Changes in heart rate variability of patients with delirium in intensive care unit

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***Abstract*— Delirium is an important syndrome in intensive care unit (ICU) patients, however, its characteristics are still unclear. Many evidences showed that this syndrome can be related to the autonomic instability. In this study, we aimed to investigate the possible alterations of autonomic nervous system (ANS) in delirium patients in ICU. Electrocardiography (ECG) of every ICU patient was measured during routine daily ICU care, and the data were gathered to evaluate the heart rate variability (HRV). HRV of total 60 patients were analyzed in time, frequency and non-linear domains. As a result, we found that heart rates of delirium patients were more variable and irregular than non-delirium patients. These findings may facilitate early detection and prevention of delirium in ICU.**

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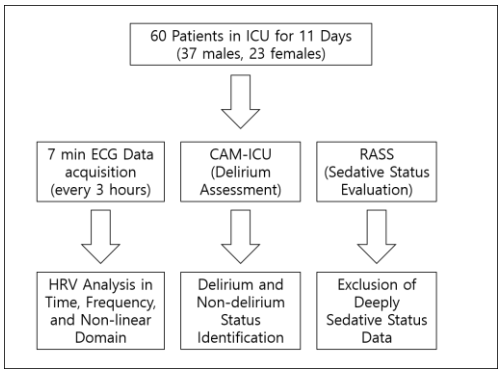

Figure 1. Flow chart of data acquisition and analysis for this study

I. Introduction

Delirium is serious syndrome that commonly occurs in critically in patients in the intensive care unit (ICU) [1]. Delirium is closely related to the increased mortality, longer ICU stay, and higher rates of mechanical ventilation [2, 3]. Thus, early detection and intervention are needed to decrease those complications. However, delirium patients are generally composed of very heterogeneous populations, so that it is very difficult to characterize the features of delirium.

There are some evidences that delirium can be related to the autonomic nervous system (ANS) instability [4]. According to the previous research, increased sympathetic nervous tone and catecholamine surge may contribute to delirium. In addition, delirium tremens is one type of delirium, and it is known to be closely related to the extreme autonomic hyperactivity [5]. In this background, it is essentially needed to elucidate whether the delirium patients have ANS changes or not. Especially, considering that ICU patients commonly have delirium, it is very important to find the possible autonomic changes in ICU patients.

Heart rate variability (HRV) is a method to measure the variation of heart beat using various indices. HRV has been believed it is mainly controlled by autonomic nervous system [6, 7]. However, the exact relationship between ANS function and each HRV component is still controversial. Particularly, low frequency activity has been linked to sympathetic nervous system activity while high frequency activity has been associated to parasympathetic nervous system activity [8, 9]. However, simultaneously, many other evidences also showed that specific frequency components do not always reflect ANS activity [10-12]. Given that the high possibility of altered ANS function in patients with delirium, it will be very important to find which HRV components are different between delirious and non-delirious states.

In this investigation, we aimed to evaluate the possible changes in HRV of delirium patients in ICU which can show the autonomic instability of the patients. We hypothesized that delirious patients would show ANS instability than non-delirious patients in ICU. We also aimed to find which HRV components can be useful to discriminate patients with delirious state from non-delirious state.

II. METHODS

A. Participants

The data of this study were collected for eleven days from the patients in an ICU of Yonsei university, Gangnam Severance hospital in Korea. During this period, 60 patients (37 males, 23 females) were stayed in ICU, and their mean ages were 64.7 ± 15.9 years old. We acquired electrocardiography (ECG) from all the participants. The ECGs of all the patients were measured every 3 hours except the patients with very little stay in the ICU or who were under medical or surgical procedures outside the ICU. Trained psychiatrists had evaluated the patients once a day whether the patients were delirious state or not by using CAM-ICU (Confusion Assessment Method for the ICU) except deeply sedated patients [13]. Sedative status was also daily evaluated by Richmond Agitation and Sedation Scale (RASS) [14]. The patients were evaluated as one of these three categories: delirium, non-delirium, or deeply sedated (RASS score = -4 or -5).

Informed consent for this investigation was waived by local institutional review board, because every study measurement was a part of routine clinical care.

B. HRV acquisition

There are 23 beds in the ICU of this hospital. We collected the ECG data from each subject for seven minutes from bed 1 to bed 23 by using automated system. After one cycle, we started to collect next cycle ECG data from bed 1 again. It took approximately two and a half hours to get the one cycle data of 23 patients. We collected ECG data 8 times a day, so that the automated data collecting system was started at every three hours from 0:00 AM. The sampling rate of ECG was 300 Hz.

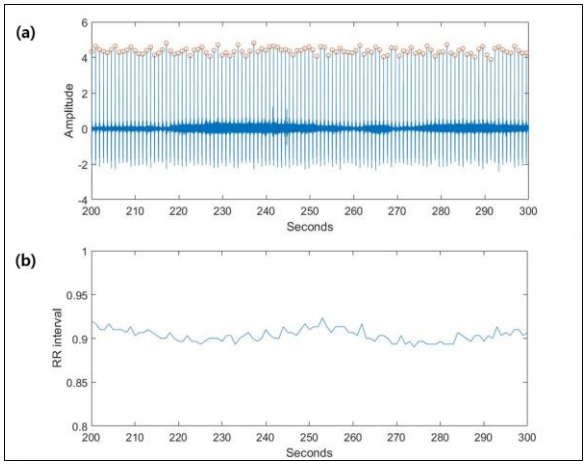

Figure 2. An example of the basic HRV analysis from the raw ECG data: (a) R peak detection from the raw ECG, (b) Acquisition of the RR intervals

C. HRV analysis

The data were analyzed in three domains: time domain, frequency domain, and non-linear domain. In terms of time domain analysis, we evaluated mean heart rate (mean HR), mean R peak to R peak interval (mean RR), standard deviation of RR interval (SDNN), and root mean square of successive differences (RMSSD). In frequency domain, we calculated absolute power of high frequency (HF), absolute power of low frequency (LF), normalized power of high frequency (nHF), normalized power of low frequency (nLF), and the ratio of low frequency to high frequency (LF/HF). Low frequency was set from 0.04 Hz to 0.15 Hz, and high frequency was defined from 0.15 Hz to 0.4 Hz. In non-linear domain, we analyzed the approximate entropy (ApEn), and sample entropy (SampEn). In these analyses, the embedding dimension m was set as 2, and the tolerance r was set as 0.15 × standard deviation. All the analyses were performed by MATLAB 2016 (MathWorks, MA, USA).

D. Statistical analysis

Every statistical analysis was conducted by SPSS 18.0 (Statistical Package for Social Science, 18.0; SPSS Inc., Chicago, IL, USA). Statistical significance level was set as $p<0.05$ and we performed independent sample t-test between the data of delirium status and those of non-delirium status.

III. RESULTS

From total 60 patients, we could get 7 minutes ECG data of 259 delirium status and 435 non-delirium status. We analyzed all the HRV data in time, frequency, and non-linear domain while comparing the data of delirium status to those of non-delirium status.

A. Time domain analysis

In terms of time domain data, we could find statistically significant difference of SDNN and RMSSD between two statuses. In other words, SDNN and RMSSD of delirium status were significantly higher than those of non-delirium status. However, any significant difference of mean HR and mean RR was not found between delirium status ECG and non-delirium status ECG. (Table I)

TABLE I. COMPRAISON OF HRV RESULTS BETWEEN DELIRIUM STATUS AND NON-DELIRIUM STATUS IN TIME DOMAIN

	HRV analysis results in time domain		
	Delirium Status	***Non-Delirium Status***	***p-value***
Mean HR (beats/min)	92.4 ± 24.3	93.5 ± 20.4	0.525
Mean RR (msec)	683.4 ± 143.3	670.1 ± 137.3	0.228
SDNN (msec)	89.1 ± 76.0	69.4 ± 64.3	0.001*
RMSSD (msec)	120.7 ± 106.3	93.4 ± 101.0	0.001*

Values are Mean ± Standard deviation.

B. Frequency domain analysis

HF, LF, nHF, nLF, and LF/HF did not exhibit any statistically significant difference between two statuses. Although it seems that there were significant differences

about absolute power of high and low frequency, there were huge standard deviation, so that they became statistically meaningless. In addition, normalized power confirmed that there was no significant difference in terms of frequency domain as well. Low to high frequency ratio also exhibited large differences, but it also became insignificant due to the large standard deviation of non-delirium status data. (Table II)

TABLE II. COMPRAISON OF HRV RESULTS BETWEEN DELIRIUM STATUS AND NON-DELIRIUM STATUS IN FREQUENCY DOMAIN

	HRV analysis results in time domain		
	Delirium Status	***Non-Delirium Status***	***p-value***
HF (S^2/Hz)	103.9 ± 1067.4	32.1 ± 364.2	0.296
LF (S^2/Hz)	2276.5 ± 30036.5	1527.5 ± 27105.9	0.735
LF/HF	1.1 ± 3.3	32.2 ± 632.1	0.429
nHF (normalized unit)	0.63 ± 0.17	0.62 ± 0.19	0.605
nLF (normalized unit)	0.37 ± 0.17	0.38 ± 0.19	0.605

Values are Mean ± Standard deviation.

C. Non-linear domain analysis

In this domain, we analyzed two entropy measures: approximate entropy and sample entropy. They showed statistically significant differences, and they were larger in delirious status than non-delirious status. Both results were statistically significant (p<0.001). (Table III)

TABLE III. COMPRAISON OF HRV RESULTS BETWEEN DELIRIUM STATUS AND NON-DELIRIUM STATUS IN NON-LINEAR DOMAIN

	HRV analysis results in time domain		
	Delirium Status	***Non-Delirium Status***	***p-value***
ApEn	1.01 ± 0.27	0.90 ± 0.38	<0.001*
SampEn	1.52 ± 0.68	1.25 ± 0.80	<0.001*

Values are Mean ± Standard deviation.

IV. DISCUSSION

In this study, we aimed to investigate possible differences of HRV features between delirious status and non-delirious status. As a result, we found that delirious status showed high SDNN and RMSSD suggesting that heartbeat became more irregular when the ICU patients were in delirious status. However, these results cannot always prove irregularity because the heartbeat can also be "regularly variated". However, we can be convinced about the irregular heartbeat of delirious status, because ApEn and SampEn were also increased in delirious state.

Generally, HRV can show the ANS function in our body, and especially, frequency domain measures mainly have been linked to ANS function [8, 9]. However, our results exhibited that only time and non-linear domain features could reveal the differences between delirious and non-delirious states. It should be noted that evidences showed power spectral analysis of RR interval variation did not accurately measure ANS functions [11, 12]. Furthermore, time or non-linear domain analysis itself can also show irregularity of heart rate, so that it has been linked to the ANS system function as well [15, 16].

It has been known that variable heart rate is an indicator of well-functioning heart. Especially, lower HRV is known to be associated with development of coronary heart disease, and even higher mortality [17, 18]. However, there was a previous paper indicated that sometimes higher HRV is not better, and it is also related to higher mortality [19]. Our results could be an evidence that delirium is related to the abnormally higher HRV, and especially, it can be exposed in time and non-linear domain features.

This investigation has some limitations. First, our analysis includes both between-subject and within-subject analysis. For example, one subject can be delirious in one day, and also can be non-delirious in another day while most patients provided ECG data in delirious status only or in normal status only. In addition, HRV can show diurnal variation[20], thus, it should be considered as well. However, in this investigation, we wanted to find general characteristics of ICU patients, and relatively large sample size could partially solve those problems. In spite of those limitations, we elucidated altered HRV patterns of ICU patients. In near future, our results can help to promote early detection or prediction of delirious patients in ICU.

V. CONCLUSION

As we have seen, heart rate of delirious state showed more irregular patterns. This higher HRV was prominent in time and non-linear domain analysis, suggesting that these features might have the potentials to correctly identify delirious patients in ICU. Our results may contribute to early detection and prediction of delirious patients in ICU.

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