Suppression of Autonomic Drive Determined by Nonlinear HRV analysis in Therapeutic Hypothermia after Cardiac Arrest

Anon Jantanukul
Medical engineering graduate program
Thammasat University (Rangsit Campus)
Pathumthani, Thailand
Non.nukul@gmail.com

Sombat Muengtaweepongsa MD,
Kesorn Suwanprasert Ph.D.
Faculty of Medicine,
Thammasat University (Rangsit Campus)
Pathumthani, Thailand
Corresponding author, kesorn.physio@gmail.com

***Abstract*—Therapeutic hypothermia is recommended as a cardiac arrest treatment for neuroprotection. In this study, we aimed to explore nonlinear heart rate variability (HRV) with other domains to clearify and setting up the significant index for survival. All patients were divided into two groups by 7 days survival outcome (n = 9 vs. 9). The limb lead II ECG signals are collected (10 minutes, sampling rate: 1000 Hz) for all phases; 6, 18 hours after induction (A and B), during rewarming (C) and recover (D). Fluctuation of heart rate (HR) was presented in both groups especially in C and D phases. Standard deviation of RR intervals (SDNN) was significantly decreased from phase A to C in survivors ($p<0.05$). Abrupt increase in SDNN was observed in non survivors and caused a significant difference compared to survivors in C phase. During A-C, low-frequency to high-frequency power ratio (LF/HF) and SD2 of Poincare's plot were suppressed in survivors and they slightly increased in D phases. Less suppression of those LF/HF ratio and SD2 was evident in non survivors. Gradual increase in sample entropy (SampEn) was consistent with prolong suppression of LF/HF ratio and SD2 in survivors. Significant difference of SampEN in both groups was presented at C phase. Prominent SampEn at rewarm of survivors was consistent with large and more scatter signals in Poincare's plot that may explain the rebound response after autonomic suppression. Contrast to survivors, less and ineffective autonomic suppression from hypothermia lead to a crisis in rewarming phase. Also, we notice significant difference of SDNN, SD2 and SampEN in non survivors. In conclusion, nonlinear HRV with SDNN and LF/HF ratio are able to determine successful, effective and rebound responses of hypothermia through autonomic suppression during A-C periods even though HR of both groups is displayed in C and D periods.**

***Index Terms*—Heart rate variability, Autonomic suppression, Therapeutic hypothermia**

I. INTRODUCTION

Cardiac arrest is a common cause of death and impaired autonomic nervous system (ANS) from brain injuries with subsequent tissue hypoxia. Hypothermia has been reported as neuroprotection and recovery of many tissues and organ injury. Therapeutic hypothermia is recommended as a guideline for cardiac arrest treatment by American Heart Association (AHA) and International Liaison Committee on Resuscitation (ILCOR). The treatment is used and defined as gradually reduced temperature which protects further brain injury by reducing brain metabolism. In general, steps of hypothermia treatment are: induction, mild hypothermia (32-33^{o}C for 12-24 hrs), rewarm (time from start rewarm to achieving normothermia) and normothermia after treatment (37^{o}C) [1, 2].

Heart rate variability (HRV) refers to the autonomic regulation of sinoatrial node of the heart and various organs. It has become as a non-invasive tool to predict outcome of many diseases such as acute myocardial infarction and sudden cardiac death [3]. Conventional HRV are assessed by time domain, which is calculated based on statistical operation on R-R intervals and frequency domain, which measures spectral analysis of a sequence of R-R intervals based on fast furrier transform to provide data on how power is distributed. Nonlinear analysis has been applied to further characterized HRV. It describes the structure of the variability dependently of the scale studied [4]. This concept relates to the observation that different fluctuation patterns are observed within specific time periods or frequencies, other self-similar fluctuation patterns may also be elicited from a broad range of data scales. Complexity in term of inconsistency, irregularity and randomness that are closely related to physiological mechanisms is determined as entropy [5]. In this study, since heart rate is fluctuated especially from 18 hours hypothermia to recovery phases, we will investigate the complexity pattern related to autonomic control throughout the time course treatment. Recently, Norman, et al. (2012) have reported inverse linear relationships between heart rate variability and brain damage after cardiac arrest in mice [6]. In patients, HRV measurement is proposed to be a predictor of 24 hrs mortality in successfully resuscitated 69 patients with out-of-hospital cardiac arrest [7]. It has been reported that in non survivors have shown a sudden significant decrease of HRV in rewarming phase compared to those in survivors [8].

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Although recent study shown the beneficial of HRV as a possible predictorbut there are few study in nonlinear HRV comparative to other domain. It should be noted that no one method has been identified as superior as or better than the others because no gold standard for HRV measurement exists and uses as comparison. These techniques may be considered to be complementary to each other based on pathophysiological process. As we known, nonlinear HRV reflects closed-loop version ofthe dynamic changes. In this present study, we investigated nonlinear HRV with other domains described changes of heart rate and distinguished those of survival and non-survival parameters. Recognized and dramatic pattern will be applied and used with oxidative stress biomarkers explaining the dynamic mechanism which will be proposed for an effective predictor.

II. METHODS

A. Patients

Eighteen cardiac arrest patients were recruited and studied in therapeutic hypothermia (age 59.78 ± 4.26 years; male: female, 8:10) which all protocols were approved by Human Research Ethics committee of Thammasat University (MTU-EC-PH-2-062/55). All patients were classified into survivors and non-survivors by 7 days survival outcome (n = 9 vs. 9).

B. Data Acquisition and HRV analysis

The electrocardiogram signals were collected at intensive care unit, Thammasat University Hospital for all phases of study; 6, 18 hours during sustainment in mild hypothermia (phase A and B), during rewarming period (phase C) and recover to normothermia (phase D). The 10 minute-lead II ECG with data sampling rate of 1000 Hz was recorded with Power Lab systems (AD Instruments). Then data were stored in personal computer, and RR intervals were extracted byusing LabchartPro7 Software (AD Instruments). After extraction of RR intervals, time domain, frequency domain and nonlinear HRV parameterswere analyzed by Heart Rate Variability Analysis Software (Kubios-HRV version 2.0) [9].

C. Statistical Analysis

Data were expressed as mean ± standard error of mean (SEM), and compared within group using Kruskal-Wallis test and then Dunn's test was used formulti-comparison post ANOVA test. Mann–Whitney U test was use to compare possible differences between two outcome groups. P-value of less than 0.05 was regarded as significant different.

III. RESULTS

All patients were divided into two groups by survival outcome. No significant difference was found between survivor group (n=9) and non survivor group (n=9) in age (52.78 ± 5.7 vs. 66.78 ± 5.7 years, respectively), sex (female, 5:5), and duration of each step of treatment; induction to mild hypothermia (6.4 ± 1.4 vs. 5.9 ± 1.6 hours, respectively); sustainment in mild hypothermia (21.8 ± 1.89 vs. 23.5 ± 0.48 hours, respectively); rewarming to normothermia (21.81 ± 0.66 vs. 20.33 ± 3.2 hours, respectively).

Heart rate (HR) in both groups were decreased in phase A to B and then they were increased during phase C to D. Significant difference of HR at B and D phases was observed in survivors (fig. 1).

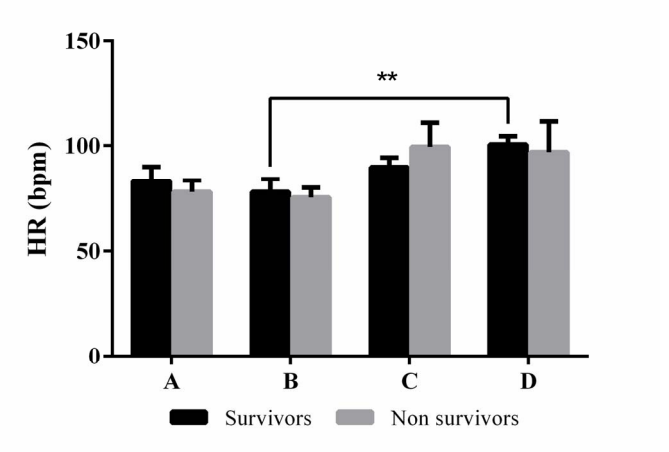

Fig.1. Heart rate (HR) fluctuation during time course treatment. Comparison of HR between survivors and non survivors; A, 6 hours after induction; B, 18 hours after induction; C, during rewarm period; D, recover tonormothermia; bpm, beat per minute; ** p< 0.05

In fig. 2. illustrates gradually reduced standard deviation of RR intervals (SDNN) in survivor group and significant difference between A vs. C. Contrast to survivor, SDNN of non survivors was abruptly increased during C phase and reached significant level when compared to survivors.

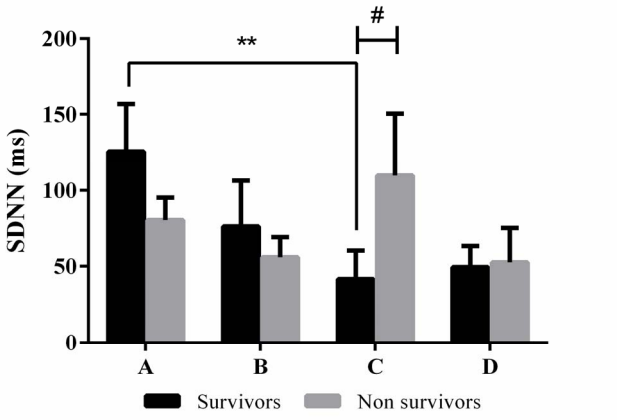

Fig. 2. Standard deviation of RR intervals (SDNN) and comparison between survivors and non survivors; A, 6 hours after induction; B, 18 hours after induction; C, during rewarm period; D, recover to normothermia.ms,milliseconds;
** p<0.05 within group; # p<0.05 among group.

Profile of low-frequency to high frequency power (LF/HF ratio) was dramatically suppressed during B and C compared with a phase in survivors and then it was released showing high level in D phase (fig. 3). Low and consistent profile of LF/HF ratio was seen in non survivors.

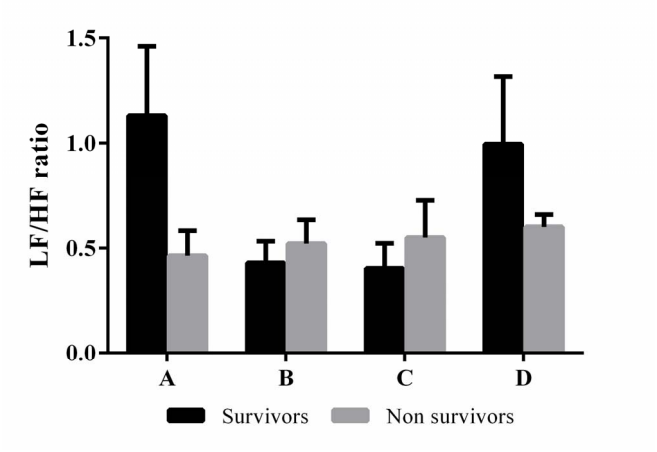

Fig. 3. Low-frequency to high frequency power (LF/HF ratio) profile of survivors and non survivors throughout time course. ; A, 6 hours after induction; B, 18 hours after induction; C, during rewarm period; D, recover to normothermia.

In fig. 4, the standard deviation of the Poincare's plot, SD2 was reduced dramatically from A-C phases in survivor group which it reached significant difference (A vs C). It then was increased in D phase. During rewarm, significant difference was seen between survivorsvs. non survivors. Interestingly, most SD2 profile was similar to LF/HF ratio except during C phase in non survivors (fig. 3). This finding suggests that prominent SD2 of non survivors will be a significant index for survival.

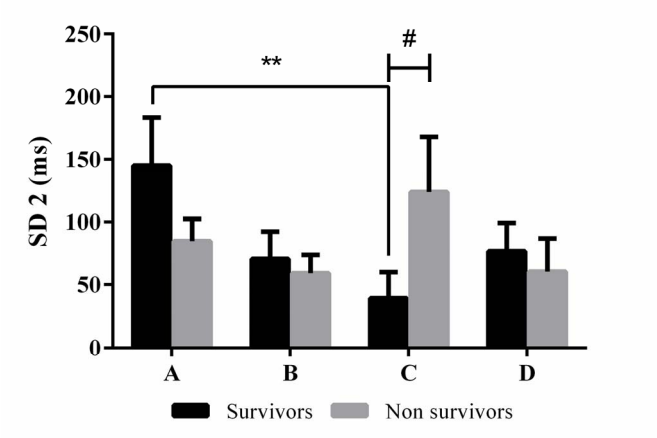

Fig. 4. SD2 of Poincare's plots parameter between survivor and non survivors; A, 6 hours after induction; B, 18 hours after induction; C, during rewarm period; D, recover to normothermia; ms, milliseconds;** $p < 0.05$ within group ; # $p < 0.05$ among group

Moreover, sample entropy (SampEn) in survivor group was significantly increased from A to C and showed significant level ($p < 0.05$). During C, greater level of sampEn in survivor vs. lower level of those in non survivor was evident and showed significance (fig. 5).

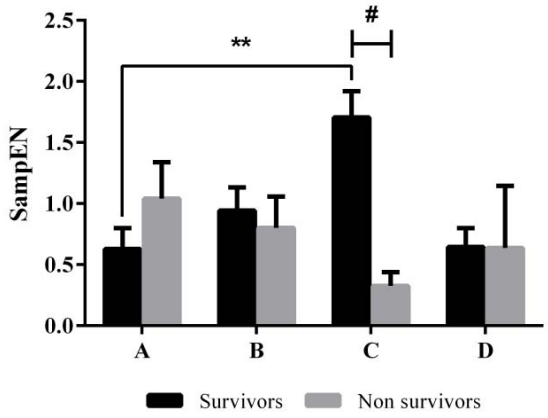

Fig .5. Comparison of SampEn between survivor and non survivors A, 6 hours after induction; B, 18 hours after induction; C, during rewarm period; D, recover to normothermia; ms,milliseconds;
** $p < 0.05$ within group ; # $p < 0.05$ among group

Figure 6 illustrates correlation between SD2 vs. HR in survivors and non survivors.

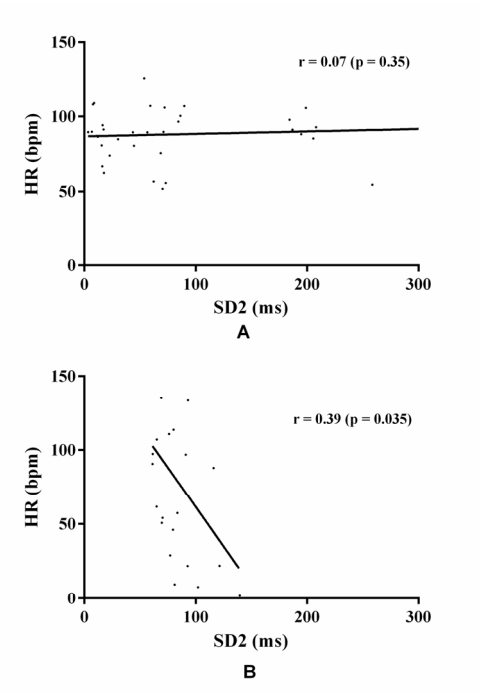

Fig. 6. Correlation between SD2 vs. HR in survivorsand non survivors; survivor (A), non survivor (B)

Scatter gram of Poincare's plots in SD1 and SD2 was depicted in figure 7.

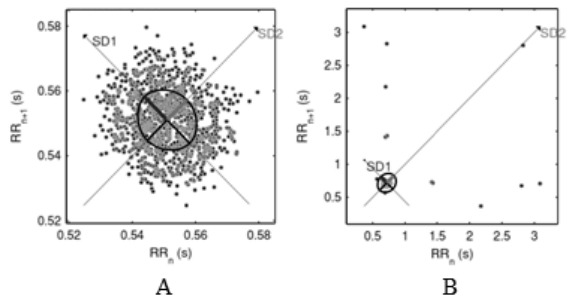

Fig. 7. Poincare's plots in survivors vs. non survivor during rewarm (phase C); survivor (A), non survivor (B)

IV. DISCUSSION

More fluctuations of heart rate during rewarm and recovery phases of both survivors and no survivors are evident in fig 1. In survivors, significant increase in HR is consistent with significant decrease in SDNN (fig. 1-2). Contrast to survivors, more fluctuation of HR is associated with suddenly increased SDNN in C phase in non survivors. It has been reported that SDNN is associated with sino-atrial node regulation [10]. Mild hypothermia affects low LF/HF ratio and SD2 during A-C phases in survivors with gradual increase in SampEn. This result indicates reduced sympatho-vagal balance and sympathetic drive by SD2. During D phase, an increase in LF/HF ratio and in SD2 as well suggests augmented ANS control after mild hypothermia to rewarm phases and those are associated with low SampEn. Large and more scatter of signals in rewarm phase is depicted in SD1 and SD2 axis of Poincare's plot (fig. 7A) in survivors. This finding indicates more complexity and irregularity dues to prolong suppression of ANS activity (18 hrs, mild hypothermia) and seems to be rebound response in physiological mechanism [5, 10, 11, 12]. Contrast to survivors, smaller and less irregularity of scatter signal is seen (fig. 7 B) in non survivors which associated with low SampEn value. This finding suggestsless suppression of ANS and ineffective response.

V. CONCLUSIONS

Critical period for survival is rewarm phase which it shows the rebound response after prolong and effective suppression of ANS from mild hypothermia, eventhough, HR is fluctuated in both survivor and non survivor. SD2 and SampEn associated with LF/HF ratio are key determinant indicating the effective of suppression mechanism from mild hypothermia.

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