Original Article

Heart Rate Variability as an Indicator of Nociceptive Pain in Disorders of Consciousness?

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Abstract

Context. Heart rate variability is thought to reflect the affective and physiological aspects of pain and is emerging as a possible descriptor of the functional brain organization contributing to homeostasis.

Objectives. To investigate whether the short-term Complexity Index (CIs), a measure of heart rate variability complexity is useful to discriminate responses to potentially noxious and nonnoxious stimulation in patients with different levels of consciousness.

Methods. Twenty-two patients (11 minimally conscious state [MCS], 11 vegetative state/unresponsive wakefulness syndrome [VS/UWS]) and 14 healthy controls (HC) were enrolled. We recorded the electrocardiographic response and calculated the CIs before (baseline), during, and after nonnoxious and noxious stimulation. Mann-Whitney and Wilcoxon's tests were used to investigate differences in CIs according to the level of consciousness (i.e., HC vs. patients and VS/UWS vs. MCS) and the three conditions (i.e., baseline, nonnoxious, noxious). The correlation between the three conditions and the Coma Recovery Scale—Revised was investigated by Spearman's correlations.

Results. We observed higher CIs values in HC as compared with patients during the baseline ($P < 0.034$) and after the noxious stimulation ($P < 0.0001$). We also found higher values in MCS versus VS/UWS patients after the noxious condition ($P < 0.001$) and lower values in the noxious versus nonnoxious condition solely for the VS/UWS group ($P < 0.007$). A correlation was found between CIs in noxious condition and Coma Recovery Scale—Revised scores.

Conclusion. Our results suggest a less complex autonomic response to noxious stimuli in VS/UWS patients. Such method may help to better understand sympathovagal response to potentially painful stimulation in brain-injured patients. J Pain Symptom Manage 2019;57:47—56. *© 2018 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Pain, heart rate, consciousness, nociception, unresponsive wakefulness syndrome, minimally conscious state

Introduction

Pain management in patients with disorders of consciousness (DOC) remains a main issue for clinicians as this population cannot, by definition, report about their own feelings. Neuroimaging studies suggest that patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS[1–3]) could maintain primary and/or more complex cortical activation in response to noxious stimuli, but this would occur as an isolated and disconnected phenomenon preventing a conscious perception of pain.[4–7] On the other hand, cortical activation encompassing primary and

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Accepted for publication: September 19, 2018.

0885-3924/$ - see front matter
https://doi.org/10.1016/j.jpainsymman.2018.09.016

associative areas (e.g., anterior cingulate and anterior insula cortices[8–11]) together with a preserved functional connectivity between those areas[12] have been observed in patients in a minimally conscious state (MCS), suggesting the possibility of integrated conscious pain processing. However, little is known about basic pain processing linked to nociception.

A better understanding of residual nociceptive pain processing is key to properly adapt treatments in this population. Heart rate variability (HRV), a measure that does not require the person's collaboration or behavioral feedback, has been proposed as a reliable indicator of nociceptive pain processing in different studies using hypnosis or analgesia in healthy individuals.[13,14]

HRV represents the fluctuation in the time intervals between adjacent heart beats and can be analyzed in the time or frequency domain or using nonlinear methods.[15] Time domain analysis quantifies the amount of variability of the interbeat interval of the heart rate observed during a monitoring lasting from five minutes (short-term variability) to more than 24 hours (long-term variability).[16] Frequency domain analysis measures the absolute or relative amount of signal energy (i.e., power spectrum) within four component bands (ultralow frequency, very low frequency, low frequency, and high frequency[16]). The power of the component bands is estimated by fast Fourier transformation, autoregressive or wavelet analysis. Finally, the nonlinear methods are used to quantify the unpredictability and complexity of the interbeat interval series providing a global representation of autonomic nervous system functioning and complexity. Poincare plot,[17] detrended fluctuation analysi,[18] approximate entropy,[19] sample entropy,[20] and multiscale entropy (MSE)[21] are among the more applied methods of nonlinear analysis used in the HRV analysis. As the heart motion is complex and nonlinear, its fluctuation is better described by the mathematical chaos, and therefore nonlinear methods.

The HRV is thought to reflect the affective, physiological, cognitive, and behavioral aspects of pain. It is emerging as a possible descriptor of the functional brain organization contributing to homeostasis (i.e., self-regulating process by which an organism tends to maintain stability while adjusting to conditions that are optimal for survival[22]) and homeostatic responses (i.e., flexibility of the organism to organize responses to the stimuli by restoring an optimal balance[22]). The central autonomic network (CAN) has been proposed as a functional integrated model involved in the tonic, reflexive, and adaptive control of autonomic functions. In particular, the insular cortex, ventromedial prefrontal cortex, anterior cingulate cortex, and amygdala are involved in modulating cardiac sympathetic and parasympathetic outflow. They allow the integration of the cardiovascular responses related to behavior and emotion through the hypothalamic area, the parabrachial region of the dorsolateral pons, nucleus of the solitary tract, nucleus ambiguous, rostral ventrolateral medulla, and intermediolateral cell columns.[23–26] Taken together, this suggests that HRV could be a good marker of CAN regulatory system and could provide information about the brain-heart integration and behavioral control in humans. Such measurements could therefore provide interesting information about the cortical processing of stimulation in patients with DOC.

In this context, previous studies have reported HRV changes in response to simple, emotional sensory inputs such as a relative's voice or music in healthy controls (HC),[27–33] supporting the idea that basic emotions have distinct autonomic nervous system signatures. Several studies investigated HRV in DOC patients in response to emotionally valenced stimuli (in particular, lower values of heart rate entropy were found in UWS patients compared to MCS and HC, when stimulated with music structurally more complex and classified as emotionally negative).[34] On the other hand, in the frequency domain, emotionally valenced stimuli (i.e., music or mom's voice) have been associated with modifications of the normalized power of the low frequency band (nuLF) both in HC and VS/UWS patient.[35–37]

Several studies including noncommunicative patients (i.e., infants, elderly with dementia, and unconscious patients) from the intensive care suggest that autonomic responses (i.e., variation in arterial pressure, heart rate or other vital signs could be due to underlying physiologic condition, medication, and homeostatic changes) cannot be used reliably in clinic to detect and manage conscious pain as it is not specific to pain.[38,39]

Other studies have used the MSE (a nonlinear method of the HRV analysis) to investigate HRV complexity. The MSE quantifies the unpredictability of a time series derived from the original signal by the sample entropy. The time series are obtained by dividing the original signal into nonoverlapping segment of equal length, and then the mean values of data points for each segment are calculated. This operation is called coarse-graining. The sum of the entropies computed for different scales is defined by Complexity Index.[40] Low values of MSE and relative Complexity Index were correlated with poor outcome and risk of death in brain injury patients .[41,42] Loss of complexity in the two-way brain-heart interaction suggests a low adaptive response to the environment/external stimuli.[43–45]

The objective of this retrospective study was to investigate whether short-term Complexity Index (CIs; sum of MSE coarse-graining scales from 1 to 5) is useful to discriminate different levels of stimulation (nonnoxious vs. noxious stimulation) in VS/UWS and MCS patients.

Based on the literature, we expected to find higher values of CIs in HC compared to MCS patients and higher values in MCS compared to VS/UWS patients, indicating a lower complex autonomic response to external stimuli. Consequently, we expected 1) higher values in CIs response in HC as compared to patients with DOC, particularly after the noxious stimuli; 2) higher values in MCS versus VS/UWS patients, particularly after the noxious stimuli; and 3) a difference between nonnoxious and noxious conditions, in particular for the VS/UWS group indicating a poor adaptive response to the noxious stimulus in this population.

Methods

Participants

The population was part of a multicentric study[46] including patients from the intensive care and the neurology units of the university hospital of Liège as well as from the neurorehabilitation centers and nursing homes that are part of the Belgian federal network for vegetative and minimally conscious states. Inclusion criteria were 1) age of 16 years old or more, 2) no administration of neuromuscular blockers or sedation within the 24 hours of enrollment, 3) the presence of periods of eye opening (indicating wakefulness and rest cycles), 4) a diagnosis of VS/UWS or MCS, based on repeated behavioral assessments performed using the Coma Recovery Scale—Revised (CRS-R;[47]). Exclusion criteria were 1) documented history of prior brain injury, 2) premorbid history of developmental, psychiatric, or neurologic illness resulting in documented functional disability up to time of the injury, 3) upper limb contusions, fractures, or flaccid paralysis; and 4) patients mechanically ventilated. A group of healthy age-matched participants was also included for comparison analyses. None of them had any neurological or psychiatric disease history and they were free of pharmacological drugs. Participants were asked not to consume alcohol, consume nicotine, or drink coffee before the study session.

Patients clinically unstable, under treatment with neuroactive drugs and beta-blockers or with concurrent systemic disorders or evidence of recurrent pain were not admitted to the study. All patients were nursed at least 30 minutes before the study protocol.

Procedure

Electrocardiographic activity was recorded in three different conditions: 1) baseline, 2) nonnoxious stimulation, and 3) noxious stimulation (as used in the study by Chatelle et al.[46]). During the first condition (i.e., baseline), we recorded the patient's spontaneous activity during five minutes. During the second condition (i.e., nonnoxious stimulation), we applied five rapid taps on the top of the patient's right and left shoulder (i.e., two stimuli). Each stimulation lasted five seconds, and the stimuli were separated by 10 seconds and followed by five minutes of rest. Finally, during the third condition (i.e., noxious stimulation), we applied pressure on the nail bed of the middle finger of the right and left hand (i.e., two stimuli) using a Newton-meter (Force Dial, FDN 200 model; Greenwich, CT; www.wagnerinstruments.com) that allows the examiner to gauge the amount of pressure applied to the patient.[48] As for the nonnoxious condition, the stimuli were administered for five seconds,[47] and they were separated by 10 seconds and followed by five minutes of rest.

Each subject's electrocardiographic activity was monitored by mean of two electrodes applied on the chest using a sampling rate of 128 Hz. The procedure for the HRV data collections was done according to the guidelines of Task Force of European Society of Cardiology and North American Society of Pacing and Electrophysiology.[15]

To ensure a sufficient level of arousal, each condition was administered while patients showed spontaneous eye opening. The entire procedure lasted less than 20 minutes. Patients' level of consciousness was randomly assessed 15 minutes before or after this procedure with the CRS-R.[47] The CRS-R consists of 23 hierarchically arranged items that comprise six subscales addressing arousal, auditory, visual, motor, oromotor/verbal, and communication functions. The lowest item on each subscale represents reflexive activity, whereas the highest item represents cognitively mediated behaviors. We did not apply the additional noxious stimulation requested in the motor subscale of the CRS-R but instead scored this item using the experimental noxious stimulation already applied.

Participants were comfortably lying either on a wheelchair or in a near-seated position in bed with minimal transient noises.

Data Extraction

The tachogram (the series of consecutive intervals between heart beats) was extracted from the electrocardiogram, and the MSE was analyzed for the baseline (300 seconds), the nonnoxious, and noxious conditions (starting at the onset of the first stimulus; for a total duration of 300 seconds) using the HRV Advanced Analysis software.[49] The 300 seconds of baseline represents the gold standard for the short-term HRV analysis. The MSE was computed to measure the complexity of the nonlinear and nonstationary signal.[21]

The calculation of the MSE was based on the benchmark from sample entropy analysis,[50] in which only single scale was analyzed (Equation 1).

$$S_E(m, r, N) = -\ln\frac{\phi^{m+1}(r)}{\phi^{m}(r)} \quad (1)$$

S_E: sample entropy; *m*: distance between time series points to be compared; *r*: radius of similarity; *N*: length of the time series; ϕ: probability that points *m* distance apart would be within the distance *r*.

Sample entropy has been suggested to be independent of data length and shows consistency over broad ranges of possible data sequence length to be compared (m), tolerance (r), and total RR (interval from the R peaks of ECG QRS complex) interval data length (*N*[51,52]).

MSE[53] extended the concept of sample entropy, evaluating the complexity of physiological signals on multiple time scales. It comprises two steps: 1) coarse-graining the signals into different time scales (Scheme 1) quantify the degree of irregularity in each coarse-grained time series using sample entropy; 2) the entropy is calculated as a function of scale, providing a measure of information richness embedded in different time scales.

Once the time scales of interest (i.e., range) have been identified, the area under the sample entropy time scale curve, known as the CI, can be calculated (Equation 2).

$$C_I = \sum_{i=1}^{N} S_E(i) \quad (2)$$

C_I summations of quantitative values of the sample entropy of *N* coarse-grained scale:

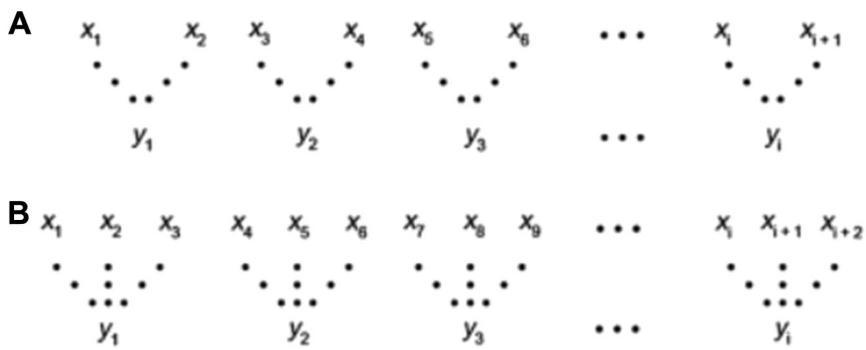
The CI provides insight into the integrated complexity of the system, over the time scales of interest. The summations of quantitative values of Scale 1−5 or Scale 6−20 represent the complexity calculated in short- and long-time scales, respectively.[53]

For the MSE analysis, the parameters m and r were set to 2 and 0.15, respectively, as used in previous studies.[53,54] Given the length of the sequence analyzed (i.e., 300 seconds), the coarse-grained series was calculated for time scale from $\tau = 1$ to $\tau = 5$ ([52]; associated with parasympathetic nervous activity and respiratory modulation[53]), and the CIs was extracted for the analysis.

Heart rate interbeat is under the influence of sympathovagal regulation as well as of the baroreflex and chemoreflex control, hormonal regulation, and others mechanisms responsible for the HRV complexity.[55] Pathological conditions impaired this complex system damaging the capacity of the system to respond to internal and external stressors. The CIs reflects the complexity of the system (larger complexity reflects a higher functionality of the system); therefore we should observe lower values of CIs in patients with more severe pathological condition.

Statistical Analyses

The normal distribution of the data was tested by the Shapiro-Wilk normal test[56,57] and the homogeneity of variance with Levene's test. At the Shapiro-Wilk normality test, the data showed a normal distribution of the data ($0.075 \leq P \leq 0.975$). As the homogeneity of variance was violated in our sample (Levene'test, $P > 0.05$), nonparametric statistics were used. HC and DOC groups were compared for the baseline, nonnoxious, and noxious stimuli using the Mann-Whitney exact test. VS/UWS and MCS patients were also compared with the three experimental conditions using Mann-Whitney exact tests. For each group, nonnoxious versus noxious conditions were compared using Wilcoxon exact tests. The effect size *r* was calculated as absolute value of $Z/\sqrt{(N)}$ where Z is the Z-statistic[58,59] of the statistical test and *N* is the total number of subjects. The effect size results were considered: $r < 0.1$ not significant; $0.1 \geq r < 0.3$ low; $0.3 \geq r < 0.5$ medium;



Scheme 1. Coarse-graining procedure. (A) Scale 2, (B) scale 3, where the "*x*" series is the original time series and the "*y*" is the new time series constructed through an averaging of the data points.

$r > 0.5$ high.[60] The correlation between CRS-R and CIs in the three different conditions was tested using the Spearman correlation test. The significance was set to $P < 0.0083$ (corrected for multiple comparison). The statistical analyses were performed with SPSS statistical software (IBM, Armonk, NY).

Results

Population

We included 22 patients of whom 11 were in VS/UWS (age range: 16–82 years; mean age 52 ± 23; seven males) and 11 MCS (age range: 23–75 years; mean age 53 ± 14; eight males) according to the behavioral assessment performed using the CRS-R. Etiology was traumatic ($n = 7$), intracerebral hemorrhage ($n = 4$), postanoxic ($n = 3$), and others ($n = 8$). Ten patients were assessed in acute stage (i.e., less than one month after injury) and 12 in subacute to chronic stage (range: one month to three years). Fourteen age-matched HC were also included in the study (eight females, mean age: 50 ± 20 years, age range: 22–83 years; see Table 1). None of the participants showed signs of overweight or underweight.

We observed higher CIs values in HC as compared with DOC in the noxious conditions (HC: median = 10.6; mean = 10.4 ± 1.4; DOC: median = 6.7; mean = 6.4 ± 2.4). Higher CIs values were also observed in HC when compared with MCS (median = 8.8; mean = 7.9 ± 1.6) and VS/UWS (median = 4.9; mean = 4.9 ± 2.2) separately in the noxious condition. Higher CIs values in MCS as compared with VS/UWS were found in the noxious condition (see Table 2 and Fig. 1). Within-subject analyses highlighted lower CIs values during the noxious condition (median = 4.9; mean = 4.9 ± 2.2) as compared with the nonnoxious (median = 8.1; mean = 6.7 ± 3.5) condition only in the VS/UWS group (Wilcoxon's test $z = -2.401$, $P = 0.007$, $r = -0.72$; see Fig. 1).

Correlation was observed between CRS-R and CIs in noxious condition (rho = 0.601, $P = 0.002$), whereas no correlations were found between the CRS-R and CIs in the baseline (rho = 0.304, $P = 0.084$) and in non-noxious conditions (rho = 0.235, $P = 0.146$; see Fig. 2).

Table 1
Demographic Information

Gender	CRS-R	Age	Status	Etiology	Detail	Days After Onset
Female	5	26	VS/UWS	Traumatic	Traumatic	441
	4	73		Nontraumatic	Hemorrhagic	31
	4	51		Nontraumatic	Other	36
	4	70		Nontraumatic	Other	13
Male	5	82		Nontraumatic	Other	15
	2	37		Nontraumatic	Anoxic	283
	2	75		Nontraumatic	Other	23
	4	75		Traumatic	Traumatic	96
	5	16		Nontraumatic	Anoxic	618
	4	43		Nontraumatic	Anoxic	32
	5	21		Traumatic	Traumatic	171
Female	11	41	MCS	Traumatic	Traumatic	26
	9	71		Nontraumatic	Hemorrhagic	25
	14	48		Nontraumatic	Other	66
	9	43		Nontraumatic	Other	9
Male	5	53		Traumatic	Traumatic	19
	9	69		Nontraumatic	Hemorrhagic	31
	12	56		Nontraumatic	Other	15
	7	60		Traumatic	Traumatic	19
	8	23		Traumatic	Traumatic	328
	6	48		Nontraumatic	Hemorrhagic	27
	8	75		Nontraumatic	Other	48
Female		23		Healthy controls		
		83				
		33				
		31				
		50				
		54				
		81				
		75				
Male		51				
		23				
		22				
		60				
		59				
		56				

CRS-R = Coma Recovery Scale–Revised; VS/UWS = vegetative state/unresponsive wakefulness syndrome; MCS = minimally conscious state.

Table 2
Test Results for Comparisons Between Groups and Different Conditions

Mann-Whitney *P* Exact Test	HC Versus DOC	HC Versus MCS	HC Versus VS/UWS	MCS Versus VS/UWS
Baseline	**ns**	ns	**ns**	ns
Nonnoxious	ns	ns	ns	ns
Noxious	**z = −4.108** ***P* < 0.0001** **r = −0.61**	**z = −1.354** ***P* = 0.001** **r = −0.28**	**z = −4.062** ***P* < 0.0001** **r = −0.85**	**z = −2.988** ***P* = 0.001** **r = −0.63**

HC = healthy controls; DOC = disorders of consciousness; MCS = minimally conscious state; VS/UWS = vegetative state/unresponsive wakefulness syndrome. Bold = $P < 0.05$; Z = Z statistical test value; P = level of significance; r = effect size ($r < 0.1$ not significant; $0.1 \geq r < 0.3$ low; $0.3 \geq r < 0.5$ medium; $r > 0.5$ high).

Discussion

In this study, we investigated whether CIs is useful to discriminate different level of stimulation (nonnoxious vs. noxious stimulation) in VS/UWS and MCS patients. Based on the literature, we hypothesized that, if the CIs is a reliable marker of adaptive response (i.e., CIs values would reflect the flexibility of the CAN to respond in adaptive way to an external stimulus), we should observe 1) a difference in CIs response between HC and patients with DOC, particularly during the noxious condition, and more pronounced in patients with VS/UWS as compared to MCS; 2) a difference between MCS and VS/UWS, specifically after the noxious condition; and 3) a difference between nonnoxious and noxious condition, especially in the VS/UWS group.

As expected, we here reported a difference between HC and DOC and between VS/UWS and MCS in the noxious condition.

Those data suggest a difference in the processing of stimulation between MCS and VS/UWS patients, supporting previous neuroimaging and behavioral findings,[5,8,9,46,48,61] and a lower adaptability and responsiveness of VS/UWS to noxious stimuli.

We could not find a difference between noxious and nonnoxious conditions in HC and MCS patients where a difference could be detected in the VS/UWS group. This is in line with previous studies showing that reduced sample entropy was observed in VS/UWS patients in response to musical stimuli of higher complexity (i.e., comparing Boccherini's music ["Celebre Minuetto"] characterized by a low musical complexity with Mussorgsky's music ["One night on base mountain"] characterized by a high musical complexity[62]) while no differences were found for HC.

Higher values of CI are indicative of a more complex ANS modulation in the two-way brain-heart interaction,[62–64] and the prognostic value of the MSE has been shown to be independent of etiology.[42] The lower CIs values observed in the noxious condition as compared with the nonnoxious condition in VS/UWS might indicate a decrease of complexity in the autonomic response in these patients, to modulate

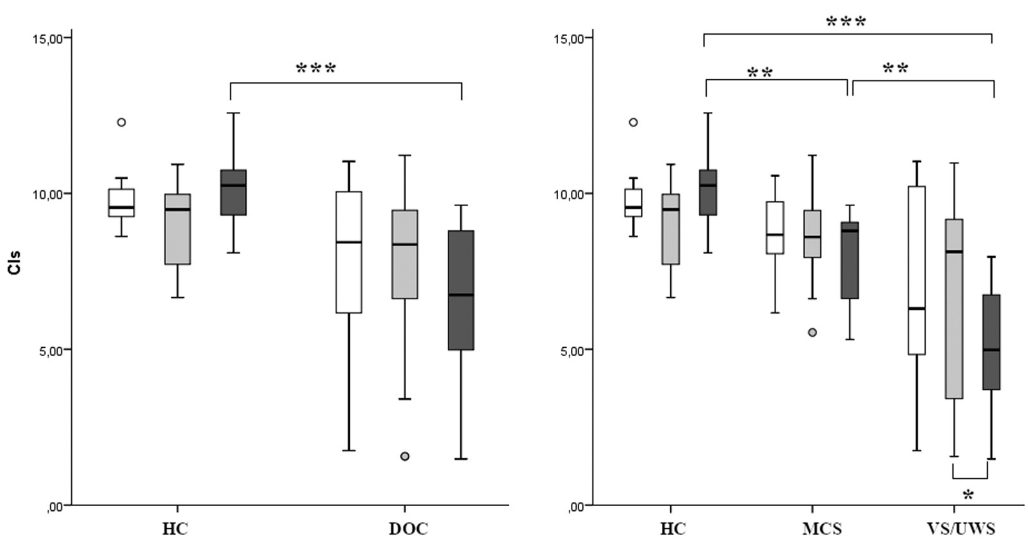


Fig. 1. Short-term Complexity Index in healthy controls (HC) and patients. On the left, CIs values for HC and all the patients (DOC), and on the right, for HC, minimally conscious state (MCS), and unresponsive wakefulness syndrome (VS/UWS) groups, in the baseline (white), nonnoxious (light gray), and noxious (dark gray) conditions. The box represents the first and third quartile, the whiskers are the 1.5 interquartile range, the black lines are the medians, and points are outliers. The asterisk (*) highlights significant differences: *$P = 0.007$; **$P = .001$; ***$P = 0.0001$.

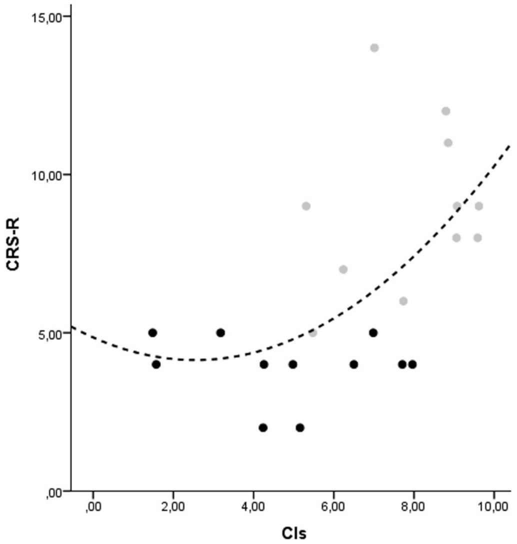


Fig. 2. Scatterplot of the Coma Recovery Scale—Revised (CRS-R) scores and the short-term Complexity Index (CIs) values in noxious condition for unresponsive wakefulness syndrome (VS/UWS; black dots) and minimally conscious state (MCS; light gray dots) patients. Dashed black line represents the quadratic trend for the group ($R^2 = 0.342$).

the response to the noxious stimulus. Supporting this idea, low CI values were associated with a worse outcome in stroke patients with stroke-in-evolution,[65] as well as high CI values were associated with a favorable outcome in acute stroke patients admitted in an intensive care unit.[45] Globally, a decrease of heart rate complexity may indicate a worsening of the patient's condition and a poor outcome.[44]

Pupillometry studies have reported that an increased autonomic activity in response to painful stimulation in HC under anesthesia was associated to an inhibition of the parasympathetic system,[66–68] supporting our assumption about the usefulness of HRV (reflecting autonomic reactivity) as a marker of the brain/heart interaction in DOC.

If our results suggest that CIs does not seem to be a good marker of conscious pain perception in HC or in MCS patients, the correlation between CIs values in the noxious condition and CRS-R scores supports the idea that a decrease in the complexity of the response to the noxious stimuli is associated with a reduced level of consciousness (i.e., degree of responsiveness). Therefore, if it cannot be used as an indicator of conscious pain, CIs seems to be an interesting parameter for studying nociception and top-down regulation in patients with DOC.[25,44,62,69–73] In addition, high values of CIs could be related to a possible better recovery of UWS/VS patients, but further longitudinal studies are necessary to observe how increasing of MSE values in the time could be related to a modification of the level of consciousness.

If the strength of this study is the continuous recording of HRV in different stimuli conditions in different levels of consciousness, there are several limitations to take into account.

The main limitations are the small sample size, the heterogeneity in the etiology, and the time since injury. Although we excluded patients under treatment with neuroactive drugs or beta-blockers, other uncontrolled pharmacological treatments may have affected the CI values. In addition, differences in the nonlinear measures of HRV, such as the MSE, were found with age (e.g., HRV entropy decrease with age) and gender in HC[74–76] with higher values in the female when compared to the male. For these reasons, higher values of CIs in the HC groups when compared with DOC patients might have been influenced by the higher percentage of female subjects in the HC groups (HC female: 57%; DOC female 36%). Nevertheless, a reduction in heart rate complexity values between genders was observed after 40 years, and in particular after menopause (probably due to hormonal changes[74]). Finally, we cannot exclude that the VS/UWS patients did not process the nonnociceptive stimuli (clapping on the left and right shoulder) as salient. However, the change observed between nonnoxious and noxious stimulation suggests a differentiated processing of the stimulus in this group. A bigger and more homogeneous sample would help us getting a more accurate analysis of the response to the stimuli in patients with severe DOC and investigate the effect of age and gender. In addition, outcome data would be needed in the future to look at the prognostic value of the CIs in this population.

Conclusion

We here recorded the electrocardiogram and analyzed the CIs responses in DOC patients during the baseline and after nonnoxious and noxious stimulation to study the interest of such method to investigate nociceptive pain processing in severely brain-injured patients. Our results suggest that the CIs could help to differentiate responses to noxious stimuli between HC, MCS, and VS/UWS. However, a difference between nonnoxious and noxious conditions was only observed in VS/UWS patients, suggesting that the CIs could be a useful marker of nociceptive processing in these patients but that it would not be directly related to the conscious processing of pain. CIs values in the noxious condition also correlated with behavioral responsiveness (i.e., CRS-R scores), indicating the potential interest of this measure for better understanding brain-heart interaction in DOC.

Future studies on larger and homogeneous groups (also with repeated observations over long periods—longitudinal studies) are necessary to define if it could be a reliable marker of nociception in this population and to better understand the correlation between the CAN and the recovery of consciousness in DOC patients.

Disclosures and Acknowledgments

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The study was supported by the University and University Hospital of Liège, the French Speaking Community Concerted Research Action (ARC 12-17/01), the Belgian National Funds for Scientific Research (FRS-FNRS), the German Research Society (DFG), Human Brain Project (EU-H2020-fetflagship-hbp-sga1-ga720270), Luminous project (EU-H2020-fetopen-ga686764), the James McDonnell Foundation, Mind Science Foundation, IAP research network P7/06 of the Belgian Government (Belgian Science Policy), the European Commission, the Public Utility Foundation "Université Européenne du Travail," "Fondazione Europea di Ricerca Biomedica." Camille Chatelle is a Marie Sklodowska-Curie fellow (H2020-MSCA-IF-2016-ADOC-752686).

Ethical approval: The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège, and written informed consent was obtained by the subject (HC) or the patients' legal representative.

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