Effects of Extracardiac Factors in Signal-Averaged Electrocardiography-measured Late Potentials from Early Anterior Myocardial Infarction in Intensive Cardiac Care Unit

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ABSTRAK

Latar belakang: *salah satu modalitas yang dapat memprediksi aritmia ventrikel pasca-infark miokardium (MI), terutama MI anterior, adalah signal-averaged electrocardiogram (SA-ECG), melalui deteksi late potentials (LP) yang merupakan substrat aritmia ventrikel. Faktor-faktor ekstrakardiak yang sekaligus menjadi faktor risiko MI, misalnya hipertensi, diabetes, dislipidemia, dan obesitas, dipikirkan berhubungan dengan kejadian aritmia ventrikel pasca-MI melalui berbagai patomekanisme, yang kemungkinan berkaitan erat dengan timbulnya LP. Penelitian ini bertujuan untuk mengetahui pengaruh faktor-faktor ekstrakardiak terhadap timbulnya LP saat awal perawatan pada pasien MI anterior yang dirawat di intensive cardiac care unit (ICCU).* ***Metode:*** *desain studi ini adalah potong lintang dengan pemeriksaan SA-ECG sewaktu terhadap 80 subjek penelitian yang mengalami MI anterior di ICCU selama periode Desember 2018-2019. Riwayat medis dan faktor risiko ekstrakardiak direkapitulasi, sedangkan data SA-ECG diambil dari pemeriksaan langsung maupun data SA-ECG pasien MI anterior ICCU dalam periode tersebut. Studi ini menggunakan analisis multivariat dengan uji regresi logistik.* ***Hasil:*** *faktor yang paling umum ditemukan adalah hipertensi (70,00%), diikuti dislipidemia (56,25%), diabetes (46,25%), dan obesitas (38,75%). Obesitas dan dislipidemia merupakan faktor ekstrakardiak yang berperan paling besar terhadap prevalensi LP. Namun, dari analisis tambahan, kami menemukan bahwa diabetes dengan hiperglikemia akut juga memiliki pengaruh terhadap terjadinya LP. Besar OR untuk diabetes dengan hiperglikemia akut, obesitas, dan dislipidemia masing-masing adalah sebesar 4,806 (IK95% 0,522-44,232), 4,291 (IK95% 0,469-39,299), dan 3,237 (IK95% 0,560-18,707). Hubungan tersebut tidak bermakna secara statistik.* ***Kesimpulan:*** *pasien MI anterior yang menderita diabetes dengan hiperglikemia akut, obesitas, dan dislipidemia cenderung memiliki prevalensi LP yang lebih tinggi, namun secara statistik hubungan tersebut tidak bermakna. Untuk meningkatkan nilai prognostik SA-ECG, diperlukan pemeriksaan serial selama perawatan.*

Kata kunci: *diabetes, dislipidemia, hipertensi, infark miokardium, late potentials, obesitas, signal-averaged electrocardiogram.*

ABSTRACT

Background: *one modality that can predict ventricular arrhythmias after myocardial infarction (MI), particularly anterior MI, is signal-averaged electrocardiogram (SA-ECG), through the detection of late potentials (LP) which is a substrate for ventricular arrhythmias. Extracardiac factors, which are also risk factors for MI, such as hypertension, diabetes, dyslipidemia, and obesity, are apparently associated with post-MI ventricular* *arrhythmias, which in turn may be correlated with LP. This study aims to determine the effect of extracardiac risk factors on LP incidence in anterior MI patients treated in the intensive cardiac care unit (ICCU).* ***Methods:*** *this was a cross-sectional study in which 80 subjects with anterior MI during the period of December 2018-2019 underwent SA-ECG examination. The medical history and extracardiac risk factors were recapitulated, and then the SA-ECG data was taken from either direct examination or ICCU patients' database in that period. This study used multivariate analysis with logistic regression test.* ***Results:*** *the most common factors found were hypertension (70.00%), followed by dyslipidemia (56.25%), diabetes (46.25%), and obesity (38.75%). Obesity and dyslipidemia are extracardiac factors with the two biggest roles in the prevalence of LP. However, from additional analysis, we found that diabetes with acute hyperglycemia also had immense influence on the occurrence of LP. The OR for diabetes with acute hyperglycemia, obesity, and dyslipidemia were 4.806 (IK95% 0.522-44.232), 4.291 (IK95% 0.469-39.299), and 3.237 (IK95% 0.560-18.707). However, the association is not statistically significant.* ***Conclusion:*** *patients with anterior MI who suffer from diabetes with hyperglycemia in admission, obesity, and dyslipidemia have a potentially higher LP prevalence, despite statistical insignificance. To increase the prognostic value of SA-ECG, serial examinations are needed during hospitalization.*

Keywords: *diabetes, dyslipidemia, hypertension, late potentials, myocardial infarction, obesity, signal-averaged electrocardiogram.*

INTRODUCTION

Annually, more than 1.5 million patients with acute coronary syndrome (ACS) worldwide have been hospitalized; as many as 25% -35% of all cases will pass away within a year, while some (20%) will experience a re-infarction within 6 months.[1-4] The ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) incidence extend to almost ¾ of the total cases with a mortality rate > five times higher than unstable angina pectoris (UAP).[5] In addition to being very common in daily practice, the main problem in myocardial infarction (MI) is the difficulty in prevention of mortality or morbidity due to complications. Additionally, although the incidence of MI complications has decreased along with the development of revascularization technology, the incidence of arrhythmias so far has not been reduced.[6-8]

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are the most common and most fatal post-MI arrhythmias (mortality reaches >20%).[9,10] Such arrhythmias can be found in 2-40% of MI cases with a median time of 78 h post-MI; although they mostly will occur within the first 48 hours.[9] This is supposed to be secondary to cell hypoxia which then causes intracellular calcium accumulation and finally triggers after-depolarization. The process then causes ventricular ectopic triggers that are spirally deteriorating.[10] Several studies suggested that the risk of ventricular arrhythmias, especially VF, was proportional to the degree of anterior myocardial damage because it was closely related to the degree of intracellular calcium accumulation.[11-13]

Signal averaged-electrocardiogram (SA-ECG) is a high-resolution electrocardiogram measurement technique. Analysis on SA-ECG could include time-time analysis and/or spectral analysis (frequency-domain), depending on the type of equipment used. In clinical aspects, SA-ECG measurement aims to capture the presence of weak-inhomogen signals from ventricular myocardium damaged by ischemia. These signals are referred to as late potentials (LP), which are responsible for after-depolarization that can further trigger VT or VF.[14,15] The American College of Cardiology (ACC) stated that SA-ECG is the recommended modality for: (1) risk stratification of ventricular arrhythmias in post-MI patients without conduction abnormality; (2) identification of VT in patients with CHD and syncope; (3) risk stratification of ventricular arrhythmias in non-ischemic cardiomyopathy, and; (4) evaluation of the success of surgery on permanent VT.[15] Extracardiac abnormalities including hypertension, diabetes, dyslipidemia, or obesity also affect the onset of LP.

Until now, SA-ECG has not been used

routinely in the acute MI care because of facility limitation. Nevertheless, if it can be done at a health service center that has an intensive cardiac care unit (ICCU), the device will play a significant role in risk stratification of ventricular arrhythmias. The presence of LP at the beginning of treatment can exclude or predict the incidence of acute or delayed phase ventricular arrhythmias during treatment; each of which can predict 30-day mortality and long-term all-cause mortality.

Therefore, this study aims to analyze the effect of extracardiac factors on the prevalence of LP measured in the early phase of anterior MI. As for the extracardiac factors of hypertension, diabetes, dyslipidemia, and obesity, they are selected as specific factors because they are also shared risk factors for LP as well as MI.

METHODS

This study is a cross-sectional study of 80 subjects with anterior MI in ICCU Cipto Mangunkusumo Hospital (RSCM). The primary data collection process was carried out for three months from July 2019 to December 2019. Secondary data was taken from December 2018 to April 2019. All patients regularly underwent routine diagnostic and therapeutic modalities according to ICCU standard operational procedures during hospitalization. If the patient met the inclusion criteria, the patient would be taken as subject, and then physical examination and additional tests to complete the data were carried out. In addition, secondary data was selected by sorting medical and SA-ECG data of ICCU patients during the study period based on similar criteria.

Subjects were excluded if they had a history of previous ventricular arrhythmias or had impaired ventricular conduction, acute heart failure, cardiogenic shock, re-infarction, mechanical complications (valve abnormalities or myocardial rupture), and/or death before SA-ECG measurements. In addition, we also excluded patients who had abnormalities that were considered to affect SA-ECG measurements but did not include risk factors that were focused on, including: kidney failure in renal replacement therapy, chronic obstructive pulmonary disease, thalassemia, psychiatric disorders, and or thyroid dysfunction.

The influence of extracardiac factors such as hypertension, diabetes, dyslipidemia, and obesity would be analyzed using multivariate analysis with the logistic regression test. In this study, an additional analysis of diabetic subjects with acute hyperglycemia was also performed.

The SA-ECG measurement was completed within 48 hours post-diagnosis. The SA-ECG tool used in this study was a portable ECG Holter created by Vasomedical-BIOX™ type 1303 Ultra Compact 3-Channel ECG Holter Recorder; it was an ECG Holter which has a special mode to detect LP with a detection threshold of 40 Hz. The tool has been certified by the American Food and Drug Administration (FDA), European CE, and the International Organization for Standardization (ISO). This ECG is also the only SA-ECG that is commercially available in Indonesia.

RESULTS

From the primary data, a total of 31 subjects with anterior MI were enrolled and tested for SA-ECG, while from ICCU patient database, 63 subjects that fulfilled recruitment criteria were included. Fourteen subjects were excluded because of routine hemodialysis (six people), cardiogenic shock (three people), ventricular arrhythmias (three people), heart conduction disorders (one person), and hypothyroidism (one person). A total of 80 subjects were obtained in this study.

The median duration of treatment in this study was 6.5 days; the subjects were predominantly men (86.26%) and smokers (72.50%). A total of 55 subjects (68.75%) had multiple risk factors for LP, especially hypertension and dyslipidemia or diabetes. The most prevalent factors were hypertension (70.00%), followed by dyslipidemia (56.25%), diabetes (46.25%), and obesity (38.75%). At hospital admission, 35/56 (62.50%) hypertension subjects and 24/37 (64.84%) diabetes subjects showed non-optimal control of each of these diseases. The mean HbA1c value of the subjects was 6.96% (SD 2.31).

Most subjects were admitted with STEMI presentations (71.25%) with multivessel disease (65% of total subjects); it was in accordance with nearly half of the total subjects having multisegmental walls involvement, namely anteroseptal and anterolateral. Although GRACE score showed low risk stratification (median of 107.5), 53 (64.94%) subjects had a decrease in EF <50% (average 45.14%). In this study, 42.50% of subjects underwent a primary or urgent PCI procedure before SA-ECG measurement (**Table 1**).

Signal-Averaged ECG Measurement

The SA-ECG measurement values of research subjects can be seen in **Table 2**. There were seven subjects who showed positive results for LP; there were three people (5.26%) who came with a STEMI diagnosis; and there were four people (17.39%) who were diagnosed with NSTEMI. Even so, the difference was not statistically significant (Fisher's Exact Test p 0.086). Of the seven patients, two (28.75%) experienced ventricular arrhythmias during treatment (p 0.60). Based on the time domain criteria, QRSd is the most common parameter that is found to be abnormal (20.00% vs. 6.25% and 7.50% for RMS40 and LAS40).

Table 1. Subject characteristics.

Characteristics	Value
Age, mean (SD), year-old	55.55 (9.15)
Gender, male, n (%)	69 (86.26)
Duration of hospitalization, median (min-max), days	6.5 (2-38)
Traditional risk factors, n(%)	
- Hypertension	56 (70.00)
- Diabetes	37 (46.25)
- Dyslipidemia	45 (56.25)
- Obesity	31 (38.75)
- > 2 risk factors	55 (68.75)
Medical history and lifestyle, n (%)	
- Myocardial infarction history	14 (17.50)
- Stroke history	7 (8.75)
- Revascularization history: PCI	6 (7.59)
- Smoking	58 (72.50)
Infarct presentation, n (%)	
- STEMI	57 (71.25)
- NSTEMI	23 (28.75)
Infarct location, n (%)	
- Anterior only	43 (53.75)
- Anteroseptal	27 (33.75)
- Anterolateral	10 (12.50)
Coronary artery involvement, n (%)	
- Single-vessel disease	28 (35.00)
- 2-vessel disease	15 (18.75)
- 3-vessel disease	37 (46.25)
- With Left main disease	11 (13.75)
LVEF, mean (SD), %	45.14 (14.35)
Troponin I level, median (min-max), ng/mL	3744 (9-500.000)
GRACE score, median (min-max)	107.5 (30-213)
Subjects underwent PCI before SA-ECG measurement, n (%)	34 (42.50)

Table 2. SA-ECG profile.

Parameter	Value
Late potentials prevalence, n (%)	7 (8.75)
Subjects with abnormal SA-ECG parameter, n (%)	
- QRSd > 114 ms	16 (20.00)
- RMS40 < 20 uV	5 (6.25)
- LAS40 > 38 ms	6 (7.50)

Extracardiac Factors and Late Potentials

Using univariate analysis (**Table 3**), diabetes, dyslipidemia, and obesity had p values <0.25. These three factors were then analyzed again using the logistic regression test. The variables dyslipidemia and obesity were determined as extracardiac factors that have the potential to play a role in LP (**Table 4**).

Additional Analysis for Acute Hyperglycemia in Diabetic Subjects

We also added the diabetes variable with acute hyperglycemia at admission in the diabetic subjects as an additional analysis for the LP prevalence. It appears that hyperglycemia at admission also had the potential to become one of the main factors influencing LP prevalence (**Table 5**). From the regression analysis, hyperglycemia at admission, obesity, and dyslipidemia were the three factors that had the largest OR in this study. Therefore, these three factors are considered as the main extracardiac factors which had the tendency to affect LP; The OR for diabetes with acute hyperglycemia, obesity, and dyslipidemia were 4.806 (95%CI 0.522-44.232), 4.291 (95%CI 0.469-39.299), and 3.237 (95%CI 0.560-18.707) respectively.

Table 3. Univariate selection of extracardiac risk factors and LP prevalence.

Variables/SA-ECG	LP positive	LP negative	P value
Hypertension			
- Yes	6	50	0.360
- No	1	23	
Diabetes Mellitus			
- Yes	5	32	0.181
- No	2	41	
Dyslipidemia			
- Yes	2	43	0.142
- No	5	30	
Obesity			
- Yes	1	30	0.178
- No	6	42	

Table 4. Multivariate model for extracardiac risk factors and LP prevalence.

Variables/SA-ECG	P	OR	95% CI
Obesity	0.253	3.609	0.401-32.514
Dyslipidemia	0.220	2.957	0.522-16.732

Even so, the relationship was not statistically significant (**Table 6**).

DISCUSSION

The characteristics of our subjects were very similar to studies from the European Society of Cardiology (ESC) and another study in Iran which found that MI patients were mostly male with an average age of> 40 who had multiple risk factors, namely smoking, hypertension, having a sedentary lifestyle, and dyslipidemia.[16-18]

Most subjects (65%) had multivessel disease; this was evident when nearly half of our subjects suffered from multisegmental wall involvement, namely anteroseptal and anterolateral. This percentage was much higher than another study that showed that multivessel disease was only found in about 38% of MI subjects.[19] We assumed that the progression of the disease was due to the high prevalence of hypertension in this study, especially high blood pressure in 62.50% of subjects with hypertension. A study states that hypertension was a strong independent predictor of multivessel disease in young adults, besides diabetes.[20] Hypertension increases the expression of intercellular adhesion molecule-1 (ICAM-1) which will stimulate the endothelial inflammatory response and then cause widespread vascular wall damage.[21]

Table 5. Univariate selection of diabetes with acute hyperglycemia and LP prevalence

Variable/SA-ECG	LP positive	LP negative	P value
Diabetes with acute hyperglycemia			
- Yes	1	29	0.163
- No	6	44	

Table 6. Multivariate model for extracardiac risk factors, including diabetes with acute hyperglycemia, and LP prevalence.

Variables/SA-ECG	P	OR	95% CI
Diabetes with acute hyperglycemia	0.166	4.806	0.522-44.232
Obesity	0.197	4.291	0.469-39.299
Dyslipidemia	0.189	3.237	0.560-18.707

Signal-Averaged ECG Measurement

The prevalence of SA-ECG abnormalities in this study was lower than another study in Mexico which indicated that the prevalence of abnormal SA-ECG in anterior MI was 37%.[22] We hypothesized that this difference was because we excluded patients with other extracardiac risk factors, such as hemodialysis, cardiogenic shock, and cardiac arrest patients which can increase the prevalence of LP.

In addition, some subjects with ventricular arrhythmias could have false negative LP results because they might have a normal time domain parameter but had positive LP from spectral domain.[11,23,24] Finally, several studies have shown that, unlike in inferior MI, SA-ECG time domain measurements in anterior MI did not immediately become abnormal within 48 hours.[25,26]

Research conducted by Rosas et al[22] showed that SA-ECG time domain parameters had a better prognostic value than spectral parameters in anterior MI. The QRSd component has the best sensitivity-specificity and the highest odds ratio (OR) (4.9, vs. 2.1 and 3.6 for RMS40 and LAS40) as the predictor of arrhythmia. Likewise, the results of another study stated that QRSd was the strongest correlated parameter for ventricular activity dispersion – and as predictor of ventricular arrhythmia -- in anterior and non-anterior MI.[27,28] The QRSd parameter became the strongest component of SA-ECG time domain parameter because it was the only variable that had a pathophysiological basis: the time interval from the beginning to the end of ventricular activation. The presence of MI would cause ventricular activation dispersion which then increased the duration of the filtered QRS. Therefore, QRSd abnormality has always been closely related to the degree of ventricular depolarization inhomogenicity.[27]

Hypertension and LP Prevalence

Hypertension in the general population would produce left ventricular hypertrophy, interstitial fibrosis, myocardial or subendocardial scarring, diastolic dysfunction, and disorders of the cardiac autonomic system. These pathological conditions would then result in the slowing of conduction referred to as LP.[29] However, this study did not find hypertension as an extracardiac risk factor for LP.

Dordevic et al[30] studied the relationship between LP and hypertension in non-MI subjects; he established that the relationship between hypertension and SA-ECG abnormalities was more pronounced in the spectral domain parameters. However, there have been no long-term studies regarding the prognostic value of LP in hypertensive populations. In addition, there were no studies that pursue the relationship between LP and hypertension in the acute phase post-MI. Therefore, the absence of the relationship between hypertension and LP prevalence can only be suspected to be caused by: (1) the number of subjects undergoing post-revascularizing SA-ECG measurements, where hypertension as the most crucial factor would experience the greatest effect, and; (2) the lack of examination of the spectral domain on SA-ECG.

Diabetes, Hyperglycemia, and LP Prevalence

In diabetes, the degree of acute autonomic and inflammatory dysfunction that occurs after MI would increase electrophysiological remodeling in the form of structural fibrosis and ion channel disruption in myocardium.[31] However, we found that diabetes alone could not be used as a predictor for LP. Various studies showed that acute hyperglycemia during post-MI admission, in both diabetic and non-diabetic patients, was more important than the patient's diabetes status.[31-33]

A study from Nasution et al[34] that used SA-ECG for MI patients found that acute hyperglycemia could increase the incidence of LP by more than fourfold. With that in mind, coupled with data from research subjects showing poor diabetes control, we made an additional analysis for the diabetic group with acute hyperglycemia at admission. Acute hyperglycemia at admission in diabetic patients was the most potentially influential factor for LP (OR 4.806 with 95% CI 0.522-44.232). However, we did not find it to be statistically significant. This was considered to be as such due to the several pathomechanisms of electrophysiological remodeling that occur simultaneously post-MI, yet they achieved their maximum effect in different time intervals: (1) cell apoptosis, phagocytosis, maturation, reparation, and cytokine activation; (2) changes in intracellular calcium ions that affected the action potential, and; (3) increased stress hormones in the form of cortisol, glucocorticoids, and catecholamines which in turn increased the production of reactive oxygen species (ROS).[34] The third mechanism was the cause of acute hyperglycemia at admission, where the process would exhibit greater effect > 48 hours post-MI. Nasution et al[34] found that the increased incidence of LP was only demonstrated after SA-ECG measurements on the fifth day, related to increased Ca2 +/calmodulin-dependent protein kinase II (CaMKII) activation -- as calcium ion channel regulator -- and increased ROS production. In this study, because SA-ECG measurements were carried out in the early MI phase < 48 hours, the effects of acute hyperglycemia as described above might have not been clearly perceived.

Dyslipidemia, Obesity, and LP Prevalence

The components of the metabolic syndrome synergistically increased insulin resistance and created electrophysiological remodeling in which cardiac conduction fibers were separated by fat infiltration, myocyte hypertrophy, inflammatory cell infiltration, and myocardial fibrosis.[35] Cholesterol, triglycerides, low density lipoproteins (LDL), and apolipoprotein-B increased the cholesterol-phospholipid ratio of cell membranes, causing cell rigidity and damaging ion channel function. Histologically, disrupted membrane function would cause ventricular repolarization-depolarization disorders.[35,36] The effect of dyslipidemia (and obesity)-mediated remodeling process was more evident in patients with acute post-MI, where disturbances of repolarization-depolarization became more pronounced due to being hypoparasymphatetic, especially in an anterior infarction.[36]

The OR for dyslipidemia and obesity were 3.237 and 4.291, respectively, which indicated that those two comorbidities potentially influenced LP prevalence. However, this effect was not statistically significant. It was considered because of administration of high-intensity statins post-MI. Several studies found that there was a gradual improvement in LP immediately after administration of high-intensity statins to patients with dyslipidemia 48 hours post-MI, peaking after > 10 days.[37] Considering this, we assessed high-dose statins for the anterior MI population with dyslipidemia and obesity, together with beta-blockers, and this could be one of the main therapies for preventing ventricular arrhythmias pronounced by LP. Our opinion was supported by studies that found statins have additional pleiotropic effects as anti-arrhythmia: it reduces oxidative stress induced by infarction, which then slows the remodeling of cardiac electrophysiology, and subsequently restores disturbed parasympathetic tone.[36,37]

The cross-sectional nature in this study did not allow us to study the full effects of extracardiac factors on the prevalence of LP. In addition, SA-ECG were only measured once within 48 hours post-diagnosis. Also, as explained earlier, we can only utilize the only SA-ECG machine that is available in Indonesia, which only has time domain parameters.

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CONFLICT OF INTEREST

The authors have no conflicts of interest. This study received no external funding.

CONCLUSION

Diabetes with acute hyperglycemia, dyslipidemia, and obesity are the extracardiac factors that potentially influence LP prevalence in anterior MI patients measured in the early phase of treatment in ICCU.

Some suggestions that can be given for further research are: (1) conduct SA-ECG measurements at least twice: within 48 hours and on the fifth-seventh day before the patient is discharged, and; (2) use SA-ECG spectral domain parameters if possible.

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