Ventricular Late Potentials Immediately after ST-Elevation Myocardial Infarction and Very Long-Term Mortality

Alexander Shturman MD[1,3*], Shira Vardi MD[1*]; Amitai Bickel MD[2,3] and Shaul Atar MD[1,3]

Departments of [1]Cardiology and [2]Surgery, Galilee Medical Center, Nahariya, Israel
[3]Faculty of Medicine in the Galilee, Bar-Ilan University, Safed, Israel

ABSTRACT: **Background:** The very long-term prognostic significance of ventricular late potentials (VLP) in patients post ST-elevation myocardial infarction (STEMI) is unclear.

Objectives: To evaluate the long-term predictive value of VLP for mortality post-STEMI.

Methods: We conducted serial signal-averaged electrocardiography (SAECG) measurements in 63 patients on the 1st, 2nd and 3rd day post-STEMI, and 30 days after discharge. We followed the patients for 10 years and correlated the presence of VLP with all-cause and cardiovascular mortality.

Results: The mean age was 59.9 ± 12.3 years. Thrombolysis was performed in 41 patients (65%). Percutaneous coronary intervention was performed pre-discharge in 40 patients (63%) and coronary artery bypass grafting in 7 (11%). Five consecutive measurements to define the presence of VLP were obtained in 52 patients (21 with VLP and 31 without). We found a higher prevalence of VLP in males compared to females (QRS segment › 114 msec, 51% vs. 12%, $P = 0.02$, duration of the low amplitude signal ‹ 40 mV) in the terminal portion of the averaged QRS complex › 38 msec, 47% vs. 25%, $P = 0.05$). Over 10 years of follow-up, 14 (22%) patients died, 10 (70%) due to cardiovascular non-arrhythmic complications, 6 with VLP compared to only 3 without (28.6% vs. 9.7%, $P = 0.125$, hazard ratio = 2.96, confidence intervals = 0.74–11.84).

Conclusions: Over 10 years of follow-up, the presence of VLP in early post-STEMI is not predictive of arrhythmic or non-arrhythmic cardiovascular mortality.

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KEY WORDS: signal-averaged electrocardiography (SAECG), electrocardiography, QRS, ST-elevation myocardial infarction (STEMI), ventricular late potentials (VLP)

Despite the significant recent reduction in clinical complications, ST-elevation myocardial infarction (STEMI) remains a leading cause of early and late morbidity and mortality [1]. QRS-segment prolongation post-STEMI, defined as longer than 120 msec, has previously been suggested as a predictor of cardiac mortality in the reperfusion era [2]. Ventricular late potentials (VLP) are additional signals at the terminal portion of the QRS complex that correlate with aberrant activation of myocardial muscle tissue. VLP are detected by signal-averaged electrocardiography (SAECG), which filters the background noise and reveals high frequency, low amplitude signals [3,4]. VLP are significantly more prevalent in patients after myocardial infarction (MI) and in patients with structural heart disease, yet uncertainty exists regarding the appropriate timing of VLP assessment post-STEMI, as VLP may also infrequently be detected in normal myocardial tissue [5].

Data on the long-term prognostic value of VLP post-STEMI are lacking. A single study previously argued that VLP are of little prognostic value over a median follow-up of 34 months post-infarction [6]. We studied the very long-term (over 10 years) prognostic value of early detection of VLP for all-cause and cardiovascular mortality in STEMI patients. We also examined the prevalence of VLP and the QRS-segment length in consecutive measurements (during hospitalization and up to 30 days post-discharge) and their association with cardiovascular and all-cause mortality.

PATIENTS AND METHODS

The study was approved by the institutional review board. The study population included consecutive patients who were admitted in 2001 to the Intensive Cardiac Care Unit (ICCU) with STEMI and treated with thrombolytic agents or did not receive reperfusion due to late arrival or contraindication to thrombolysis. We excluded patients with atrial fibrillation, atrial flutter or supraventricular tachycardia in the first 24 hours post-admission, and patients with a permanent pacemaker. The patients were evaluated with SAECG on the 1st, 2nd and

*The first and second authors contributed equally to this study

3rd day after admission, as well as 1 week and 1 month post-STEMI. On each examination, a standard 12-lead ECG and filtered and non-filtered SAECG (General Electric Marquette Mac 5000 Resting ECG Analysis System®, GE, USA) of the QRS segment were performed using a filtering frequency of 40–250 Hz. This signal averaging system enhances measurement accuracy by enabling the filtration of background electrical noise and disqualified scale compared to a standard ECG. The SAECG software performs calculations based on algorithms that reveal small electrical changes (of 1–25 mV) in the QRS complex. According to the Consensus Document on Signal-Averaged Electrocardiography [4], VLP were defined as present when a QRS duration > 114 msec was accompanied by at least one of the following: a signal < 20 mV in the last 40 msec of the filtered QRS complex, or duration of the low amplitude signal (< 40 mV) in the terminal portion of the averaged QRS complex > 38 msec high frequency low amplitude signal (HFLA). After reviewing the measurements of VLP in the first 3 consecutive days post-STEMI, we found a higher prevalence on VLP on the 3rd day post-STEMI and therefore used them for the determination of the significance of VLP as a predictor of mortality. The SAECG examinations were performed in the ICCU.

Two-dimensional transthoracic echocardiography (TTE), M-Mode and Doppler echocardiography were performed according to standard methods. Significant left ventricular (LV) dysfunction was defined as LV ejection fraction (LVEF) < 40%, as assessed on the second day of admission by TTE. Treatments were given according to the relevant clinical guidelines and standard of care during the time of the study. We called the patients 2 years after the index event to verify their status. We collected data regarding very late (10 years) survival following the index STEMI from the Israel Ministry of Interior Affairs registry, and data on the cause of death from the hospital's records.

MEASURED VARIABLES

Clinical and demographic data were collected from patients' files. Infarct size was measured according to maximal creatine phosphokinase (CPK) levels in the first 24 hours post-STEMI. Post-MI complications were ventricular or supraventricular arrhythmias including atrial fibrillation or flutter, congestive heart failure, post-MI angina pectoris and re-infarction.

STATISTICAL ANALYSIS

Quantitative data are described by averages and standard deviations, medians and range, whereas qualitative data are evaluated by percentages and prevalence. Evaluation of differences in QRS-segment length among different groups of patients, with or without complication and/or left ventricular dysfunction, was done by the *t*-test for independent variables or by the Wilcoxon test for two independent variables. This analysis was conducted at all time points. The decision as to which test to use was made according to its compatibility with the distribution of data. Correlation between qualitative variables such as ejection fraction, and quantitative variable such as QRS-segment length, was achieved using relation tests such as the Pearson correlation coefficient or the Spearman correlation coefficient test, respectively. The relation of qualitative variables and QRS-segment length, after dividing it into categories, was examined using relation tests such as chi-square test and/or Fisher's exact test, respectively. Dividing the variables and QRS-segment length into categories was based also on setting cutoff values per variable according to the complication ratio of the segment's length, by using receiver operator curve (ROC). Sensitivity and specificity were determined based on these principles. The Kaplan-Meier estimator was used to evaluate survival as a function of time from the index STEMI.

RESULTS

We studied 63 consecutive patients. Their mean age was 59.9 ± 12.3 years; 54 were male (86%). The baseline patient characteristics are presented in Table 1. Thrombolytic therapy was administered to 41 patients (65%). Coronary angiography after thrombolysis was performed in 55 patients (87%), with percutaneous coronary intervention (PCI) in 40 (63%) and coronary artery bypass graft (CABG) in 7 (11%).

Three consecutive measurements of VLP were obtained by SAECG on days 1, 2 and 3 after STEMI. For the filtered duration of QRS-segment, the highest median value was observed on the 1st day after the index event (111.0 ± 29.8 msec, range 89–223). As defined according to filtered QRS-segment duration > 114 msec, the highest percentage of patients (45.3%) was observed on the 3rd day post-STEMI. In terms of HFLA signal duration, the highest mean value was observed on the 3rd day post-

Table 1. Clinical characteristics of patients on admission

Characteristic	N (%)
Age (years)	59.9 ± 12.3
Gender (male)	54/63 (86)
Previous MI	12/63 (12)
Peripheral arterial disease	11/63 (18)
s/p CABG	1/63 (2)
Congestive heart failure	1/63 (2)
Smoking	36/63 (57)
Peripheral arterial disease	11/63 (18)
Arterial hypertension	29/63 (46)
Diabetes mellitus	18/63 (29)
Hypercholesterolemia	30/63 (48)
Morbid obesity	4/63 (7)

MI = myocardial infarction, CABG = coronary artery bypass graft

STEMI (47.3 ± 29.8 msec). As for HFLA signal duration > 38 msec, the highest percentage (45.3%) was observed on the 2nd day after the index event. Regarding the mean voltage of the terminal 40 msec of QRS-segment, the highest median value (26.0 ± 15.4 mV, range 1–64) was observed 1 month post-STEMI. As defined according to mean voltage < 40 mV, the highest percentage (94.3%) was observed on the 3rd day post-STEMI.

We found a significant gender distribution, because the male group exhibited higher prevalence of SAECG abnormalities compared to the female group. We found both abnormal duration of filtered QRS-segment (> 114 msec) on the 2nd (40% vs. 0%, $P = 0.02$), 3rd (51% vs. 12%, $P = 0.02$) and 30th day (27% vs. 0%, $P = 0.01$) post-STEMI, and of HFLA signals (> 38 msec) on the 2nd (47% vs. 37%, $P = 0.05$), 3rd (47% vs. 25%, $P = 0.05$) and 30th (42% vs. 0%, $P = 0.005$) days post-STEMI.

In patients with inferior MI, a higher prevalence of SAECG abnormalities was observed on the 2nd and 3rd days after the event. SAECG was considered pathological due to abnormal duration of both filtered QRS-segment on the 2nd (55% vs. 21%, $P = 0.03$) and 3rd (62% vs. 34%, $P = 0.07$) day post-STEMI and of HFLA signals on the 2nd (55% vs. 39%, $P = 0.04$) and 3rd (52% vs. 37%, $P = 0.07$) day post-STEMI.

The average value of CPK in the study cohort was 1541 ± 2229.1 IU/L, median 1053 IU/L. We did not find a correlation between infarct size, rate of complications and left ventricular function and QRS-segment length and prevalence of VLP in all time-point measurements.

On the 30th day post-STEMI, a higher prevalence of SAECG abnormalities was observed in patients who underwent PCI during hospitalization compared to those who did not. SAECG was considered pathological due to abnormal duration of both QRS-segment (26% vs. 10%, $P = 0.08$) and HFLA signals (43% vs. 10%, $P = 0.01$).

POST-MI COMPLICATIONS AND SURVIVAL

Complete measurements to define the presence of VLP were obtained in 52 patients on the 3rd day post-STEMI. VLP were detected in 21 patients; 31 patients did not have VLP. As shown in Table 2, there was no significant difference in the clinical characteristics of patients with or without VLP. After 2 years of follow-up 5 patients had died (8%), and after 10 years of follow-up an additional 14 patients (22%) had died, 10 (71%) due to cardiovascular complications (8 due to heart failure and 2 to recurrent STEMI). As presented in Figure 1, over 10 years of follow-up six patients with VLP died, compared to only three patients without. However, this difference did not reach statistical significance (28.6% vs. 9.7%, $P = 0.125$). The predictors of survival post-STEMI are presented in Table 3. None of the patients received an automatic implantable cardiodefibrillator (AICD), suffered SCD, or had documented ventricular tachyarrhythmias during 10 years of follow-up. None of the variables included in our analysis reached statistical significance. In addition, we did not find a correlation between infarct size, post-STEMI complications or left ventricular function with the QRS-segment length or the presence of VLP in all time-point measurements. However, patients with VLP had higher mortality over 10 years of follow-up (hazard ratio = 2.896).

Table 2. Clinical characteristics according to the presence of VLP

	VLP+	VLP-	*P* value
Age (years)	61.1 ± 11.0	61.0 ± 13.1	0.582
Male (%)	95.2	77.4	0.084
LVEF ‹ 40% (%)	38.1	25.8	0.261
Smoking (%)	61.9	45.2	0.183
DM (%)	33.3	22.6	0.293
Hypertension (%)	52.4	41.9	0.323
Hyperlipidemia (%)	57.1	38.7	0.153
PCI (in hospital) (%)	80.9	71.8	0.246
CABG (in hospital) (%)	19.0	9.3	0.133

VLP = ventricular late potentials, LVEF = left ventricular ejection fraction, DM = diabetes mellitus, PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft

Figure 1. Kaplan-Meier curve of long-term survival post ST-elevation myocardial infarction (STEMI) according to the presence of ventricular late potentials (VLP)

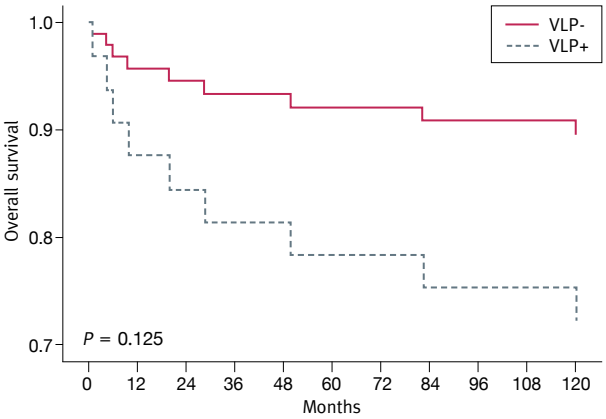

Table 3. Univariate analysis of predictors of very late mortality

	HR	95%CI	*P* value
VLP	2.896	0.646–12.986	0.165
Post-MI complications	7.481	0.770–72.703	0.083
Age	1.048	0.983–1.117	0.153
LVEF ≥ 40%	1.160	0.268–5.033	0.842

HR = hazard ratio, CI = confidence interval, VLP = ventricular late potentials, MI = myocardial infarction, LVEF = left ventricular ejection fraction

DISCUSSION

Our observational and retrospective study suggests that the detection of VLP early after STEMI has no prognostic value

for increased risk of very late (10 years) non-arrhythmic or arrhythmic cardiovascular mortality. Our results emphasize the general agreement that SAECG is a poor predictor of SCD risk.

We studied the association of VLP, as measured by SAECG in consecutive measurements in the first few days post-STEMI, with morbidity and mortality early, late and very late after STEMI, in order to supplement evidence that will help reveal the long-term prognostic value. Our study has some unique features. We included only patients with STEMI [6], defined the presence of VLP according to standard criteria [4], and followed the patients' survival for 10 years. We did not find previous studies with such a long-term follow-up.

In previous studies, VLP were found to have a mid-term prognostic value for predicting sudden cardiac death (SCD). In a prospective study, programmed electrical stimulation of the myocardium and measurements of SAECG were performed in 306 patients 1 month post-MI. Abnormal SAECG was observed in one-third of patients. After a follow-up period of 2 years, a linear correlation ($P < 0.001$) between the presence of VLP and the ability to induce ventricular tachycardia was noted [7]. Another study [8] showed a linear correlation between VLP and delayed myocardial activation. In addition, when several variables were examined in parallel, the combination of abnormal SAECG with low ejection fraction (< 40%) had the highest predictive ability for life-threatening arrhythmias [8-10]. All these results emphasize the potential clinical importance of VLP as a predictor of SCD and ventricular tachyarrhythmia.

Experimental studies in dogs with myocardial infarction have shown a significant reduction in VLP after administration of anti-arrhythmic drugs [11]. In addition, there is evidence that some therapeutic interventions, such as successful thrombolytic therapy and PCI, shorten the QRS-segment and resolve the persistence of VLP [12,13]. In a small study of seven patients with previous MI and documented ventricular tachycardia or VLP, resection of scar tissue and partial or complete sub-endocardial encircling ventriculotomy was performed. In five of the seven patients it resulted in the abolishment of VLP [14].

Abnormal SAECG may assist in localizing infarcted areas, as some researchers found greater prevalence of VLP in patients with inferior wall MI as compared to anterior MI [15]. This emphasizes the significance of characterizing VLP, since it may enable us to predict the dynamic course of the disease. The linear correlation between the prevalence of VLP and ventricular tachyarrhythmia is evidence based, but very few studies have examined their effect on early and long-term survival post-STEMI. In a study performed on 150 patients presenting with syncope over a period of 20 months, SAECG measurements were recorded [16]. Results were positive for VLP in nearly one-fifth of patients. Ventricular tachycardia (VT) was identified in 10% of those, and 75% had an abnormal SAECG. The sensitivity of SAECG increased to 82% in patients with evidence of coronary artery disease [16]. A significant correlation was found between VLP and ventricular tachyarrhythmia, but no difference in survival or recurrence of syncope was found among those with or without VLP [16]. In post-MI patients, decreased survival was observed in the setting of abnormal SAECG and additional clinical variables, making it difficult to isolate the effect of VLP on survival [3,7,8,14-16]. However, a normal SAECG has a high negative predictive value for ventricular tachyarrhythmia, and thus further investigation of arrhythmogenicity may be unnecessary [17]. This emphasizes the need for determining the prognostic value of VLP to improve early and long-term risk stratification and preventive care.

In our study we found no statistically significant correlation between the presence of VLP and infarct size or left ventricular function. However, the prevalence of VLP was more common in patients who underwent PCI during their index hospitalization, probably identifying VLP as a marker of a more severe and diffuse coronary artery disease and lower LVEF, leading the treating physician to perform PCI or send the patient to CABG. Moreover, in patients treated with PCI, a higher prevalence of VLP was observed 1 month post-STEMI. These results are the opposite of what we expected, since others found that reperfusion therapy decreases the occurrence of VLP [6]. Again, we assume that a selection bias exists, as the sickest patients underwent PCI in an era when angiography and PCI was not a mandatory pre-discharge procedure in patients who received thrombolytic therapy.

We found a higher prevalence of VLP in the male group compared with the female group. Electrocardiographic differences between men and women do exist and include a faster resting heart rate and a longer corrected QT interval in women than men. The paradox of a longer QT interval and higher incidence of torsades de pointes, but lower population-based incidence of sudden cardiac death in women, remains unresolved [18]. If we consider VLP as markers of an increased risk of SCD, then our results correlate with the higher incidence of SCD in men. Yet the results do not correlate with the shorter repolarization interval seen in men. We could not find other studies with similar results. The results exhibited statistical significance; yet, our small study included mostly male patients. Further research is required to determine whether this finding has any clinical relevance.

We also found a higher prevalence of VLP in patients with inferior wall MI. This finding is consistent with other studies that show a higher proportion of abnormal SAECG in patients with inferior wall compared to anterior wall infarction [19,20]. This concurs with the notion that VLP results from non-homogeneity in myocardial conduction because the right coronary artery partially supplies the myocardial conduction system. However, it is hard to draw firm conclusions from our relatively small study as half the results showed borderline statistical significance.

STUDY LIMITATIONS

Our study has several limitations. It included only a small number of patients: 63 consecutive patients who had been admitted to the ICCU in 2001 and received thrombolytic therapy with or without in-hospital additional revascularization. The patients were treated according to the standard of care and clinical guidelines applicable in 2001, and thus the results may not be applicable to the current era of early reperfusion with primary PCI and contemporary adjunctive treatments. The study was performed under conditions that were not ideal, considering the numerous pieces of electronic instrumentation used in the ICCU. Therefore, one cannot exclude interference from other factors such as electromagnetic fields or other mechanical noises that may have affected the results of the SAECG measurements. During such a very long-term follow-up, the clinical characteristics of the patients may develop and change continuously, thus affecting the probability of cardiovascular and all-cause mortality.

CONCLUSIONS

Over a long-term follow-up of 10 years, this relatively small study suggests that the presence of VLP early post-STEMI does not detect patients with a higher risk of cardiovascular arrhythmic or non-arrhythmic mortality.

Correspondence
Dr. S. Atar
Dept. of Cardiology, Galilee Medical Center, Nahariya 22100, Israel
Phone: (972-4) 910-7273
Fax: (972-4) 910-7279
email: shaul.atar@gmail.com

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