulla), the limbic system (amygdala and hypothalamus), the prefrontal cortex (anterior cingulate, insula, and orbitofrontal and ventromedial cortices), the cerebellum, and other regions (dorsolateral prefrontal cortex, mediodorsal thalamus, hippocampus, caudate, septal nucleus, and middle temporal gyrus) that seem to be unique to the human brain (Benarroch, 2007; Lane et al., 2009). One can postulate that the presence of HRV is associated with the functional integrity of the components of the CAN, and thus a marker of less extensive structural hypoxic damages.

4.2. HRV in other pathologies

Decreasing variability of the heart rate is a marker and predictor of morbidity and mortality in several pathologies (Bianchi AM et all., 2010); (Norris et al., 2008), (Norris et al., 2006) and in critically injured patients (King et al., 2009; Ryan et al., 2011). In sedated patients with severe Disorders of Consciousness (ie, patients with Unresponsive Wakefulness Syndrome or in Minimally Conscious State) CI_l , was informative of the severity of patients' clinical condition. (Riganello et al., 2018). Following a similar trend to what we found in comatose patients, Unresponsive Wakefulness Syndrome patients had mostly values of CI_l below 4.9.

The HRV represents a powerful tool for exploring neurocardiac dysfunction in patients with cardiac and autonomic disorders, showing how non-linear dynamics, abnormal variability of the heart rate, and spectral changes in the low-frequency band can identify patients at high risk of sudden cardiac death (Huikuri and Stein, 2013). Low values of HRV have been shown to be predictive of increased mortality in post-myocardial infarction patients and heart failure patients and can predict long-term postoperative mortality (Laitio et al., 2007; Sessa et al., 2018). Altered cardiac autonomic activity, especially lower parasympathetic activity, was associated with the risk of developing Coronary Heart Disease (Liao et al., 1997) and the area under the MSE curve for time scales 6 to 20 can help to stratify the risk for the prognoses of patients with Cardiac Heart Failure (Ho et al., 2011).

5. Limitations

This study was performed on prospectively recorded datasets of patients but retrospectively analysed. The dataset was selected to eliminate the risk of analysing patients who died from "self-fulfilling prophecy" based on perceived unfavorable outcome after premature withdrawal of life support by the treatment team or by request of the families upon advanced care directives. Only patients who had withdrawal according to current guidelines were included. This induces a bias toward FO that can be seen in the relatively high percentage of patients with FO.

Multimodal assessment of prognostic markers is recommended for this patient population, though we still do not know the best weights of the different assessments or the best timing. The role of these promising HRV indices in this early clinical setting is unknown, and they might be improved by adding a late assessment, evaluating trends, and combining them with existing methods. Another problem with applicability is that cardiac arrest patients sometimes depend on an artificial pacemaker, and based on the mode, this may render HRV numbers useless.

6. Conclusions

Analysis of the HRV in terms of MSE is a non-invasive and inexpensive method based on ECG recording, an easy-to-acquire signal with an excellent signal-to-noise ratio compared to other approaches used in clinical neurophysiology (Comanducci et al., 2020). The potential for accurate prediction of long-term patient outcomes on the first day of coma encourages validation in a larger cohort to enable future clinical use. Our results show it is possible to derive accurate predictions of patient outcomes in sedated patients during TTM. This is consistent with previous reports in the same population type when analyzing the EEG during rest (Kustermann et al., 2020, (Kustermann et al., 2019)) or sensory stimuli presentation (Tzovara et al., 2016, (Alnes et al., 2021)). It adds to the increasing evidence that the first 24 hours of coma are the most informative for outcome prediction (Hofmeijer et al., 2015).

From the clinical point of view, UO can be predicted with a high degree of certainty in about 1/3 of comatose survivors of cardiac arrest, which leaves a large group of patients for whom outcomes cannot be predicted. Thus, prediction of FO based on HRV in the early course of treatment after CA would be a great advantage.

Similar to previous EEG studies, the HRV may be influenced by patient sedation level. Sedation likely reduces HRV complexity as suggested by previous reports in patient under anaesthesia (Naraghi et al., 2015). Understanding the extent to which sedation reduces the HRV and its complexity and how this depends on the severity of the clinical condition would require the inclusion of patients during the first day of coma without sedation and TTM. This is unfeasible due to current clinical guidelines. Nevertheless, the fact that sedation is administered during the first day of coma, when clinical prognostication is very uncertain, shows it is unlikely that HRV-based prediction is due to different sedative regimes or therapeutic decisions in patients, regardless of favorable or unfavorable outcome.

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

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2021.10.019.

References

Alnes Sigurd, De Lucia Marzia, Rossetti Andrea, Tzovara Athina. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma. Neuroimage 2021;245:118638. https://doi.org/10.1016/j.neuroimage.2021.118638.

Benarroch EE. The autonomic nervous system: basic anatomy and physiology. Continuum (Minneap Minn) 2007;13:13–32. https://doi.org/10.1212/01.CON.0000299964.20642.9a.

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346(8):557–63. https://doi.org/10.1056/NEJMoa003289.

Berntson GG, Bigger JT, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34:623–48.

Bianchi AM, Mendez MO, Ferrario M, Ferini-Strambi L, Cerutti S. Long-term correlations and complexity analysis of the heart rate variability signal during sleep. Comparing normal and pathologic subjects. Methods Inf Med 2010;49:479–83. https://doi.org/10.3414/ME09-02-0037.

Bongiovanni F, Romagnosi F, Barbella G, Di Rocco A, Rossetti AO, Taccone FS, Sandroni C, Oddo M. Standardized EEG analysis to reduce the uncertainty of outcome prognostication after cardiac arrest. Intensive Care Med 2020;46(5):963–72. https://doi.org/10.1007/s00134-019-05921-6.

Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA 2004;291:870–9. https://doi.org/10.1001/jama.291.7.870.

Carney RM, Blumenthal JA, Freedland KE, Stein PK, Howells WB, Berkman LF, Watkins LL, Czajkowski SM, Hayano J, Domitrovich PP, Jaffe AS. Low heart rate variability and the effect of depression on post–myocardial infarction mortality. Arch Intern Med 2005;165(13):1486. https://doi.org/10.1001/archinte.165.13.1486.

Carney RM, Freedland KE. Depression and heart rate variability in patients with coronary heart disease. Clev Clin J Med 2009;76(4 suppl 2):S13–7. https://doi.org/10.3949/ccjm.76.s2.03.

Chen W-L, Tsai T-H, Huang C-C, Chen J-H, Kuo C-D. Heart rate variability predicts short-term outcome for successfully resuscitated patients with out-of-hospital cardiac arrest. Resuscitation 2009;80(10):1114–8. https://doi.org/10.1016/j.resuscitation.2009.06.020.

Choi A, Shin H. Quantitative Analysis of the Effect of an Ectopic Beat on the Heart Rate Variability in the Resting Condition. Front Physiol 2018;9. https://doi.org/10.3389/fphys.2018.00922.

Comanducci A, Boly M, Claassen J, De Lucia M, Gibson RM, Juan E, et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. Clinical Neurophysiology 2020;131(11):2736–65. https://doi.org/10.1016/j.clinph.2020.07.015.

Costa M, Cygankiewicz I, Zareba W, Bayes de Luna A, Goldberger AL, Lobodzinski S. Multiscale complexity analysis of heart rate dynamics in heart failure: Preliminary findings from the music study. Comput Cardiol 2006:101–3.

Costa M, Goldberger AL, Peng C-K. Multiscale entropy analysis of biological signals. Phys Rev E 2005;71(2). https://doi.org/10.1103/PhysRevE.71.021906.

Cronberg T, Greer DM, Lilja G, Moulaert V, Swindell P, Rossetti AO. Brain injury after cardiac arrest: from prognostication of comatose patients to rehabilitation. Lancet Neurol 2020;19(7):611–22. https://doi.org/10.1016/S1474-4422(20)30117-4.

Dougherty CM, Burr RL. Comparison of heart rate variability in survivors and nonsurvivors of sudden cardiac arrest. Am J Cardiol 1992;70(4):441–8. https://doi.org/10.1016/0002-9149(92)91187-9.

Endoh H, Kamimura N, Honda H, Nitta M. Early prognostication of neurological outcome by heart rate variability in adult patients with out-of-hospital sudden cardiac arrest. Crit Care 2019;23:323. https://doi.org/10.1186/s13054-019-2603-6.

Garan H. Heart Rate Variability in Acute Myocardial Infarction. Cardiology 2009;114(4):273–4. https://doi.org/10.1159/000235567.

Gräsner J-T, Bossaert L. Epidemiology and management of cardiac arrest: What registries are revealing. Best Pract Res Clin Anaesthesiol 2013;27(3):293–306. https://doi.org/10.1016/j.bpa.2013.07.008.

Ho Y-L, Lin C, Lin Y-H, Lo M-T. The Prognostic Value of Non-Linear Analysis of Heart Rate Variability in Patients with Congestive Heart Failure—A Pilot Study of Multiscale Entropy. PLoS One 2011;6:e18699. https://doi.org/10.1371/journal.pone.0018699.

Hofmeijer J, Beernink TMJ, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, van Putten MJAM. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85(2):137–43. https://doi.org/10.1212/WNL.0000000000001742.

Hopfe J, Pfeifer R, Ehrhardt C, Goernig M, Figulla HR, Voss A. Investigation of Heart Rate Variability after Cardiopulmonary Resuscitation and Subsequent Hypothermia. In: Vander Sloten J, Verdonck P, Nyssen M, Haueisen J, editors. 4th European Conference of the International Federation for Medical and Biological Engineering, vol. 22, Berlin, Heidelberg: Springer Berlin Heidelberg; 2009, p. 1762–4. https://doi.org/10.1007/978-3-540-89208-3_420

Huikuri HV, Stein PK. Heart Rate Variability in Risk Stratification of Cardiac Patients. Prog Cardiovasc Dis 2013;56:153–9. https://doi.org/10.1016/j.pcad.2013.07.00.

King DR, Ogilvie MP, Pereira BMT, Chang Y, Manning RJ, Conner JA, et al. Heart Rate Variability as a Triage Tool in Patients With Trauma During Prehospital Helicopter Transport. J Trauma 2009;67:436–40. https://doi.org/10.1097/TA.0b013e3181ad67de

Kustermann T, Ata Nguepnjo Nguissi N, Pfeiffer C, Haenggi M, Kurmann R, Zubler F, et al. Brain functional connectivity during the first day of coma reflects long-term outcome. NeuroImage Clin 2020;27:102295. https://doi.org/10.1016/j.nicl.2020.102295

Kustermann T, Nguepnjo Nguissi NA, Pfeiffer C, Haenggi M, Kurmann R, Zubler F, et al. Electroencephalography-based power spectra allow coma outcome prediction within 24 h of cardiac arrest. Resuscitation 2019;142:162–7. https://doi.org/10.1016/j.resuscitation.2019.05.021.

Laitio T, Jalonen J, Kuusela T, Scheinin H. The Role of Heart Rate Variability in Risk Stratification for Adverse Postoperative Cardiac Events. Anesth Analg 2007;105:1548–60. https://doi.org/10.1213/01.ane.0000287654.49358.3a.

Lane R, Mcrae K, Reiman E, Chen K, Ahern G, Thayer J. Neural correlates of heart rate variability during emotion. NeuroImage 2009;44(1):213–22. https://doi.org/10.1016/j.neuroimage.2008.07.056.

Liao D, Cai J, Rosamond WD, Barnes RW, Hutchinson RG, Whitsel EA, Rautaharju P, Heiss G. Cardiac autonomic function and incident coronary heart disease: a population-based case-cohort study. The ARIC Study. Atherosclerosis Risk in Communities Study. Am J Epidemiol 1997;145(8):696–706.

Lombardi F, Mortara A. Heart rate variability and cardiac failure. Heart 1998;80(3):213–4. https://doi.org/10.1136/hrt.80.3.213.

Mandrekar JN. Receiver Operating Characteristic Curve in Diagnostic Test Assessment. J Thorac Oncol 2010;5(9):1315–6. https://doi.org/10.1097/JTO.0b013e3181ec173d.

Moseby-Knappe M, Westhall E, Backman S, Mattsson-Carlgren N, Dragancea I, Lybeck A, Friberg H, Stammet P, Lilja G, Horn J, Kjaergaard J, Rylander C, Hassager C, Ullén S, Nielsen N, Cronberg T. Performance of a guideline-recommended algorithm for prognostication of poor neurological outcome after cardiac arrest. Intensive Care Med 2020;46(10):1852–62. https://doi.org/10.1007/s00134-020-06080-9.

Naraghi L, Peev MP, Esteve R, Chang Y, Berger DL, Thayer SP, Rattner DW, Lillemoe KD, Kaafarani H, Yeh DD, de Moya MA, Fagenholz PJ, Velmahos GS, King DR. The influence of anesthesia on heart rate complexity during elective and urgent surgery in 128 patients. J Crit Care 2015;30(1):145–9. https://doi.org/10.1016/j.jcrc.2014.08.008.

Nolan JP, Soar J, Cariou A, Cronberg T, Moulaert VRM, Deakin CD, Bottiger BW, Friberg H, Sunde K, Sandroni C. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive Care Med 2015;41(12):2039–56. https://doi.org/10.1007/s00134-015-4051-3.

Norris PR, Anderson SM, Jenkins JM, Williams AE, Morris Jr JA. Heart rate multiscale entropy at three hours predicts hospital mortality in 3,154 trauma patients. Shock 2008;30:17–22. https://doi.org/10.1097/SHK.0b013e318164e4d0.

Norris PR, Ozdas A, Cao H, Williams AE, Harrell FE, Jenkins JM, Morris JA. Cardiac uncoupling and heart rate variability stratify ICU patients by mortality: a study of 2088 trauma patients. Ann Surg 2006;243(6):804–14. https://doi.org/10.1097/01.sla.0000219642.92637.fd.

Perkins GD, Handley AJ, Koster RW, Castrén M, Smyth MA, Olasveengen T, Monsieurs KG, Raffay V, Gräsner J-T, Wenzel V, Ristagno G, Soar J, Bossaert LL, Caballero A, Cassan P, Granja C, Sandroni C, Zideman DA, Nolan JP, Maconochie I, Greif R. European Resuscitation Council Guidelines for Resuscitation 2015: Section 2. Adult basic life support and automated external defibrillation. Resuscitation 2015;95:81–99. https://doi.org/10.1016/j.resuscitation.2015.07.015.

Richman JS, Lake DE, Moorman JR. Sample entropy. Method Enzymol 2004;384:172–84.

Riganello F. Responsiveness and the Autonomic Control–CNS Two-Way Interaction in Disorders of Consciousness. In: Monti MM, Sannita WG, editors. Brain Function and Responsiveness in Disorders of Consciousness. Cham: Springer International Publishing; 2016. p. 145–55.

Riganello F, Larroque SK, Bahri MA, Heine L, Martial C, Carrière M, Charland-Verville V, Aubinet C, Vanhaudenhuyse A, Chatelle C, Laureys S, Di Perri C. A Heartbeat Away From Consciousness: Heart Rate Variability Entropy Can Discriminate Disorders of Consciousness and Is Correlated With Resting-State fMRI Brain Connectivity of the Central Autonomic Network. Front Neurol 2018;9. https://doi.org/10.3389/fneur.2018.0076910.3389/fneur.2018.00769.s001.

Riganello F, Larroque SK, Di Perri C, Prada V, Sannita WG, Laureys S. Measures of CNS-Autonomic Interaction and Responsiveness in Disorder of Consciousness. Front Neurosci 2019;13. https://doi.org/10.3389/fnins.2019.00530.

Ryan ML, Thorson CM, Otero CA, Vu T, Proctor KG. Clinical Applications of Heart Rate Variability in the Triage and Assessment of Traumatically Injured Patients. Anesthesiol Res Pract 2011;2011:1–8. https://doi.org/10.1155/2011/416590.

Sandroni C, D'Arrigo S, Cacciola S, Hoedemaekers CWE, Kamps MJA, Oddo M, Taccone FS, Di Rocco A, Meijer FJA, Westhall E, Antonelli M, Soar J, Nolan JP, Cronberg T. Prediction of poor neurological outcome in comatose survivors of cardiac arrest: a systematic review. Intensive Care Med 2020;46(10):1803–51. https://doi.org/10.1007/s00134-020-06198-w.

Sessa F, Anna V, Messina G, Cibelli G, Monda V, Marsala G, Ruberto M, Biondi A, Cascio O, Bertozzi G, Pisanelli D, Maglietta F, Messina A, Mollica MP, Salerno M. Heart rate variability as predictive factor for sudden cardiac death. Aging (Albany NY) 2018;10(2):166–77.

Shaffer F, Ginsberg JP. An Overview of Heart Rate Variability Metrics and Norms. Front. Public Health 2017;5. https://doi.org/10.3389/fpubh.2017.00258.

Silva LEV, Lataro RM, Castania JA, da Silva CAA, Valencia JF, Murta LO, Salgado HC, Fazan R, Porta A. Multiscale entropy analysis of heart rate variability in heart failure, hypertensive, and sinoaortic-denervated rats: classical and refined approaches. Am J Physiol Regul Integr Comp Physiol 2016;311(1):R150–6. https://doi.org/10.1152/ajpregu.00076.2016.

Tarvainen MP, Niskanen J-P, Lipponen JA, Ranta-aho PO, Karjalainen PA. Kubios HRV–heart rate variability analysis software. Comput Methods Programs Biomed 2014;113(1):210–20.

Thayer JF, Lane RD. Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. Neurosci Biobehav Rev 2009;33(2):81–8. https://doi.org/10.1016/j.neubiorev.2008.08.004.

Tiainen M, Parikka HJ, Mäkijärvi MA, Takkunen OS, Sarna SJ, Roine RO. Arrhythmias and heart rate variability during and after therapeutic hypothermia for cardiac arrest. Crit Care Med 2009;37(2):403–9. https://doi.org/10.1097/CCM.0b013e31819572c4.

Tsetsou S, Novy J, Oddo M, Rossetti AO. EEG reactivity to pain in comatose patients: Importance of the stimulus type. Resuscitation 2015;97:34–7. https://doi.org/10.1016/j.resuscitation.2015.09.380.

Tzovara A, Rossetti AO, Juan E, Suys T, Viceic D, Rusca M, Oddo M, Lucia MD. Prediction of awakening from hypothermic postanoxic coma based on auditory discrimination. Ann Neurol 2016;79(5):748–57. https://doi.org/10.1002/ana.24622.

Wagner F, Hänggi M, Weck A, Pastore-Wapp M, Wiest R, Kiefer C. Outcome prediction with resting-state functional connectivity after cardiac arrest. Sci Rep 2020;10:11695. https://doi.org/10.1038/s41598-020-68683-y.