Ventricular vulnerability assessed by programmed ventricular stimulation in patients with and without late potentials

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ABSTRACT Late potentials can be recorded noninvasively with the averaging technique in about one-third of patients with coronary heart disease in whom ventricular tachyarrhythmias have not been previously documented. The prognostic significance of these findings has not yet been established. Therefore, the presence or absence of late potentials was correlated to the results of programmed ventricular stimulation (single and double premature stimuli during sinus rhythm and a paced ventricular rhythm, cycle lengths 500, 430, 370, and 330 msec) in 110 male patients (age 52 ± 5.9 years, mean ± SD). The end of the stimulation protocol was reached as soon as 4 or more ventricular echo beats (defined as an abnormal response) were induced. Late potentials were recorded in 40 patients (36.4%). The duration of late potentials was less than 20 msec in 12 patients, between 20 and 39 msec in 16 patients, and 40 msec or more in another 12 patients. In those patients with late potentials, four or more consecutive ventricular echo beats (repetitive ventricular response) were recorded more frequently (63%) than in those without (33%). The incidence of abnormal responses increased from 42% in those with late potentials of less than 20 msec to 56% in those with late potentials of between 20 to 39 msec and to 92% in those with late potentials of 40 msec or more. There was a significant correlation between left ventricular function and presence and duration of late potentials (χ² = 12.96; p < .0115) and between left ventricular function and the results of programmed ventricular stimulation (χ² = 16.24; p < .0003). In contrast, late potentials and the results of programmed ventricular stimulation were less closely associated (χ² = 5.49; p < .0643). In conclusion, late potentials proved to be a noninvasive indicator of abnormal left ventricular function, indicating an increase in ventricular vulnerability in patients that were free of symptomatic ventricular tachyarrhythmias. The predictive value of both late potentials and repetitive ventricular responses alone or in combination with regard to the occurrence of ventricular tachycardia or sudden death is still to be established.

nature of the study and had given written informed consent and the study protocol was approved by the Ethical Committee of the Medical Faculty of the University of Düsseldorf. Coronary and biplane left ventricular angiograms were recorded when all patients had been off any cardioactive drugs for at least four to five half-lives. All patients were referred to our hospital for coronary angiography to establish or exclude the diagnosis of coronary artery disease. Patients with a history of symptomatic sustained ventricular tachycardia or syncope were excluded as were patients with unstable angina pectoris that was not responding to drug therapy. Because of transient limitations in time, during part of the study only male patients born on an odd-numbered year were included. Otherwise participants were consecutive patients meeting the entrance criteria. Participation in the invasive study was refused by less than 10% of all patients eligible.

On the basis of the angiographic study, patients were classified as either normal or as having coronary artery disease with or without left ventricular contraction abnormalities. The pattern of left ventricular contraction was classified on visual evaluation of left ventricular cineangiograms (right anterior oblique projection) by two independent observers as a normal contraction pattern, regional or diffuse hypokinesia, or akinisia or dyskinesia (aneurysm). Coronary artery disease was defined as coronary arterial narrowing of greater than 50% of vessel diameter, as determined by examination of multiple projections.

Coronary angiograms revealed normal coronary arteries in 33 patients, 24 of whom also had a normal pattern of left ventricular contraction. The remaining nine patients had a dilated and diffusely hypokinetic left ventricle (dilative cardiomyopathy). One-vessel disease was present in 23, two-vessel disease in 30, and three-vessel disease in 24 patients. On the left ventricular angiograms the left ventricle was normal in 31 patients and diffusely hypokinetic in 15 patients and in 24 patients regional hypokinesia was observed. Akinisia or an aneurysmatic zone was present in 14 and 26 patients, respectively.

Determination of presence or absence and duration of late potentials from the surface body with high-gain amplification and the signal averaging technique was performed as recently described.4,11 Four electrodes for recording of bipolar electrograms were fixed on the thorax as follows: electrode 1 was placed between the sternum and the second right intercostal space parasternally, electrode 2 was placed about 5 cm medial to the apex, electrode 3 was placed in the second left intercostal space in the midclavicular line, and electrode 4 was placed in the posterior axillary line at the height of the fifth intercostal space. With these four electrodes at least four bipolar recordings were obtained in each patient by connecting the electrodes in the following way: 1 to 2, 2 to 3, 2 to 4, and 3 to 4. These electrodes were connected to a high-gain, low-noise battery-powered preamplifier (Princeton Applied Research, Model 113) with shielded leads. The preamplifier was selected on the basis of its high signal/noise ratio. It was usually used at a gain of 25-103. Band-pass filter settings (single-pole analog filters; 6 DB/octave) of 100 to 300 Hz appeared to be optimal. The high pass cutoff of 100 Hz was necessary to eliminate respiratory baseline drifts and to flatten the ST segment that otherwise would have had a steep upstroke at the gain used. The low-pass cutoff of 300 Hz was chosen in order to eliminate any noise originating from muscular activity. The preamplified signal was connected to a dual-channel signal averager (Princeton Applied Research, Signal Averager Model 4202). Both channels were combined to a single 2048 word memory. The averager was externally triggered from the QRS complex of two additional bipolar leads that were chosen to yield a high-amplitude monophasic QRS signal. The threshold was adjusted for consistent triggering at the time of averaging and the jitter for triggering was ±1.5 msec. The trigger signal initiated a sweep that, at the selected positions, lasted 204.8 msec (consisting of 2048 consecutive dwell time intervals, each lasting 100 μsec). In this mode of operation, the signal was digitized at a sampling rate of 10 kHz. The signal averager allowed continuous monitoring of the progress of the averaging process on a storage oscilloscope. In most cases the number of cardiac cycles that were averaged was between 150 to 200. Care was taken not to include premature ventricular beats. For this purpose, a special circuit was included that automatically measured the RR intervals on a beat-to-beat basis. The possibility of triggering premature complexes was thus eliminated. The total system gain was 5×105, which provides an adequate resolution of the recordings. Accordingly, the photographic tracings had a gain corresponding to 2 μV per vertical division on the oscilloscopic screen. The averaged signals were photographed with a Polaroid camera.

Late potentials were visually identified in the high-gain averaged recordings as low-amplitude activity appearing at the end of the QRS complex (figure 1). At a high amplification, it is often difficult to define the exact end of the QRS complex. Moreover, late potentials frequently constitute the terminal portion of the QRS complex from which they continuously emerge.9,17 Therefore, in contrast to our previous report,6,5 no attempt was made to time the given late potential relative to the QRS complex in the standard surface electrocardiogram. Instead, only the presence and duration of a late potential were noted. If a low-amplitude signal was identified visually at the end of the high-gain QRS complex, the first step in measurement of the duration of the late potential was to define its end. The level of baseline noise late in the ST segment was used as a reference signal. The transition between a late potential and the level of baseline noise was made at the point in time at which the low-amplitude signal exceeded three times the level of baseline noise. The onset of the late potential was then identified visually by recognizing an isoelectric section between the QRS complex and the late potential. In the more frequent situations in which the late potential continuously merged with the QRS signal, the onset of the late potential was defined as the point at which the signal amplitude markedly exceeded the midportion and terminal portion of the late potential. The duration of a given late potential was measured between the onset and the end of the signal, as defined above. The minimum required duration of a late potential was 10 msec and the maximum QRS duration was 60 msec. The electrophysiologic studies were performed within 24 hr before or after averaging. All patients were in the postabsorptive and nonsedated state and all antiarrhythmic drugs had been withheld for at least four to five half-lives.

One No. 4F (Cordis) bipolar electrode catheter (interelectrode distance 10 mm) was inserted percutaneously and positioned in the right ventricle under fluoroscopy. All signals were recorded simultaneously on an eight-channel ink-writing recorder (modified Mingograph, Siemens-Elema), care being taken to ensure appropriate isolation and grounding. Besides the intracardiac signal, leads I, II, and V1 were recorded. Programmed ventricular stimulation was performed with the Conduct System Analyzer (Medtronic; 5325). The stimuli were 1.8 msec in duration and twice diastolic threshold (always less than 2 mA).

The stimulation protocol included the introduction of single and double ventricular extrastimuli during sinus rhythm and paced ventricular rhythms at rates of 120, 140, 160, and 180 beats/min. After every eighth beat one premature stimulus was introduced at the beginning in late diastole and then progressively earlier until ventricular refractoriness was reached. The coupling interval of the premature stimulus (S1) was then prolonged again until effective capture of the ventricles was achieved. A second premature stimulus (S2) was introduced beginning at a
coupling interval about 150 msec longer than $S_1-S_2$ and then at intervals decreasing in decrements of 10 msec. A repetitive ventricular response was considered to be present if one or more nonstimulated premature depolarizations occurred after single or double premature stimulation. Since the patients studied did not have documented ventricular tachycardia, programmed ventricular stimulation was stopped as soon as 4 or more consecutive ventricular echo beats were induced. On the basis of results of a previous study, this response was considered abnormal. Ventricular tachycardia was defined as 10 or more consecutive echo beats. If ventricular tachycardia lasted longer than 30 sec (sustained ventricular tachycardia) or hemodynamic deterioration occurred before that time, the first attempt to terminate it by overdrive pacing was made.

For statistical analysis of the relationship between presence and duration of late potentials and the results of programmed ventricular stimulation, $R \times C$ contingency tests were applied. The relationship between duration of late potentials and rate of inducible ventricular responses was analyzed by analysis of variance. Finally, the complex relationship between late potentials, repetitive ventricular responses, and left ventricular function were analyzed by multiway frequency tables (log-linear model) with the BMDP program.

Results

Programmed ventricular stimulation. In all but two patients a repetitive ventricular response was induced by programmed ventricular stimulation. The results are listed in detail in table 1. Four or more consecutive ventricular echo beats were induced in 48 patients (43.6%). Ventricular fibrillation was not induced in any patient.

Averaging. Late potentials were detected by use of the averaging technique from the body surface in 40 of 110 patients (36.4%; table 2). In 12 patients the duration of these late potentials was less than 20 msec, in 16 patients between 20 and 39 msec, and in the remaining 12 patients 40 msec or more. In patients with late potentials the mean duration was 30.4 ± 15.8 msec. There was no essential difference in the mean ages of these various subgroups.

The proportion of patients with late potentials in the group with hypokinetic left ventricles without coronary artery disease (dilative cardiomyopathy) (44%) and the proportions in groups with one-vessel (48%), two-vessel (40%), and three-vessel (42%) disease did not differ substantially. However, more of those with three-vessel disease (25%) had late potentials greater

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Visual identification of a late potential at different degrees of amplification in a patient after myocardial infarction. Upper panel. At low amplification (10 $\mu$V/division), a low-amplitude signal (between arrows) is apparent after the steep upstroke of the high-amplitude part of the QRS complex. Middle panel. After rough visual identification of a late potential, a higher magnification is used (2 $\mu$V/division) for better definition of the onset and end of the late potential (see text). The median amplitude of the late potential is estimated from that part of the signal that has been identified at lower amplification (upper panel). Onset and end of the late potential is marked by arrows. Lower panel. Dual-channel recording from the same patient showing the late potential (upper tracing) at 4 $\mu$V/division and the unfiltered terminal part of the surface electrocardiogram in order to demonstrate that the late potential appears within the ST segment.

**Table 1**

<table>
<thead>
<tr>
<th>No. of echo beats</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>1</td>
<td>27 (24.5)</td>
</tr>
<tr>
<td>2</td>
<td>24 (21.8)</td>
</tr>
<tr>
<td>3</td>
<td>9 (8.2)</td>
</tr>
<tr>
<td>4</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>≥4 to 9</td>
<td>25 (22.7)</td>
</tr>
<tr>
<td>≥10</td>
<td>7 (6.4)</td>
</tr>
<tr>
<td>Sustained VT</td>
<td>12 (10.9)</td>
</tr>
</tbody>
</table>
Correlation between programmed ventricular stimulation and detection of late potentials

<table>
<thead>
<tr>
<th>Patients without late potentials</th>
<th>n</th>
<th>4–9 VE</th>
<th>≥10 VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>70</td>
<td>17 (24.3%)</td>
<td>6 (8.6%)</td>
</tr>
</tbody>
</table>

Patients with late potentials of:

| ≤20 msec | 12 | 2 (16.7%) | 3 (25%) |
| 20–39 msec | 16 | 5 (31.3%) | 4 (25%) |
| ≥40 msec | 12 | 5 (41.7%) | 6 (50%) |

VE = ventricular echo beat.

than or equal to 40 msec compared with those in the other groups (7% to 11%).

Correlation between results of averaging, programmed ventricular stimulation, and left ventricular function. In the 70 patients in whom no late potentials could be detected from the body surface, the induction of 4 or more ventricular echo beats was less frequent than in those with late potentials (table 2). Specifically, 4 or more ventricular echo beats were induced in 23 of these 70 patients (32.9%) without and in 25 of the 40 patients (62.5%) with late potentials. In the latter group the incidence of abnormal responses (4 or more ventricular echo beats or ventricular tachycardia) increased in relation to the duration of late potentials (table 2). This relationship proved significant by R × C contingency tests ($\chi^2 = 20.97; p < .01$). Of note is the fact that 11 of 12 patients (92%) with late potentials of 40 msec or more had 4 or more consecutive ventricular echo beats.

The incidence of late potentials was greater in patients with left ventricular contraction abnormalities (36 of 79 patients, 45.6%) than in those with normal findings on their left ventricular angiograms (4 of 31 patients, 12.9%; $p < .01$). Late potentials were closely associated with left ventricular function ($\chi^2 = 12.96$, $p < .0115$ as evaluated by the log-linear model). Late potentials of 40 msec duration or more were observed in two patients with hypokinesia and 10 patients with akinesia or aneurysm, but in no patient with normal left ventricular function (table 3). Of the 28 patients with late potentials of shorter duration, 10 (35.7%) had hypokinesia, 14 (50%) had aneurysms, and four (14.3%) had angiographically normal left ventricles. The four patients with late potentials and normal left ventricular angiograms had marked perfusion defects that were apparent on their thallium scans. In contrast, the association between late potentials and the results of programmed ventricular stimulation was less apparent (table 3; $\chi^2 = 5.49$, $p < .0643$ by the log-linear model), whereas inducible ventricular responses were significantly associated with left ventricular function ($\chi^2 = 16.24$, $p < .0003$). In the group of patients with 4 or more consecutive ventricular echo beats, those with aneurysms predominated (30 of 48 patients, 62.5%); only 10 of 62 patients (16.1%) with less than 4 echo beats had left ventricular aneurysms (table 3).

In patients in whom 4 or more echo beats were induced the rate (mean ± SD) of the induced responses decreased from 267 ± 33 beats/min in those without late potentials to 258 ± 37 beats/min in those with late potentials of less than 20 msec and further to 254 ± 54.5 beats/min in those with late potentials of 20 and 39 msec and to 242 ± 37.6 beats/min in those with late potentials of 40 msec or more. These differences were not significant by analysis of variance, however.

### Discussion

Previous studies have demonstrated that late potentials, recorded noninvasively with high-gain amplification, band-pass filtering, and signal averaging techniques, can be identified in a high percentage of patients with documented ventricular tachycardia, especially those with underlying left ventricular akinesia or aneurysm.\(^4\)\(^–\)\(^16\) The close correlation between the detection of late potentials and the propensity to ventricular tachycardia suggests that they reflect regional slow ventricular activation, mainly in the border zone of old myocardial infarctions.\(^17\)\(^–\)\(^24\) Recent studies using epi-

<table>
<thead>
<tr>
<th>LV function</th>
<th>&lt;4 VE</th>
<th>≥4 VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No late potentials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>20</td>
<td>47</td>
</tr>
<tr>
<td>Akinesia/aneurysm</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Late potentials &lt;40 msec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Akinesia/aneurysm</td>
<td>3</td>
<td>11</td>
</tr>
<tr>
<td>Late potentials ≥40 msec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypokinesia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Akinesia/aneurysm</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>62</td>
<td>48</td>
</tr>
</tbody>
</table>

LV = left ventricular; VE = ventricular echo beat.
PATHOPHYSIOLOGY AND NATURAL HISTORY–ARRHYTHMIA

cardial and endocardial mapping in 11 patients with left ventricular aneurysms and either without or with ventricular tachyarrhythmias have confirmed previous observations that delayed fractionated activity originates from the endocardial border zone of an aneurysm. The loss of the ability to initiate ventricular tachycardia after successful surgery for ventricular tachycardia corresponds to the abolition or decrease in duration of late potentials after surgery. The results of a prospective pilot study in 160 patients who had had recent myocardial infarctions suggest a possible value of these potentials for the identification of those patients prone to sudden death or ventricular tachycardia. Apart from these studies in patients with either documented ventricular tachycardia or after recent myocardial infarction, another group of patients without documented ventricular tachycardia or syncope has been identified in whom late potentials are detectable. Seventeen of 104 patients (16.3%) without and 32 of 69 patients (46.4%) with left ventricular akinesia or aneurysms had late potentials of varying duration. Because late potentials can be detected in about 80% of patients with documented ventricular tachycardia, one might also expect late potentials to be a predictor of ventricular tachyarrhythmia in those without previously documented episodes. However, since the former studies were done retrospectively, the true prognostic significance of late potentials in those patients apparently free of ventricular tachyarrhythmias up to the time of the study remains obscure. Whether they indeed indicate an increased susceptibility to serious ventricular arrhythmias remains to be established by long-term follow-up of these patients. Therefore, this study was undertaken to get an idea of the pathophysiologic significance of late potentials in these patients. The presence or absence of late potentials recorded from the body surface was correlated to the results of programmed ventricular stimulation, which was used as an estimate of ventricular vulnerability.

During recent years, programmed ventricular stimulation has been used to reproducibly initiate ventricular tachycardia in patients with previously observed episodes. The underlying mechanism of these inducible arrhythmias is generally believed to be reentry. The prerequisites for the genesis of reentry are unidirectional block, slow conduction, and recovery of excitability of the tissue ahead of the wavefront of excitation. Late potentials are regarded as an indicator of regional slow conduction. Thus, the presence of late potentials correlates to the second of the three prerequisites of reentry. On the basis of these considerations, one might expect patients without previously documented ventricular tachycardia in whom late potentials are present to have more vulnerable myocardium than those without late potentials.

This hypothesis proved correct in this study of 110 patients without previously documented ventricular tachycardia or syncope. Late potentials were detected by use of the averaging technique in 40 of 110 patients (36.4%). In 12 patients late potentials were longer than 40 msec in duration. In those patients in whom no late potentials could be detected, an abnormal response to programmed ventricular stimulation (defined as 4 or more consecutive echo beats) was observed less frequently than in those with late potentials. Four or more consecutive echo beats or sustained ventricular tachycardia was induced in 33% of those without late potentials and in as much as 92% of patients with late potentials equal to or greater than 40 msec (table 2).

It should be kept in mind that, due to the protocol, the initiation of 4 or more consecutive echo beats was considered to be an end point for stimulation. This was to avoid unnecessary countershocks in this population of patients that had been asymptomatic with regard to ventricular tachyarrhythmias. If the stimulation procedure had been continued, there might well have been a greater incidence of ventricular tachycardia in those patients in whom 4 to 9 ventricular echo beats were induced.

Noninvasively recorded late potentials are longer in those patients with than in those without ventricular tachycardia. Similar data were recently reported by Wiener et al. who used an epicardial and endocardial mapping method. Fragmented electrograms were recorded in from 33.0% to 58.3% of the border zone of aneurysms in patients with ventricular tachyarrhythmias but only in from 0 to 16.7% of the border zone in patients without. Endocardial activity in the border zone that extended beyond the QRS complex was noted in five of six patients with ventricular tachycardia and in one of five patients without. This suggests that a critically prolonged conduction delay may favor the occurrence of reentry. Accordingly, in the present study, the incidence of inducible ventricular tachycardia or of 4 or more ventricular echo beats increased with greater duration of late potentials. Nevertheless, conduction delay in none of the cases in this study or the previous one was sufficiently long to reach beyond ventricular refractoriness, which would make reexcitation of normal tissue possible. Thus, it has to be assumed that some stress is necessary to prolong regional conduction delay to a critical value. Similar responses to premature beats of regional fragmented
activity have been observed in experimental myocardial infarction.22

The crucial question is what relationship exists between late potentials, ventricular responses, and left ventricular function. Statistical analysis with multway frequency tables (log-linear model) indicated that left ventricular function was the predominant factor, with late potentials and repetitive ventricular responses being highly significantly correlated with it. In contrast, late potentials and repetitive ventricular responses were less closely associated. However, late potentials of 40 msec duration or more predicted, with high sensitivity, the induction of 4 or more consecutive ventricular echo beats. The observation that, even in the absence of late potentials, ventricular tachycardia could be induced in 9% of patients (table 2) demands further comment. Several mechanisms may be responsible. First, induced ventricular tachycardia may not be related to regional slow conduction but to some other mechanism, such as triggered automaticity.36 Although this explanation cannot be disregarded, another seems to be more likely. Depending on the time of arrival of excitation, a given area of slow conduction may still be activated so early that it is completely hidden within the QRS complex. Again, slow conduction may extend far enough into diastole only if some stress such as premature stimuli is exerted. One reason for the absence of inducible ventricular responses despite the presence of late potentials may be that only one site of stimulation was used; the number of positive results might have been increased if two or more sites had been used. However, it should be noted that the stimulation protocol used was extensive.

Thus, the results of this study show a close correlation between late potentials and inducibility of ventricular arrhythmias in patients without previously documented ventricular tachycardia or syncope. Although several studies were not able to show any prognostic significance of single premature stimuli induced during sinus rhythm,27-41 as originally proposed by Greene et al.,42 current studies are aimed at evaluation of patients in more extended stimulation programs, such as the one we used.43-47 The single and combined prognostic power of the results of programmed ventricular stimulation and of averaging with detection of late potentials will have to be determined. Some limited follow-up data suggest that some patients with late potentials may later develop ventricular tachycardia or suffer sudden death.5 On the other hand, programmed ventricular stimulation alone may prove to be of prognostic significance after myocardial infarction.43-47 Prolonged follow-up of patients such as those in the present study or long-term follow-up of patients beginning early after myocardial infarction will be necessary before any conclusions with regard to the value of late potentials for the identification of patients at risk of sudden cardiac death can be drawn.

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