

The Ability of Detecting Heart Rate Variability with the Photoplethysmography to Predict Major Adverse Cardiac Event in Acute Coronary Syndrome

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ABSTRAK

Tujuan: mengetahui kemampuan heart rate variability (HRV) yang diukur melalui metode pulse photoplethysmograph (PPG) dalam memprediksi major adverse cardiac event (MACE) pada pasien sindrom koroner akut (SKA). **Metode:** studi kohort prospektif dilakukan pada pasien SKA yang menjalani perawatan di ICCU. Pemeriksaan HRV dengan metode PPG dilakukan dalam 48 jam pertama perawatan dan kejadian MACE diidentifikasi selama perawatan di ICCU. Kemampuan HRV dalam memprediksi MACE selama perawatan dinilai dengan menghitung area under ROC curve (AUC) dari parameter low frequency (LF), high frequency (HF), dan rasio LF/HF. **Hasil:** dari 75 subyek penelitian, 14 (18.7%) di antaranya mengalami MACE selama perawatan. Parameter HRV berupa LF memiliki AUC 0,697 (IK95% 0,543-0,850) dan rasio LF/HF memiliki AUC 0,851 (0,741-0,962). Dengan menggunakan titik potong 89.673 ms², LF memiliki nilai duga positif (NDP) sebesar 13% dan nilai duga negatif (NDN) sebesar 71%, sementara dengan dengan titik-potongan 1.718 rasio LF/HF memiliki NDP 6% dan NDN 50%. **Kesimpulan:** parameter HRV berupa LF dan rasio LF/HF merupakan prediktor yang cukup baik terhadap MACE, terutama dalam memprediksi pasien pasca SKA yang tidak akan mengalami MACE selama perawatan.

Kata kunci: sindrom koroner akut, heart rate variability, major adverse cardiac events, pulse photoplethysmograph.

ABSTRACT

Aim: to assess heart rate variability (HRV) measurements using pulse photoplethysmograph (PPG) in predicting major adverse cardiac event (MACE) in acute coronary syndrome (ACS) patients. **Methods:** a prospective cohort study was conducted among hospitalized ACS patients. Heart rate variability as predictor was measured by PPG within 48 hours after admission and the incidence of MACE as outcome was identified during ICCU stay. The ability of HRV in predicting MACE during hospitalization was determined by area under ROC curve (AUC) of low frequency (LF), high frequency (HF), and LF/HF ratio parameters. **Results:** among 75 subjects included in the study, 14 (18.7%) were experienced MACE during hospitalization. HRV parameters of LF and LF/HF ratio have AUC of 0.697 (95% CI, 0.543-0.850) and 0.851 (0.741-0.962), respectively. Using cut-off point of 89.673 ms², LF had PPV and NPV of 13% and 71%, respectively; while LF/HF ratio of 1.718 had PPV and NPV of 6% and 50%, respectively. **Conclusion:** the HRV parameters of LF and LF/HF ratio are moderate predictors for MACE and predict better ACS patients who will not develop MACE during hospitalization.

Keywords: acute coronary syndrome, heart rate variability, major adverse cardiac events, pulse photoplethysmograph.

INTRODUCTION

Data from World Health Organization (WHO) shows that heart disease is the main cause of death globally. It is responsible for 30% of total deaths across the world.¹ In Indonesia, the prevalence of heart disease diagnosed by health providers is 7.2% of population with coronary heart disease in 1.5%.² Survei Kesehatan Rumah Tangga (SKRT) also indicated a rise in cardiovascular mortality, which is mainly instigated by coronary heart disease with more than 1.5 times increase in prevalence in just a decade (16% in 1992 to 26.9% by 2001).³ Nevertheless, prevention of mortality and morbidity in acute coronary syndrome (ACS) is hard to be achieved due to its various complications, ranging from mechanic complications such as ventricular rupture and mitral regurgitation to electrical complications/arrhythmia.⁴⁻⁶

Several studies have shown that heart rate variability (HRV), defined as fluctuation of heart rate frequency around its mean value, is an independent prognostic factor for long-term mortality/morbidity in post-ACS patients.⁷⁻¹³ The HRV measurement is non-invasive and real time, thus it is suitable for intensive hemodynamic monitoring. To date, HRV measurement can be done by pulse photoplethysmography (PPG) method with finger plethysmogram (FPG) which only needs 2-30 minutes to complete the measurement but yields a very similar result from Holter ECG measurement.¹⁴⁻¹⁷

Although the use of HRV measurement using PPG method as prognostic factor for long-term mortality and morbidity after ACS has been widely studied, its use in predicting in-hospital outcomes is limited. As the technique becomes more practical, HRV measurements using PPG method, is expected to be a routine non-invasive modality in assessing post-ACS risks in addition to well-established risk prediction models. Therefore, we conducted this study to assess HRV ability with PPG method in predicting major adverse cardiac events (MACE) during hospitalization in ACS patients.

METHODS

Design, Setting, and Patients

A prospective cohort study was conducted among adult ACS patients admitted to Intensive Cardiac Care Unit (ICCU) from September to November. Acute coronary syndrome (ACS) was diagnosed based on typical chest pain complaint, increase in cardiac marker enzymes, and ECG changes, by the physician-in-charge after a consultation to cardiologist. Patients were excluded if they were admitted to ICCU more than 48 hours after ACS diagnosis in Emergency Unit and were having MACE before HRV measurement. Patients were dropped out if they did not comply with the measurement protocol, withdrew from the study, or died from unrelated causes.

Eligible subjects were asked for their written consent before included in the study. The study protocol has been reviewed and approved by Medical Research Ethics Committee Faculty of Medicine Universitas Indonesia/Cipto Mangunkusumo Hospital.

Baseline Data and HRV Measurements

On the first day of admission, demographic and clinical data was obtained from all subjects including types of ACS, risk factors, previous cardiovascular events, and, if available, coronary vessels involvement. The heart rate variability was measured using photoplethysmography (PPG) method during first 48 hours after diagnosis. The variables of PPG method including low frequency (LF), high frequency (HF), LF/HF ratio, standard deviation of normal-to-normal interval (SDNN), and square root of mean squared differences of consecutive normal-to-normal intervals (RMSSD).

Assessment of Outcomes

All subjects were followed up during their stay in ICCU and were determined whether they experienced major adverse cardiac events (MACE), i.e. fatal arrhythmia, acute heart failure, cardiogenic shock, re-infarction, and mechanic complications (such as valve abnormalities or myocardium rupture). Confirmation regarding MACE diagnosis was done by principal investigator and supervisor of ICCU.

Statistical Analysis

Minimal subjects required for this study was calculated using formula for determining area under the curve (AUC). Subjects' characteristics were presented descriptively in a baseline table according types of data. MACE incidence was presented in mean of proportion. The abilities of HRV to predict MACE were determined by AUC values of SDNN, RMSSD, LF, HF, and LF/HF ratio. Cut-off of HRV parameters with favorable prediction value (AUC >50% and 95% CI excluded 0.5) and were further presented as positive predictive value (PPV) and negative predictive value (NPV) based on the cut-off values according to the optimal sensitivities and specificities.

RESULTS

There were 101 ACS patients admitted to ICCU during the study period and 26 were excluded because of earlier MACE before HRV measurement, resulting 75 subjects included in this study, with mean age of 58.7 (11.5) years old and predominantly male (69.3%). Unstable angina pectoris (UAP) and Non ST-Elevation Myocard Infarction (NSTEMI) were most common diagnosis, while hypertension was the most common risk factors followed by diabetes and hypercholesterolemia. (**Table 1**)

Subjects admitted to ICCU <48 hours post-diagnosis were studied and the median of HRV measurement for each parameter is presented in **Table 2**.

Mean length of ICCU stay in all subjects was 6.7 (SD 3.1) days. During hospitalization, MACEs were occurred in 14 (18.7%) subjects; nine of them were found in STEMI subjects. Almost (93%) all of those events occurred in the first two days of ICCU admission (mean duration 1.1 days). Proportion of each events is presented in **Table 3**.

Parameters of HRV with the best AUC were LF and LF/HF ratio (**Table 4**). Both of the parameters were then assessed for their risk cut-off points. For LF and LF/HF ratio, the cut-off were 89.673 ms² and 1.718, respectively.

Both parameters were then converted into categorical data to determine their positive predictive values (PPV) and negative predictive

Table 1. Subjects' characteristics

Characteristics	Total (N=75)
Age (years), mean (SD)	58.7 (11.5)
Male, n (%)	52 (69.3)
Length of stay in ICCU (days), mean (SD)	67 (31)
ACS subtype, n (%)	
- UAP	29 (38.7)
- NSTEMI	28 (37.3)
- STEMI	18 (24.0)
Anterior infarction, n (%)	53 (70.7)
TIMI score, mean (SD)	3,4 (1.7)
Hypertension, n (%)	49 (65.3)
Systolic blood pressure (mmHg), mean (SD)	125.1 (19.7)
Diastolic blood pressure, mmHg (mean (SD))	70.5 (12.4)
Diabetes, n (%)	31 (41.3)
HbA1c (%), mean (SD)	7.7 (1.8)
Hypercholesterolemia, n (%)	25 (33.3)
LDL (mg/dL), mean (SD)	116.8 (45.1)
LVEF (%), mean (SD)	49.4 (14.5)
Smoking, n (%)	36 (48)
Previous myocardial infarction, n (%)	36 (48)
Previous stroke, n (%)	6 (8)
History of revascularization, n (%)	12 (16)
- percutaneous coronary intervention	9 (12)
- coronary artery bypass grafting	3 (4)
Coronary artery involvement, n (%)	
- Single-vessel disease	22 (29.3)
- 2-vessel disease	17 (22.7)
- 3-vessel disease	36 (48)

ACS=acute coronary syndrome; HbA1c=glycated hemoglobin; ICCU=intensive cardiac care unit; LDL=low-density lipoprotein; LVEF= left ventricular ejection fraction; NSTEMI=Non ST-elevation myocard infarction; STEMI=ST-elevation myocard infarction; TIMI=Thrombolysis in Myocard Infarction; UAP=unstable angina pectoris

Table 2. Subjects' HRV measurement

Parameter	Median (Interquartile range)
Mean HR, times per minute	75 (20)
SDNN (ms)	24268 (21332)
RMSSD (ms)	25450 (23787)
LF (ms ²)	63644 (131822)
HF (ms ²)	74714 (124271)
Rasio LF/HF	0915 (1571)

HF=high frequency (HF); HR=heart rate; LF=low frequency; ms=miliseconds; RMSSD=square root of mean squared differences of consecutive normal-to-normal intervals; SDNN=standard deviation of normal-to-normal interval

Table 3. MACE proportion in subjects during hospitalization

Event	Number of subjects (N=14)
Death (sudden cardiac death)	1
Fatal arrhythmia	
Ventricular tachycardia	2
Bradycardia	2
Cardiogenic shock	4
Acute heart failure	5

Table 4. AUC of HRV parameters

Variables	AUC (95% CI)
Mean HR (times per minute)	0.622 (0.446-0.797)
SDNN (ms)	0.567 (0.380-0.753)
RMSSD (ms)	0.559 (0.396-0.721)
LF (ms ²)	0.697 (0.543-0.850)
HF (ms ²)	0.446 (0.283-0.610)
Rasio LF/HF	0.851 (0.741-0.962)

HF=high frequency; HR=heart rate; LF=low frequency; ms=milliseconds; RMSSD=square root of mean squared differences of consecutive normal-to-normal intervals; SDNN=standard deviation of normal-to-normal interval

values (NPV). The PPV and NPV of LF were 13% (CI 95%, 3 to 22%) and 71% (CI 95%, 55 to 88%), respectively; while PPV and NPV of LF/HF ratio were 6% (CI 95% -1 to 12%) and 50% (CI 95% 25 to 71%), respectively.

DISCUSSION

To our knowledge, this was the first study which assessed the ability of HRV measurement using PPG method to predict MACE during hospitalization in ACS patients. We found that the HRV parameters measured in the first 48-hours of hospitalization were lower than those of normal population stated by Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. The Task Force found the mean values of SDNN, RMSSD, LF, HF, and LF/HF ratio in normal population were 141 ms, 27 ms, 1170 Hz, 975 Hz, and 1.5-2.0, respectively.¹⁸⁻²⁴ The lower value of HRV was attributable to the autonomic nervous imbalance in ACS,^{8-11,25} which in turn played a role in patients' prognosis.^{8-13,26,27} The decrease in convalescence HRV value was associated with non-SCD complications²⁸ while the decrease in early HRV value was associated

with SCD.²⁹

Major adverse cardiac events (MACE) occurred in 18.7% of ACS patients in this study. The result is lower than other comparable studies in ICCU RSCM (21.6%-29.9%),^{30,31} but higher compared to other studies which used more limited criteria of MACE; only death, stroke, and repeated revascularization.³² In general, due to exclusion of patients which were having MACE during 48-hours of hospitalization, the events in our study were slightly lower than in other study.³³

The events occurred more frequently in STEMI (50%) than in NSTEMI (10.7%) and UAP (6.8%) patients. Acute heart failure (35.7%) and cardiogenic shock (28.6%) were the most common MACE, and anterior segment involvement was found in 71% event. These findings were in accordance with other studies when ACS complications were much more frequent in anterior STEMI in the form of: acute heart failure, cardiogenic shock, and or arrhythmias.³⁴⁻³⁶

We found that LF parameter has AUC of 0.697 (95% CI, 0.543-0.850) and LF/LH ratio has AUC of 0.851 (95% CI, 0.741-0.962), and were considered as better predictors for MACE incidence during hospitalization than any other HRV parameters. This finding is consistent with other studies which shown that frequency domain parameters (LF, HF, LF/HF) had a better predictive value in short-term HRV measurement due to their independence to heart rate modulation.^{8,13,24,37}

The limitations in discrimination value were more readily explained in LF/HF ratio. Formerly, increase in LF/HF ratio was considered as a state of sympathetic domination, and vice versa. Recent studies showed that such assumption was far from truth, because: (1) LF was also influenced by parasympathetic system and sympathetic system played a role in HF; (2) changes in one side of autonomic system were not always accompanied by other reciprocal changes (e.g. sympathetic and parasympathetic could be increased simultaneously), and; (3) changes in autonomic balance were often not linear.^{37,38} Therefore, the parameter, while still related to outcome, could not express sympathovagal balance precisely.³⁹

Additionally, difference in subjects' characteristics was believed as another main cause of HRV limitation in this study; this study utilized early HRV measurements in the first 48 hours post-ACS diagnosis in Asian population. Ethnicity would influence HRV variance^{39,40} and the time of measurement should be as close as possible to the time when the diagnosis was made (<45 minutes) for better risk stratification.³⁷ In addition, our subjects had already treated with initial ACS therapy in emergency room before ICCU admission which would change their prognosis. Therefore, a better predictor for MACE might be a persistent decrease in HRV parameters. Nevertheless, we believed that this method has a more realistic and practical value for HRV measurement because until now there had not been any measurement standard, including time of measurement, for HRV examination.

The advantages of this study lie in its originality. This is the first study assessing HRV ability to predict MACE in ACS patients. In addition, because we used short-term measurement with PPG method in the intensive care, this study also emphasizes the practical points of HRV. Overall, this study can be vital for future studies focusing on clinical applicability and modern medical technology.

However, reflecting our result, we recommend to take serial measurement with longer follow-up time to strengthen the prognostic value of HRV. We also recommend doing a further study in which HRV measurement will be correlated with other prognostic factors such as baseline heart rate, ejection fraction, etc.

CONCLUSION

The HRV parameters of LF and LF/HF ratio have moderate abilities to predict MACE during hospitalization in ACS patients. Both parameters have better NPV than PPV, which have a cut-off 89.673 for LF and 1.718 for LF/HF ratio.

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