Effects of a β-Blocker on Ventricular Late Potentials in Patients With Acute Anterior Myocardial Infarction Receiving Successful Thrombolytic Therapy

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SUMMARY

Late potentials (LP) detected on the signal-averaged electrocardiogram (SAECG) predict arrhythmic events after acute myocardial infarction (AMI). It is also well established that successful thrombolytic therapy reduces the incidence of LP. Our aim was to evaluate the effects of a beta-blocker on LP in patients receiving thrombolytic therapy. We studied 40 patients presenting with anteroseptal AMI (< 6 hours). All patients received thrombolytic therapy and were evaluated with coronary angiography at predischarge. Eighteen patients received metoprolol (5 mg IV on admission followed by 50 mg BID). SAECG recordings were obtained serially using an ART system (40-250 Hz filter, noise < 0.5 mV) prior to thrombolytic therapy, after 48 hours and after 10 days. LP was defined as positive if the SAECG met at least 2 of the Gomes criteria. Changes observed in SAECG recordings after thrombolytic therapy were correlated with angiographic and clinical data with regard to the usage of BB. The frequencies of LP before and after thrombolytic therapy were compared with the McNemar test. There were no significant differences between the clinical characteristics, risk factors, and angiographic findings (including infarct related artery patency and LV functions) of the groups. Baseline SAECG findings were also similar between the groups. The incidence of LP significantly decreased after TT in the BB group, however, this change was not observed in patients who did not receive BB (P = 0.012, McNemar test). Beta-blockers reduce the incidence of LPs following thrombolytic therapy in patients with anterior AMI. This might be explained by the possible beneficial effect of BB on the arrhythmogenic substrate. (Jpn Heart J 2004; 45: 11-21)

Key words: Late potential, Acute myocardial infarction, Signal-averaged electrocardiography, Beta-blocker

MOST sudden cardiac deaths are caused by fatal ventricular arrhythmias precipitated by early myocardial ischemia of acute myocardial infarction (AMI).

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Electrical signals with high frequency and low amplitude following the QRS complex are termed ventricular late potentials (VLPs) and when detected on a signal-averaged electrocardiogram (SAECG) predict spontaneous or inducible ventricular arrhythmias or sudden death after AMI.[1] VLPs have been more frequently documented in AMI with reduced ejection fraction (EF%) and their prognostic significance is independent of the EF% itself.[2-5] These VLPs have been recorded in 70 to 90% of patients with sustained and inducible ventricular tachycardia after myocardial infarction, in only 0 to 6% of normal volunteers, and in 7 to 15% of patients after myocardial infarction that do not have ventricular tachycardia.[6] Early administration of beta-blockers (BB) and thrombolytic agents has shown beneficial effects on both short and long-term prognoses in AMI.[7] BB treatment is frequently used in AMI for its cardioprotective, antiarrhythmic, antianginal and antihypertensive effects. The mode of action, however, is not known. It is also well established that BB reduce the incidence of sudden deaths.[8-10] Therefore, treatment strategies that reduce the VLP incidence at the same time could reduce mortality in AMI. Until now several studies have suggested that treatments decreasing the frequency of late potentials following AMI may improve prognosis.[11,12] This study was designed to test the hypothesis whether BB treatment has possible beneficial effects on the arrhythmogenic substrate.

METHODS

Patients and study protocol: This clinical study initially included 63 consecutive patients with acute anterior myocardial infarction who were admitted to a coronary care unit within 6 hours after symptom onset. All patients received thrombolytic therapy (tissue plasminogen activator, 100 mg accelerated regimen) and were evaluated with coronary angiography at predischarge. Nitrates and aspirin administration were started in the emergency room just before the initiation of thrombolytic therapy. Heparin was first given as a 5000 U intravenous bolus and then coadministered with the thrombolytic therapy. ACE inhibitors were given upon the initiation of thrombolytic therapy. SAECG recordings were obtained serially before, 48 hours after, and 10 days after reperfusion therapy.

The diagnosis of AMI was established by the presence of at least 2 of the following WHO criteria: typical chest pain at least 30 minutes in duration, typical ST segment elevation (in at least 2 consecutive precordial leads > 0.2 mV), and elevation of serum creatine phosphokinase levels to at least twice the upper limit of normal. The success of reperfusion therapy was defined as positive if at least 2 of the following reperfusion criteria were met: 1) ST segment resolution of ≥ 50%, 2) appearance of reperfusion arrhythymias, or 3) resolution of chest pain within 90 minutes. Exclusion criteria were: (1) contraindications for thrombolytic

therapy, (2) age > 75 years, (3) history of myocardial infarction, (4) history of previous revascularization procedures, (5) presence of intraventricular conduction delay (QRS ≥ 120 ms), bundle branch block, atrioventricular block, atrial fibrillation or pacemaker dependency, (6) ejection fraction < 40% on echocardiography (for excluding the effect of reduced ejection fraction on VLPs), (7) presence of a noise level > 0.5 μV in the composite lead of the SAECG, (8) presence of clinical failure of reperfusion, (9) presence of nonpatent infarct-related arteries on coronary angiogram, (10) presence of previous beta-blocker treatment, (11) presence of continuous antiarrhythmic treatment before and after an in-hospital period, and (12) patients with heart failure (Killip class ≥ 2). Three patients who died due to cardiogenic shock during the reperfusion therapy, eight who refused to undergo coronary angiography, two with nonpatent infarct related arteries on coronary angiogram, nine with an ejection fraction < 40%, and one with normal coronaries were excluded. Therefore, the study group consisted of 40 patients. Careful continuous arrhythmia monitoring was performed by a cardiologist or trained nurses for at least 3 days in a coronary care unit, and by telemetric monitorization (Space Lab, Inc) until discharge. Life-threatening ventricular tachyarrhythmia was defined as ventricular fibrillation or sustained ventricular tachycardia. Changes observed in SAECG recordings after thrombolytic therapy were correlated with angiographic and clinical data with regard to the usage of beta-blocker treatment. Informed consent was obtained from all participants. The local ethics committee approved the study protocol. All patients received intravenous nitrates and heparin infusions (≤ 2 days) and angiotensin converting enzyme inhibitor treatment on the first day of hospitalisation.

Beta-blocker treatment protocol: Metoprolol was given as a beta-blocker. Patients with heart failure (Killip class ≥ 2, these patients were also excluded from the study), hypotension (BP < 90 mm Hg), bradycardia (heart rate < 60 bpm), or heart block (PR > 0.24 sec) were excluded and thus not given BB treatment.[13] Metoprolol was given as 5 mg intravenous boluses three times on admission. Patients were observed for 2 to 5 minutes after each bolus and if the heart rate fell below 60 beats/min or systolic blood pressure decreased below 100 mmHg, no further drug was given; a total of three intravenous doses (15 mg) was administered. If hemodynamic stability continued, 15 minutes after the last intravenous dose, the patients were started on oral metoprolol, 50 mg every 6 hours for 2 days, and then switched to 100 mg twice daily. A total of 18 patients tolerated the BB after the first administration of a low dose (group I), and 22 did not tolerate the BB after the first administration (group II).

Angiographic evaluation: Routine coronary angiography was performed 8 ± 4 days after acute anterior myocardial infarction. The severity of coronary artery stenosis was assessed and classified according to the American Heart Association

system.[14] The percent stenosis of a coronary artery was determined by a hand-held caliper measurement. Significant angiographic coronary stenosis was defined as the presence of stenosis > 70% of the luminal diameter. Multivessel disease was defined as the presence of significant stenosis in more than 1 of the 3 major epicardial coronary arteries. The presence of stenosis in the left main coronary artery with > 50% luminal diameter was also considered to be multivessel disease. Left ventricular ejection fraction was measured angiographically at the right anterior oblique view according to the area-length method. The perfusion status of the infarct-related vessel was determined according to the Thrombolysis In Myocardial Infarction (TINI) trial classification (coronary patency being defined by a grade > 2).[15] An experienced observer who was blinded to the patient's history and SAECG findings interpreted the angiographic data.

Signal-averaged electrocardiography: The SAECGs were obtained 3 times in all participating patients. SAECG recordings were performed prior to, 48 hours after, and 10 days after thrombolytic therapy. Time domain signal-averaged recordings were performed using Arrhythmia Research Technology (ART) model 1200 EPX (Austin, Texas) equipment. This system constituted a vector magnitude with a bidirectional bandpass filter system between 40 and 250 Hz combined with standard bipolar orthogonal (X,Y, Z) leads. Signal averaging of > 300 beats was performed to obtain a diastolic noise level of < 0.5 μV. The onset and offset of the QRS complex were determined by an algorithm that calculated the total QRS duration (QRSd), the root mean square voltage of the last 40 ms (RMS 40) of the QRS complex, and the duration of the terminal low (< 40 μV) amplitude signals (LAS 40) of the QRS complex. The late potentials were defined to be present if the SAECG met 2 of the following criteria: filtered QRSd > 114 ms, RMS 40 < 20 μV, or LAS 40 > 38 ms.[16]

Echocardiographic examination: Echocardiographic examinations were performed to detect patients having a left ventricular EF > 40% in the early period. At a mean of day 2 (range, 1-3), patients underwent echocardiographic evaluation using a Hewlett Packert Sonos 2500 system equipped with a 2.5 MHz transducer. Parasternal long axis and apical four chamber views were assessed according to the recommendations of American Society of Echocardiography.[17] EF was calculated using a modified Simpson formula.

Statistical analysis: Data are expressed as proportions or the mean ± SD, with statistical significance set at the 0.05 level. Students *t* test was used for the evaluation of continuous variables in the 2 groups. Chi-square analysis and Student's unpaired *t* test were used to compare variables between groups for univariate analysis. The paired Studen's *t* test was performed to compare SAECG variables before and after thrombolytic therapy. Changes in the frequency of late potentials

were compared with the McNemar test according to the presence of beta-blocker treatment.

RESULTS

The β-blocker (BB) metoprolol was administered to 18 (45%) patients. As summarized in Table I, there were no significant differences between those with and without BB in terms of clinical characteristics, including coronary risk factors, angiographic findings (including infarct related artery patency and left ventricular function), and previous medications. Clinical variables related to the reperfusion therapy were also similar in the two groups.

The SAECG findings are listed in Table II. There was no overall difference between the baseline SAECG parameters of the groups. After thrombolytic ther-

Table I. Clinical Characteristics of Patients

	Group I (with beta-blocker)	Group II (without beta-blocker)	*P* value
Number of patients	18	22	
Age (yr, mean ± SD)	54 ± 11	56 ± 9	NS
Gender (female/male)	6/12	8/14	NS
Cardiac risk factors, *n* (%)			
Family history of CAD	6 (33%)	8 (36%)	NS
Hypertension	7 (39%)	9 (41%)	NS
Diabetes mellitus	2 (11%)	3 (14%)	NS
Cigarette smoking	13 (72%)	17 (77%)	NS
Lipidemia	4 (18%)	5 (22%)	NS
Obesity (BMI >30 kg/m^2)	3 (16%)	4 (18%)	NS
Time from chest pain to thrombolysis (min, mean ± SD)	245 ± 115	250 ± 110	NS
IRA % diameter stenosis (mean ± SD)	80 ± 13	78 ± 15	NS
IRA, *n* (%)			
LAD	18 (100%)	22 (100%)	NS
One vessel disease, *n* (%)	6 (33%)	9 (41%)	NS
Multivessel disease, *n* (%)	12 (67%)	14 (59%)	NS
Echocardiographic LVEF (%, mean ± SD)	46 ± 5	45 ± 4	NS
Ventricular arrhythmias during in-hospital period, *n* (%)	6 (33%)	10 (46%)	NS
Medication before infarction			
Aspirin	3 (18%)	4 (18%)	NS
Ca antagonists	0 (0%)	0 (0%)	NS
Beta-blockers	0 (0%)	0 (0%)	NS
Anti-arrhythmics	0 (0%)	0 (0%)	NS
ACEI	0 (0%)	0 (0%)	NS

BMI = body mass index; CAD = coronary artery disease; IRA = infarct related artery, LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; ACEI; angiotensin converting enzyme inhibitors, SD = standard deviation; NS = not significant.

Table II. SAECG Parameters

	Group I (n = 18) with beta-blocker	Group II (n = 22) without beta-blocker	P value
Total QRSd (ms)			
Baseline	115 ± 32	112 ± 16	NS
48th hour	93 ± 22	110 ± 13	0.02
10th day	90 ± 10	98 ± 11	NS
LAS 40 (msec)			
Baseline	27 ± 8	30 ± 11	NS
48th hour	23 ± 7	32 ± 13	0.01
10th day	22 ± 8	33 ± 12	0.007
RMS 40 (μV)			
Baseline	41 ± 9	35 ± 18	NS
48th hour	47 ± 12	39 ± 15	NS
10th day	58 ± 7	40 ± 16	0.002

All data are expressed as the mean ± SD. LAS 40 = low amplitude signals < 40 μV; QRSd = QRS duration; RMS 40 = root-mean square voltage of terminal 40 ms of QRS complex.

apy, both the 48th hour values of total QRS and LAS, and the 10th day values of LAS and RMS were significantly better in the BB group patients. After thrombolysis, the total QRS duration and RMS 40 values changed significantly at the 10th day SAECG recording in group I (total QRS: 115 ± 32 ms versus 90 ± 10 ms after the treatment [P = 0.02]; RMS 40: 41 ± 9 μV versus 58 ± 7 μV after the treatment [P = 0.03]). The group II patients did not show any significant changes in quantitative SAECG parameters after reperfusion therapy.

The effect of successful thrombolysis on the incidence of late potentials is shown in Figure 1. The incidence of late potentials was not statistically different between the groups (22% vs 23%, $P > 0.05$) at baseline recordings of SAECG, however, in the 10th day recordings the incidence of late potentials was less frequent in the BB group than in group II (Figure 1). In group I, 4 patients (22%) had late potentials at baseline before the thrombolytic therapy and both of these patients had lost them by the 10th day, while 14 late potential negative patients had no change, and none had a change from normal to abnormal (Figure 2). These changes in group I were statistically significant (P = 0.012, McNemar test). In group II, the prethrombolytic late potentials were positive in 5 (23%) patients who remained positive on the 10th day also, but 1 changed from normal to abnormal and 16 late potential negative patients had not changed 10 days later. These changes were not statistically significant ($P > 0.05$, McNemar test). Patients in group I also experienced less frequent life-threatening ventricular arrhythmias during the in-hospital period although the difference between the groups was not

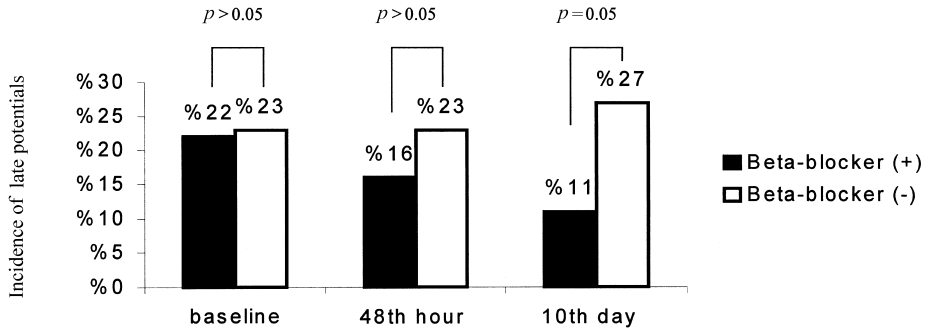

Figure 1. The incidence of late potentials decreased significantly after thrombolytic therapy in patients with beta-blocker treatment, however, this change was not observed in patients without beta-blocker treatment.

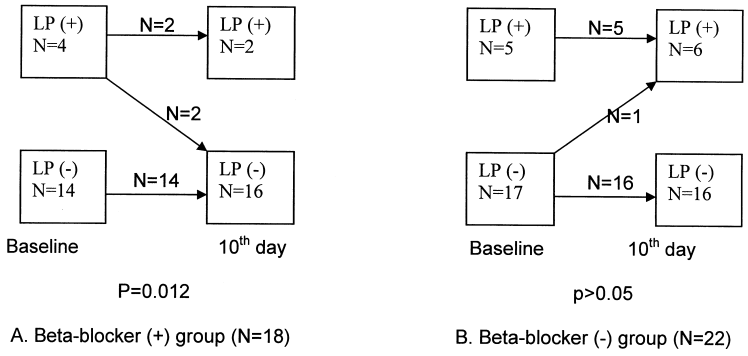

Figure 2. The change in late potential incidences in patients treated with and without the beta-blocker metroprolol.

statistically significant [6 (33%) patients in group I vs 10 (46%) patients in group II, $P > 0.05$)].

DISCUSSION

Electrical signals with high frequency and low amplitude following the QRS complex are termed ventricular late potentials and are detected on signal-averaged electrocardiograms (SAECG). Ventricular late potentials result from the

slowed down electrical transmission across the damaged myocardial area.[18-21] The presence of VLPs constitutes an anatomical substrate for repeated ventricular arrhythmia.[22] Late potentials can be detected as early as 3 hours after the onset of the chest pain and increase in prevalence in the first week of infarction. Early use of thrombolytic agents may reduce the prevalence of the late potentials after coronary occlusion.[6] Ventricular tachycardia and fibrillation are considered to be the most important mechanisms leading to sudden death following AMI. Therefore, interventions to decrease the frequency of VLPs may provide a valuable contribution to the prognosis.[12,20]

Several studies have suggested that BB reduce the incidence of overall death and sudden cardiac death after myocardial infarction.[23-25] The mechanism of this reduction in mortality is not entirely clear and may be related to a reduction in the extent of ischemic drainage, autonomic effects, a direct antiarrhythmic effect, reduction in VLP incidence, or a combination of these factors. Despite the well known clinical importance of VLP and BB, the effects of BB on VLP are not clear, although a few studies have suggested that treatment decreases the frequency of late potentials following AMI.[11] Determination of the effects of beta-blockers on VLP may help in decisions regarding antiarrhythmic treatment following AMI and to determine the mechanisms of the drugs.

In this study, we attempted to evaluate the protective effect of beta-blocker treatment on ventricular arrhythmias, by observing the changes in late potentials during successful thrombolysis. There were no significant differences between patients with and without BB treatment with regard to previous medication, left ventricular ejection fraction, and concomitant medication during the hospitalization period. None of the patients had received parenteral anti-ischemic therapy before AMI. Therefore, the changes that we observed in late potentials after successful thrombolysis in patients with BB cannot be the result of previous medication. In our study, we found that the use of BB leads to a significant decrease in the frequency of VLP. Our result was similar to that of Santarelli, *et al* who reported in the LAPIS (Late Potential Italian Study) multicenter trial that VLPs were less frequently found in patients treated than in those not treated with beta-blockers during hospitalization (15 vs 27%; $P = 0.007$); however, this effect was found only in those with an ejection fraction greater than or equal to 40%.[26] Santarelli, *et al* also found that independent predictors of VLPs by multivariate analysis were an ejection fraction < 40%, ventricular fibrillation in the acute phase, and absence of beta-blocking therapy even though the patients receiving BB were younger, had lower peak values of creatine kinase, and more frequently received thrombolysis than those who did not receive BB in their study. However, there were no significant differences between the clinical characteristics, risk factors, and angiographic findings (including infarct related artery patency and LV func-

tions) in our patient groups. So, the observed differences in VLP incidence between the groups may be related to the β-blockade in our study, but may also be due to the difference in hemodynamic response. Left ventricular ejection fraction and life-threatening ventricular arrhythmias in the early phase of AMI were not different between the two groups in our study.

To the best of our knowledge, this study is the first to investigate the serial changes observed in SAECG parameters during successful thrombolysis in patients who tolerate and do not tolerate β-blockade. In group I, the mean QRS duration and RMS 40 values changed significantly at the 10^{th} day evaluation (Table II) after thrombolysis. But patients without BB did not show any significant changes in any of the quantitative SAECG parameters after reperfusion. Also, both the late potential positive patients in the BB group before thrombolysis lost them, while there were no changes in the incidence of late potentials after thrombolytic therapy in group II patients. Therefore, our results are slightly different from other trials in the literature. In our study, we found that the use of thrombolytic treatment without BB did not lead to a decrease in the frequency of VLP. However, Tobe, *et al* suggested that thrombolytic treatment only (streptokinase, 1.5 million units) lead to a significant decrease in the frequency of VLP in the first month after AMI compared to the nonstreptokinase group.[27] They did not separate the patients with respect to clinical variables (AMI localization, LV function, infarct related artery patency, and medication). We believe that this difference can be explained by our relatively earlier SAECG recording time and because we included patients only with patent infarct related arteries, EF > 40%, and anterior AMI. Beauregard, *et al* found the high frequency QRS duration was significantly shortened and an increase in RMS 40 voltage in patients with and without BB after thrombolytic therapy.[28] They also found that the prevalence of VLP was higher in patients with Q wave infarctions or with occluded infarct related arteries. Thus, they reported that these changes in myocardial activation might be related to ischemia and reperfusion. Their study did not exclude patients with nonpatent infarct related arteries, an ejection fraction < 40%, or non-Q waves AMI, while our study was consisted of more homogenous groups and excluded patients with nonpatent infarct related arteries. Therefore, the change in VLP incidence may not be correlated with ischemia and may be related to arrhythmogenic substrates that originated from infarcted regions in our study.

The major limitation of this study is the small sample size. However, the study population was very homogeneous. Additionally, our limited number of patients and very short duration of cardiac monitoring were not sufficient to determine mortality or the anti-arrhythmic effect of metoprolol. However, patients in group I also experienced less frequent life-threatening ventricular

arrhythmias during the in-hospital period, although the difference between the groups was not statistically significant (Table I).

Conclusion: In conclusion, our results suggest that beta-blocker treatment reduces the incidence of late potentials following successful thrombolytic therapy in AMI. The arrhythmogenic substrate in the infarcted region of the ventricular myocardium and VLPs that originated from the infarcted region are electrophysiological indicators of arrhythmogenic substrate. This might be explained by the possible beneficial effect of beta-blockers on the arrhythmogenic substrate in the left ventricle. Further studies in a larger number of patients and long-term cardiac monitorization are needed to support the opinion that the effect of BB on sudden death in post-AMI patients is via a reduction in VLPs.

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