Is the Change of Late Potential Over Time Related to Enzyme Levels? *Ischemic Burden in Acute Myocardial Infarction*

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Background: The ventricular late potential (VLP) detected using the technique of signal average electrocardiography (SAECG) interacts with several factors, primarily time.

Method: In this study, we examined the interaction, over time, of VLP with the initial ischemic burden and enzyme levels in acute myocardial infarction. Patients diagnosed as having acute myocardial infarction were included in the study. On the first day, the patients underwent enzyme analysis and electrocardiography (ECG) follow-up every 6 hours. A 24-hour ambulatory ECG was performed on the seventh day in order to determine the ischemic burden. SAECG findings (TQRS, RMS, LAS) were obtained on the seventh day, in the first and third months. The study was continued with the patients who did not require angioplasty as decided with angiographic evaluation in the first month.

Results: The study included 30 patients with acute myocardial infarction (mean age 51 ± 12, 28 males and 2 females). The initial mean CK-MB levels and the mean ischemic burden were 98 ± 31 U/L and 44 ± 96 minutes. The TQRS (ms), LAS (ms), and RMS (μV) values (mean ± SD) obtained at day 7, month 1, and month 3 are 97 ± 12, 96 ± 9, 103 ± 11, P = 0.01; 31 ± 10, 31 ± 11, 32 ± 10, P = 0.46; 43 ± 28, 41 ± 26, 33 ± 25, P = 0.01, respectively. We observed that the TQRS and RMS values changed significantly with time, but these levels of significance disappeared when adjusted for the initial ischemic burden and CK-MB levels (P = 0.06; P = 0.53). The VLP frequency was 33% at day 7 and 23% at month 3. Unlike the CK-MB level, the initial ischemic burden was significantly different between the patients with and without VLP at month 3 (150.85 ± 149.28, 12.34 ± 26.48, P = 0.001). When tested together with age and gender, it was found that the high initial ischemic burden increased the possibility of VLP (OR: 24, CI: 2.09-279.52, P = 0.01) at month 3.

Conclusion: SAECG findings in patients with myocardial infarction changed with time; however, this change occurred depending on the initial ischemic burden and CK-MB levels. Of these, only the initial ischemic burden, especially in high levels, was a determinant for the presence of VLP in the late period of myocardial infarction. **A.N.E. 2002;7(3):242–246**

SAECG; ischemic burden; CK-MB; late potential

The ventricular late potential (VLP), detected using signal average electrocardiography (SAECG), is accepted as one of the major predictors of malign ventricular tachyarrhythmic events after myocardial infarction (MI).[1-2] Any impairment and delay in the integrity of the activation in the site of the infarct plays an important role in the development of arrhythmia after MI. SAECG findings are affected by a multitude of factors such as the localization of infarct,[3] thrombolytic therapy,[4] sex, and the period after the infarct.[5] The relation of these findings to the ischemic burden and enzyme levels

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in the acute phase have not adequately been questioned so far. This study aims to investigate the interaction of the variation of SAECG findings over time with ischemic burden, CK-MB levels in the early MI, and to investigate whether the initial ischemic burden and CK-MB levels have the potential to predict the presence of VLP in the post-MI at month 3.

METHODS

Seventy-six patients diagnosed with acute MI in our clinic were included in the study. The patients who met at least one of the following criteria were excluded from the study: Those who underwent coronary angioplasty, received thrombolytic treatment, those with left and right bundle block, and those who had ejection fraction below 40%. During the follow-up, all patients received the same treatment (nitrate, aspirin, beta blocker, and angiotensin-converting enzyme inhibitors). At admission to hospital, CK-MB measurements were done every 6 hours and the greatest one was recorded; MI (MI) locations were detected by ECG. On the seventh day of hospitalization, 24-hour ambulatory ECG with a derivation of 12 (Rozzin Electronics, Inc.) were performed in order to determine the ischemic burden, and the sum in minutes of horizontal or down sloping ST depressions that continued 80 ms after the point J and lasted at least 1 mV and 1 minute was accepted as ischemic burden. On the time-domain SAECG were recorded on the seventh day of the infarct using arrhythmia research technology (LP-Pac Q) with standard bipolar orthogonal X, Y, and Z leads filtered bidirectionally between 40 and 250 Hz signal averaging of > 300 beats was performed so as to achieve a diastolic noise level of 1 μV. SAECG findings were obtained in the supine position and after a 15-minute rest. The presence of VLP was defined as the presence of two of the following three criteria: (1) filtered QRS complex > 115 ms; (2) root mean square voltage of the last 40 ms of the filtered QRS complex (RMS) < 20 μV; and (3) duration of low amplitude signals < 40 μV in the terminal QRS complex (LAS) > 38 ms. Angiography for every patient 1 month after the hospital discharge was planned, as a result of which the study was continued with 30 patients who did not require revascularization. SAECG was repeated in the first and third (late period of MI) month after MI. All study patients were divided into two groups according to criterion of the presence of VLP at month 3.

Statistical analyses were done with SPSS for Windows10.0 package program; quantitative data were expressed as mean value ± standard deviation The differences between continuous variables were tested with General Linear Model-univariate and repeatedmeasures, comparison of the ratios with Chi-square test and predictability with logistic regression analysis. A cut-off value of 27 minutes for ischemic burden was detected by ROC analysis (sensitivity: 86%, specificity: 83%) and the values more than 27 minutes were categorized as high ischemic burden. As post hoc test, Sidak was used, and $P < 0.05$ was accepted as statistically significant.

Table 1. TQRS, LAS, RMS Values Adjusted to Ischemic Burden and CK-MB

	7th Day	1st Month	3rd Month	P
TQRS (ms)	97 ± 12	96 ± 9	103 ± 11	0.06
LAS (ms)	31 ± 10	31 ± 11	32 ± 10	0.76
RMS (μV)	43 ± 28	41 ± 26	33 ± 25	0.53

TQRS = filtered QRS duration; RMS = a root mean square voltage; LAS = low-amplitude signal duration.

RESULTS

Of the 30 patients in the study, 28 were male and 2 were female, their mean age was 51 ± 12. Diabetes mellitus was present in 4, hypertension in 4, hyperlipidemia in 22, and smoking habits in 23 patients as the risk factors for coronary artery disease. Of the patients, 17 had anterior and 13 inferior MI.

The mean maximum CK-MB on the first day was 98 ± 31 U/L, and the ischemic burden found at the Holter examination on the seventh day was 44 ± 96 minutes. Of SAECG findings, obtained on the seventh day of the infarct, 1 and 3 months after their hospital discharge, TQRS (97 ± 12 ms, 96 ± 9 ms, 103 ± 11 ms; P = 0.01) and RMS (43 ± 28 μV, 41 ± 26 μV, 33 ± 25 μV; P = 0.01) changed significantly over time, but these levels of significance disappeared when adjusted for ischemic burden and CK-MB values in the early period of MI (P = 0.06; P = 0.53). SAECG findings are presented in Table 1.

Table 2. Basal Clinical Features of Groups With and Without VLP at Month 3

	With VLP N: 7	Without VLP N: 23	P
Age	59 ± 13	49 ± 12	0.08
Sex			
Female	14%	4%	
Male	86%	96%	0.41
Hypertension	57%	35%	0.29
Diabetes mellitus	29%	26%	0.62
Smoking habit	57%	83%	0.16
LVEF	58.57 ± 14.06	56.26 ± 9.28	0.61
CK-MBU/L	113.57 ± 33.30	93.39 ± 29.89	0.13
Ischemic burden (minute)	150.85 ± 149.28	12.34 ± 26.48	0.001
TVES	84 ± 187	28 ± 34	0.17
Inferior MI	57%	39%	
Anterior MI	43%	61%	0.40

TVES = Total ventricular premature beats; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

The basal clinical features of groups with and without VLP at month 3 are presented in Table 2. The VLP frequency was 33% at day 7 and 23% at month 3. VLP, at month 3, was present in six of the ten patients who had VLP at day 7; and a fresh VLP developed in one patient at month 3 (P = 0.002). Initial CK-MB values were not different between the groups with and without VLP at month 3 (113.57 ± 33.30, 93.39 ± 29.89, P = 0.139, respectively), but the initial ischemic burden was significantly different (150.85 ± 149.28, 12.34 ± 26.48, P = 0.001). When adjusted for age and gender, it was found that the initial ischemic burden increased the possibility of VLP (odds ratio: 1.02, Confidence interval: 1.00-1.04, P = 0.04) at month 3, and that the initial CK-MB levels did not have any predictive value for the possibility of VLP (odds ratio: 0.98, Confidence interval: 0.95-1.01, P = 0.14) at month 3. When tested by categorizing as high level, ischemic burden became more predictive of VLP, giving the high odds ratio of 24 (Confidence interval: 2.09-279.52, P = 0.01).

DISCUSSION

Ventricular late potentials, which have an important place in predicting ventricular arrhythmia and sudden deaths following an MI, occur as a result of deceleration of the electrical conduction in the viable myocardial cells that have lost their integrity owing to fibrosis after the infarct.[6] In the 1-year-follow-up after the infarct, it was detected that ventricular late potentials disappeared over time and this was related to the initial QRS duration, male sex, and the occurrence of Q waves.[7] The variation or disappearance of ventricular late potentials over time can be explained with the reduction of ischemia due to the development of collaterals, and resolution of the stunned myocardium around the site of infarction.[8,9] It is also reported that the development of ventricular late potentials is affected by such factors as thrombolytic therapy, infarct localization, left ventricular functions and infarct size, ischemia, and suggested that further prospective studies considering these factors are needed to establish the clinical value of SAECG after MI.[10] In the present study, we examined the interaction, over time, of SAECG findings with the initial enzyme levels and ischemic burden in acute MI.

In the current study, despite the decrease in VLP frequency at month 3, TQRS and RMS changed significantly over time towards the values accepted as ventricular late potential. However, this level of significance has disappeared after adjustment for CK-MB values and ischemic burden. The observed change between the mean values of TQRS and RMS and the frequency of VLP, over time, seems to be a paradoxical case. Since the number of our study patients was low, we have thought that the excessive changes in SAECG recordings in several patients, probably occurring depending on the levels of ischemic burden and CK-MB, lead to this status. Furthermore, it was found that, unlike CK-MB levels, the initial ischemic burden has pre-

dictive potential for VLP in the postmyocardial infarction at month 3. The relationship between myocardial ischemia and ventricular late potential development has been reported so far to be controversial.[11-13] It has been detected in several studies that thrombolytic therapy[14,15] and percutaneous transluminal coronary angioplasty[16] decreased ventricular late potentials. Ventricular late potentials associated with temporary ischemia arise with the inflation of the balloon during angioplasty in patients who had MI.[11] While Turitto et al. demonstrated that angina had no effect on ventricular late potentials,[12] Tamura et al. demonstrated that ischemia lasting long enough to cause dynamic dysfunction on the ventricular wall in patients with unstable angina caused the development of ventricular late potentials.[13] In our patients, we think the ischemic burden detected on the seventh day was similar to that which they would have presumably been faced with for 3 months, because revascularization was not considered to be necessary and their treatment was continued with the same medication they had at hospital discharge. It may be assumed that our patients, all having noncritical coronary lesions, were subjected to a continual ischemia at the moment of psychological, physical stress, or potential spasms. Therefore, with its effects such as, though intermittent, mural dynamic dysfunction, activation, and deceleration of conduction in the exposed tissue, the continuity of the ischemic burden around to initial levels will affect the findings of SAECG in the postmyocardial infarction at month 3. The decrease in the frequency of VLP in the postmyocardial infarction at month 3, on the other hand, could be explained with the recovery of myocardium over time despite unfavorable factors such as ischemia.

No study has been done so far directly related to enzyme levels. The occurrence of greater fibrosis depending on the size of the necrotic area, and thus the impairment of the integrity of myocardial cells leading to the emergence of ventricular late potentials is an expected pathophysiological phenomenon. According to a study by Ringborn et al., it has been implied that major necrotic areas, by prolonging ventricular activation, might act as a substrate in ventricular late potential development.[17] In patients with MI who are not on thrombolytic therapy, the enzyme levels in the acute phase are high in proportion to the size of the necrotic area.[18] Because higher CK-MB levels mean larger necrotic areas, ventricular late potential development can be expected to be related to enzyme levels. In our study patients, SAECG findings changed over time depending on initial CK-MB levels. On the other hand, the decrease in the VLP frequencies at month 3 may be explained with the recovery of stunned myocardium, which is accepted as akinesis at angiographic evaluation.

After MI, in a series of studies that an abnormal SAECG it was shown predicted the occurrence of spontaneous arrhythmic events, with prognostic significance and a low positive predictive accuracy.[19-21] In the light of this knowledge, our study patients, although having preserved left ventricular function, are faced with an arrhythmic risk, though low, due to the underlying disease, i.e., coronary artery disease. We, too, found that the number of TVES was high, though it failed to reach statistical significance, in the patients with VLP.

We found that the overall changes in TQRS and RMS values occurring with progressing time towards the limit, accepted as ventricular late potential depended on acute ischemic burden and enzyme levels, but LAS was not affected. Thus we can say that CK-MB level and ischemic burden in the early phase of MI have an effect on the progression of VLP in the late period of MI. But it was detected that only the initial ischemic burden, especially in high levels, among these has the potential of prediction about the presence of VLP in the postmyocardial infarction at month 3. Therefore, we think that these factors should be taken into consideration when SAECG findings are assessed in the late period of MI.

REFERENCES

1. Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction: Natural history and prognostic significance. Circulation 1986;74:1280-1289.
2. Zimmermann M, Sentici A, Adamec R, et al. Long-term prognostic significance of ventricular late potentials after a first acute myocardial infarction. Am Heart J 1997;134: 1019-1028.
3. Gomes JA, Winters SL, Martinson M, et al. The prognostic significance of quantitative signal averaged variables relative to clinical variables, site of myocardial infarction, ejection fraction and ventricular premature beats: A prospective study. J Am Coll Cardiol 1988;13:377-384.
4. Chew EW, Morton P, Murtagh JG, et al. Intravenous streptokinase for acute myocardial infarction reduces the occurrence of ventricular late potentials. Br Heart J 1990;64:5-8.
5. Savard P, Rouleau JL, Ferguson J, et al. Risk stratification after myocardial infarction using signal-averaged electrocardiographic criteria adjusted for sex, age, and myocardial infarction location. Circulation 1997;96:202-213.
6. Gardner PI, Ursell PC, Fenoglio JJ, et al. Electrophysiologic and anatomic basis for fractionated electrograms recorded

from healed myocardial infarction. Circulation 1985;72: 596-611.
7. Kuchar DL, Thorburn CW, Sammel NL. Prognostic implications of loss of late potentials following acute myocardial infarction. PACE 1993;16:2104-2111.
8. Buckingham TA, Greenwalt T, Lingle A, et al. In anterior myocardial infarction, frequency domain is better than time domain analysis of the signal-averaged ECG for identifying patients at risk for sustained ventricular tachycardia. PACE 1992;15:1681-1687.
9. Levine JH, Moore EN, Becker LC, et al. Abnormal action potential characteristics and cell coupling are present in postischemic stunned myocardium. Circulation 1985; 72(suppl III):238.
10. Tsunakawa H, Nakayama M. Clinical value of signal averaged electrocardiogram for the prediction of ventricular tachycardia after myocardial infarction. Nippon Rinsho 1995;53:412-420.
11. Rubin DA, Sorbera C, Cook J, et al. Reversible late potentials due to ischemia. PACE 1992;15:2250-2254.
12. Turitto G, Caref EB, Zanchi E, et al. Spontaneous myocardial ischemia and the signal-averaged electrocardiogram. Am J Cardiol 1991;67:676-680.
13. Tamura K, Tsuji H, Masui A, et al. Prevalence, resolution, and determinants of late potentials in patients with unstable angina and left ventricular wall motion abnormalities. Am Heart J 1996;131:731-735.
14. Peters W, Kowallýk P, Wilhelm K, et al. Evolution of late potentials during first 8 hours of myocardial infarction treated with thrombolysis. PACE 1996;19:1918-1922.
15. Gang ES, Lew AS, Hong M, et al. Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. N Engl J Med 1989;321:712-716.
16. Boehrer JD, Glamann B, Lauge RA, et al. Effect of coronary angioplasty on late potentials one to two weeks after acute myocardial infarction. Am J Cardiol 1992;70:1515-1519.
17. Ringborn M, Pahim O, Wagner GS, et al. The absence of high-frequency QRS changes in the presence of standard electrocardiographic QRS changes of old myocardial infarction. Am Heart J 2001;141:573-579.
18. Roberts R. Enzymatic estimation of infarct size: Thrombolysis induced its demise: Will it now rekindle its renaissance? Circulation 1990;8:707.
19. Farrell TG, Bashir Y, Cripps T, et al. Risk stratification for arrhythmic events in postinfarction patients based on heart rate variability, ambulatory electrocardiographic variables and the signal-averaged electrocardiogram. J Am Coll Cardiol 1991;18:687-697.
20. Denniss AR, Richards DA, Cody DV. Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction. Circulation 1986;74:731-745.
21. Kuchar DL, Thorburn CW, Sammel NL. Prediction of serious arrhythmic events after myocardial infarction: Signal-averaged electrocardiogram, Holter monitoring, and radionuclide ventriculography. J Am Coll Cardiol 1987;9:531-538.