Nonuniform Recovery of Excitability in the Left Ventricle

Joseph A. Vassallo, MD, Dennis M. Cassidy, MD, K. Elizabeth Kindwall, MD, Francis E. Marchlinski, MD, and Mark E. Josephson, MD

The purpose of this study was to determine left ventricular activation, dispersion of refractoriness, and total recovery time in patients with coronary artery disease and ventricular tachycardia and in patients with the long QT syndrome and to compare these patients with a group of normal patients. Left ventricular endocardial catheter mapping and left ventricular refractory period determination were performed in 18 patients. Group 1 consisted of seven patients with no heart disease and no arrhythmia; group 2 consisted of six patients with previous infarction and sustained ventricular tachycardia; and group 3 consisted of five patients with prolonged QT interval and previous cardiac arrest. Total left ventricular endocardial activation was significantly longer in group 2 (75±23 msec, mean±SD) compared with group 1 (34±9 msec, p<0.01) and group 3 (42±5 msec, p<0.05). Dispersion of refractoriness was significantly greater in group 3 (87±27 msec) than in group 1 (40±14 msec, p<0.01) and group 2 (53±14 msec, p<0.05). Dispersion of total recovery time was significantly greater in group 2 (90±30 msec) than in group 1 (52±14 msec, p<0.05) as well as group 3 (114±43 msec) compared with group 1 (p<0.01). We conclude that 1) compared with a control group, patients with long QT syndrome have greater dispersion of total left ventricular recovery time that is predominantly due to a wide dispersion of local refractory periods; 2) patients with previous infarction and ventricular tachycardia have a greater dispersion of total recovery times than the control group; however, this is due to a wide dispersion of activation times rather than refractoriness; and 3) potentially arrhythmogenic nonuniform recovery of excitability in the left ventricle may be due to dispersion of refractoriness or activation times, depending on the pathophysiological substrate. (Circulation 1988;78:1365–1372)

Abnormalities of activation and repolarization are believed to play an important role in the mechanism of ventricular arrhythmias.1–3 The physiological and anatomic substrate of arrhythmias is variable depending on such factors as the clinical presentation, underlying heart disease, and the response to ventricular stimulation. Ventricular tachycardia in patients with coronary artery disease and previous myocardial infarction is generally believed to be reentrant and accompanied by abnormalities of ventricular activation, whereas ventricular tachycardia in patients with the long QT syndrome and no evidence of structural heart disease is thought to be related to abnormalities of ventricular repolarization.6 Although there are data available from animal studies and in vitro preparations suggesting the above abnormalities, there are few data on activation and repolarization available in humans studied in the electrophysiology laboratory.7–11

The purpose of this study was to determine the normal dispersion of local refractory periods and total recovery time in patients with a normal left ventricle and without history of arrhythmia and to compare with the normal group the left ventricular dispersion of refractoriness and total recovery time in patients with coronary artery disease and ventricular tachycardia and in patients with the long QT syndrome.

Patients and Methods

Patient Population

The study population consisted of 18 patients. The mean age was 46 years with a range from 17 to 72 years. There were 10 men and eight women.
Group 1 consisted of seven patients (age, 45±17 years; mean±SD) with no evidence of underlying heart disease based on invasive or noninvasive evaluation and without history of ventricular tachycardia. These patients were studied for evaluation of supraventricular arrhythmias, and after informed consent was obtained, they underwent the experimental protocol. Group 2 consisted of six patients (age, 63±8 years) with coronary artery disease, previous myocardial infarction, and documented spontaneous ventricular tachycardia. All patients in group 2 had ventricular aneurysm documented at ventriculography. Group 3 consisted of five patients (age, 31±18 years) with the long QT syndrome. These patients had no evidence of underlying structural heart disease based on invasive or noninvasive testing, had a long QT interval, and experienced documented spontaneous cardiac arrest. After informed consent was obtained, all patients underwent electrophysiological evaluation while not taking antiarrhythmic medications. Programmed electrical stimulation was performed in all patients with up to triple ventricular extrastimuli according to methods previously described.12 No patient in groups 1 or 3 had ventricular tachycardia or fibrillation induced, whereas all patients in group 2 had reproducibly induced sustained uniform ventricular tachycardia.

**Catheter Mapping Technique**

Catheter mapping studies were performed according to previously described methods.13-15 Informed, written consent was obtained from all patients. All mapping studies, refractory period determinations, and programmed stimulation were performed during the same study. All protocols have been approved by the Hospital of the University of Pennsylvania Committee on Studies Involving Human Beings, Philadelphia, Pennsylvania. A left ventricular catheter was positioned in each patient by the retrograde arterial approach. A catheter at the right ventricular apex was used as a fixed reference during left ventricular mapping. There were 12 standard mapping sites in the left ventricle (Figure 1). The catheter position during left ventricular mapping was verified by fluoroscopy in multiple planes. Standard 6F quadripolar electrode catheters with a 5-mm interelectrode distance were used for mapping. Intracardiac electrograms were displayed simultaneously with three surface electrocardiographic leads (leads I, aVF, and V4) on a switch beam oscilloscope at filter frequencies of 30–500 Hz. Individual sites were mapped with a fixed reference point, and maps were constructed based on activation times determined from the fixed reference (onset of the surface QRS complex).

**Mapping Analysis**

All data were stored on a magnetic tape and simultaneously recorded with an ink-jet recorder at speeds of 150–200 mm/sec. Local electrograms were recorded for determination of activation times with electrodes having a 10-mm interelectrode distance at variable gain. The onset of the QRS complex taken from three simultaneous surface leads was used as a zero point of reference to determine activation times. The local activation time at each site was taken as the point on the electrogram at which the highest amplitude rapid deflection crossed the baseline.16 In instances in which the local electrogram was fractionated and had no discrete deflection greater than 1 mV in amplitude, the point where the rapid deflection of the highest amplitude component of the electrogram crossed the baseline was used as the local activation time. In instances where the highest amplitude deflection did not cross the baseline, the component of the highest amplitude deflection with the greatest slope was used as the local activation time.

**Refractory Period Determination**

Ventricular effective refractory periods were determined at each left ventricular site with bipolar stimulation at two times diastolic threshold. Refractory periods were determined after an eight-beat drive at a cycle length of 600 msec. At least two refractory period determinations were made at each site to ensure reproducibility. Refractory periods...
Table of Definitions

Local refractory period: Longest S1–S2 coupling interval that failed to elicit a response after an eight-beat drive from each left ventricular site.

Local activation time: Interval (msec) from the onset of the surface QRS complex to the point where the rapid deflection of the largest deflection of the local electrogram crossed the baseline.

Total endocardial activation time: Duration (msec) from the earliest to the latest site of left ventricular activation.

Total recovery time: Local activation time (relative to the surface QRS complex) and the local refractory period (msec) at each left ventricular site (Figure 2).

Dispersion of refractoriness: The widest range of refractory periods within the left ventricle for each patient.

Dispersion of total recovery time: The difference between the earliest and latest recovery times in the left ventricle for each patient.

and local activation times were determined at a mean of 10±2 left ventricular sites/patient.

Statistical Analysis

Analysis was performed with one-way analysis of variance with p less than 0.05 considered significant.

Results

QT Interval

The corrected QT interval was longer in patients with coronary artery disease and ventricular tachycardia (group 2) (422±40 msec) (mean±SD) than in patients with no heart disease and no arrhythmia (group 1) (380±22 msec), but this difference was not significant. The corrected QT interval in patients with the long QT syndrome (group 3) was 528±31 msec and was significantly longer than in group 1 (p<0.001) and group 2 (p<0.005).

Control Group

Total left ventricular endocardial activation time was a mean of 34±9 msec in group 1 patients. The mean dispersion of ventricular refractoriness in this group was 40±14 msec, and the mean dispersion of total recovery time was 52±14 msec (Table 1).

Ventricular Tachycardia and Coronary Artery Disease

Patients with coronary artery disease had the most abnormal endocardial activation (Table 1). The mean endocardial activation time was significantly prolonged at 75±23 msec compared with group 1 patients (p<0.01). Dispersion of refractory periods in this group was not significantly longer than in control group 1 (53±14 vs. 40±14 msec) (Table 1). Total recovery times in group 2 were longer than group 1 (90±30 vs. 52±14 msec, p<0.05) (Table 1).

Long QT Syndrome

There was no significant difference in total endocardial activation time in group 3 (42±5 msec) compared with group 1 (34±9 msec) (Table 1). Group 3 had a significantly greater dispersion of left ventricular refractoriness (87±27 msec) than group 1 (40±14 msec) at p<0.01 (Table 1). Similarly, group 3 had a significantly greater dispersion of total recovery time (114±43 msec) than group 1 (52±14 msec) at p<0.01 (Table 1). Examples of representative patients from each group are shown in Figures 2–4.

Adjacent Left Ventricular Sites

In addition to a comparison of total endocardial activation time of the left ventricle and dispersion of refractoriness and total recovery time based on the whole left ventricle, further analysis was performed based on adjacent left ventricular sites. These data present the greatest differences of local activation time, refractory periods, and total recovery time determined at adjacent sites mapped in each patient. These data are presented in Table 2.

Discussion

Background

Potential mechanisms of ventricular tachyarrhythmias include triggered activity, enhanced automaticity, and reentry.17–20 These mechanisms are influenced by a number of factors including the clinical presentation of the arrhythmia, underlying heart disease of the patient, morphological characteristics of the tachycardia, and the response of the tachy-
cardia to programmed stimulation. Although abnormalities of ventricular activation and repolarization have been shown to be important in the genesis and maintenance of arrhythmias, the exact role of these abnormalities regarding the above mechanisms has not been defined.

The mechanism of reentry has the most apparent relation to abnormalities of activation and recovery. To initiate reentry, an initial circulating impulse must travel in only one direction around the closed circuit from the point of its initiation. Thus, unidirectional block must be present. In addition, conduction must be slow to allow recovery in the initial area of activation and maintenance of the reentrant circuit. The cause of unidirectional block and slow conduction may be due to differences in refractory periods or due to the influence of nonuniform anisotropy or both. The abnormalities of conduction in coronary artery disease most certainly are caused by nonuniform anisotropy produced by the infarction. Dispersion of refractoriness and failure of conduction in anisotropic tissue have been shown experimentally to produce the unidirectional block associated with reentry. It is thus important to evaluate the activation and repolarization process to further characterize the substrate of ventricular arrhythmias.

Normal Heart and No Arrhythmia

Our data on duration of endocardial activation are similar to those reported by Durrer et al. and consistent with those previously reported from our laboratory with the same mapping techniques in a separate group of patients.

This study is an attempt to determine the normal range of refractory periods at a large number of left ventricular sites with programmed stimulation. Wellens et al. reported the dispersion of refractory periods measured at six right and left ventricular sites in a patient with the long QT syndrome, and they reported this to be 35 msec. Monophasic action potentials have been used as a measure of repolarization in the right and left ventricles; however, refractory period determinations have not been reported, and the number of sites was far more limited.

We believe the concept of “total recovery time” is important and may not be adequately addressed in other studies. Previous investigators have used the term “nonuniform recovery of excitability” and have looked at only local refractory periods or action potential duration in determining this variable. In our study, we defined total recovery time at each left ventricular site as the sum of the local activation time (relative to the onset of the
surface QRS complex) and the refractory period determined at that site. As shown in Figure 2, it is only after this interval of time that a given site can be activated again. For instance, site 4 is activated at 30 msec and has a refractory period of 235 msec; thus, site 4 can only be activated again 265 msec after the onset of the initial QRS complex.

Thus, the ability of a given left ventricular site to be reactivated at any point in time is dependent on two factors: its activation time relative to the QRS complex; and the refractory period at that site. In the normal human heart, activation of the left ventricle is relatively uniform (within about 34 msec) and is followed by relatively uniform refractory periods, a difference of only 40 msec between the shortest and longest refractory period.

With these definitions, the dispersion of total recovery time is a manifestation of uniform or nonuniform recovery of excitability. A diagrammatic representation of this is presented in Figure 2. The dispersion of total recovery times in this patient is the difference between the earliest site activated and the fully recovered (site 5) and the latest site activated and the fully recovered (site 12). Clearly, from this figure, total recovery times are dependent not only on local refractory periods but also on local activation times. The earliest site of activation, therefore, may not be the earliest site fully recovered because its local refractory period may be longer than the refractory period at a site activated later with a shorter refractory period. Our data suggest that in the normal left ventricle in a patient without a history of ventricular arrhythmia the dispersion of total recovery times is about 50 msec.

**Coronary Artery Disease and Ventricular Tachycardia**

There are several studies indicating that the surface QRS complex and the QT interval of patients suffering from myocardial infarction increase in duration after infarction and that these changes may be associated with increased risk of arrhythmias and sudden death. Data with the signal-averaged electrocardiogram also suggest a relation between the duration of the signal-averaged QRS complex and arrhythmic events after infarction. Extrapolation from such data indicates that abnormalities of ventricular activation and repolarization after myocardial infarction may play a role in the development of ventricular arrhythmias.

We have previously shown that patients with myocardial infarction and ventricular tachycardia have prolonged endocardial activation times compared with a normal group. The present study population also had significantly longer total endocardial activation times than the control group; however, there was no significant difference between the two groups regarding dispersion of refractoriness.

Analysis of Figure 3, a diagrammatic representation of activation and recovery time in a patient with coronary artery disease and ventricular tachycardia, shows that despite relatively normal dispersion of left ventricular refractoriness, this patient does have significantly greater dispersion of total recovery time than the control group. The figure

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**Table 2. Data Based on Adjacent Left Ventricle Sites**

<table>
<thead>
<tr>
<th></th>
<th>Endocardial activation time (msec)</th>
<th>Dispersion of refractoriness (msec)</th>
<th>Dispersion of total recovery time (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal left ventricle (no ventricular tachycardia)</td>
<td>25±7</td>
<td>32±11 pawn&lt;0.05</td>
<td>41±14 pawn&lt;0.05</td>
</tr>
<tr>
<td>Coronary artery disease (with ventricular tachycardia)</td>
<td>42±11 pawn&lt;0.05</td>
<td>42±20 pawn&lt;0.01</td>
<td>75±41 pawn&lt;0.01</td>
</tr>
<tr>
<td>Long QT interval</td>
<td>31±9 pawn&lt;0.05</td>
<td>77±31 pawn&lt;0.05</td>
<td>85±33 pawn&lt;0.05</td>
</tr>
</tbody>
</table>

Data are mean±SD.
shows that in this population, dispersion of total recovery time is increased relative to the normal group (90 vs. 52 msec) as a function of prolonged endocardial activation time (75 vs. 34 msec) rather than an increase in the dispersion of local refractoriness (see Table 1).

Thus, based on our data, patients with coronary artery disease and ventricular tachycardia (manifested clinically and induced with programmed stimulation) demonstrate abnormal recovery of excitability in the left ventricle. The major contribution to this nonuniform recovery of excitability is an abnormality of activation rather than repolarization as measured by local refractory periods.

**Long QT Syndrome**

Patients with the long QT syndrome are regarded as having either an acquired form of QT prolongation (pharmacological or metabolic) or congenital QT prolongation.\(^6\) Our study group includes only patients in the latter group. Patients with a long QT interval are reported to be at an increased risk of suffering from ventricular arrhythmias, and these arrhythmias are usually polymorphic in nature and are not usually induced by programmed stimulation.\(^6,36\) It is generally believed that QT prolongation represents delayed ventricular repolarization related to either abnormal action potential duration or refractory periods and that these abnormalities lead to the development of ventricular arrhythmias.\(^6\)

Although there is a great deal of clinical data available on this group of patients, there is little data on ventricular activation or left ventricular refractory periods in this group. Our data suggest that these patients, who otherwise have normal left ventricular function, also have normal total endocardial activation times. However, compared with the normal population, dispersion of left ventricular refractory periods was greatly increased in this population.

Analysis of Figure 4 shows that dispersion of total recovery time was markedly increased in this population compared with the normal group. However, as opposed to the patients with coronary artery disease and ventricular tachycardia, total recovery time in patients with the long QT interval was prolonged as a result of a wide dispersion of local refractory periods in the setting of normal endocardial activation times.

Of interest, our patients with a prolonged QT interval and history of ventricular arrhythmias did not have ventricular tachycardia or ventricular fibrillation induced by standard techniques of ventricular stimulation, a finding consistent with other studies. The absence of inducibility by programmed stimulation indicates that these arrhythmias are probably not due to reentry. Recent studies have focused on early afterdepolarizations as a possible mechanism of arrhythmias in this syndrome.\(^37,38\) Based on our data, we are unable to comment on the relation between the wide dispersion of refractoriness in this group of patients and the mechanism of arrhythmia in the long QT syndrome. The commonly held implication is that a wide dispersion of refractoriness is characteristic of reentry. Our data do not support this because those patients with arrhythmias that are most certainly reentrant (i.e., sustained ventricular tachycardia due to coronary artery disease) exhibit a "normal" dispersion of refractoriness. The abnormalities of conduction thus appear more important for inducibility. It should be emphasized that we used dispersion of refractoriness and total recovery time only to characterize the "substrate" or "markers" present in these patient groups. Studies with mapping at higher densities may show that localized dispersion of refractoriness is critical to reentry; however, this was not possible in our study. The actual role of these markers in the mechanism of tachycardia is not established.

**Limitations**

There are several important limitations to our study. Despite having evaluated endocardial activation times and refractory period determinations at two to three times as many sites as previous investigators, we still recognize that this represents a limited number of left ventricular sites. Although we have demonstrated significant differences among the three patient groups studied, the role of these differences in the genesis of arrhythmias has not been addressed. Of importance, the size of a reentrant circuit or a "site" of increased automaticity or triggered activity has not been established. Thus, the concept of "local" activation and "local" refractory periods must be kept in perspective. We have analyzed our data at adjacent left ventricular sites in an attempt to look at local differences; however, because our mapping sites represent a relatively large endocardial area, this attempt at identifying local differences is obviously crude when compared with the more precise mapping techniques used by the "cellular" electrophysiologist. If more sites were studied, further differences possibly would be demonstrated. However, this cannot be reliably and reproducibly done in the clinical electrophysiology laboratory at the present time. Further studies with high-density mapping and refractory period determinations performed in the operating room may be more fruitful. Rather than comment on a particular role that the abnormalities of activation and recovery may play, we present this data as part of the arrhythmogenic physiological substrate in each group.

The reproducibility of activation times and refractory period determinations also is limited with standard mapping techniques. Certainly, refractory periods may vary, depending on such factors as the autonomic nervous system. This may especially be relevant in studying patients with the long QT syndrome. However, all refractory periods were measured multiple times to ensure reproducibility, and our laboratory has the greatest experience in activation mapping by catheter.
Finally, we should point out, again, the limitations of catheter mapping in general. These include the accuracy of sites sampled, limited number of sites sampled, and the determination of local activation times when analyzing abnormal electrograms.

Regarding activation, it should be noted that activation times were determined during sinus rhythm. These would obviously be different after premature depolarizations. Thus, dispersion of total recovery times would be different after premature beats. This is important because premature beats are important in both the clinical initiation of ventricular arrhythmias and the induction of arrhythmias by programmed stimulation. Despite these limitations, we should point out that the same techniques were applied to all three patient groups and that the significant differences presented stand firm.

Conclusion

From this data, we conclude that 1) compared with patients with a normal left ventricle and without ventricular arrhythmias, patients with the long QT syndrome have greater dispersion of total left ventricular recovery time that is predominantly due to a wide dispersion of local refractory periods; 2) patients with coronary artery disease and ventricular tachycardia have a greater degree of dispersion of total recovery time than normal patients; however, this is due to a wide dispersion of activation times rather than refractoriness; and 3) potentially arrhythmogenic nonuniform recovery of excitability in the left ventricle may be due to dispersion of refractoriness or activation times depending on the pathophysiological substrate.

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