METHODS

Programmed Electrical Stimulation Studies for Ventricular Tachycardia Induction in Humans. I. The Role of Ventricular Functional Refractoriness in Tachycardia Induction

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Closely coupled extrastimuli are frequently necessary to induce ventricular tachycardia at electrophysiologic study. Although induction usually requires propagated extrastimuli, systematic evaluations of minimal coupling intervals have focused on nonpropagated measures (effective refractory periods) rather than on propagated measures (functional refractory periods). The effects of procedural factors on ventricular functional refractory periods were examined in 10 patients. Like the effective refractory period, the functional refractory period shortens with rapid pacing cycle lengths ($281 \pm 12$ ms at a cycle length of 600 ms; $260 \pm 15$ ms at a cycle length of 400 ms) and with multiple extrastimuli ($279 \pm 16$ ms with one extrastimulus; $214 \pm 16$ ms with two extrastimuli). The effects of multiple extrastimuli exceed those of shortening pacing cycle length. Unlike the effective refractory period, the functional refractory period is affected by recording site (increasing as the distance from the pacing site increases) but is not affected by increasing the stimulus intensity above twice diastolic threshold ($282 \pm 14$ ms at 2 times threshold; $282 \pm 13$ ms at 16 times threshold) or by increasing the pulse width above 2 ms ($282 \pm 13$ ms at a pulse width of 2 ms; $282 \pm 14$ ms at a pulse width of 5 ms).

The effect of varying stimulus intensity on ventricular tachycardia induction was examined in a second group of 11 patients with documented, spontaneous ventricular tachycardia. No change in ventricular tachycardia inducibility accompanied changes in stimulus intensity from 2 to 10 times threshold. These data support the use of a stimulus intensity of twice threshold and a pulse width of 2 ms for clinical ventricular tachycardia induction studies with progressive potency provided first by shortening pacing cycle length and then by multiple extrastimuli.

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Programmed electrical stimulation during transvenous catheter electrophysiologic study is widely used in the investigation and management of patients with ventricular tachyarrhythmias (1–4). Although some minimal standards have been established (5), there is no consensus as to the most appropriate design for a ventricular tachyarrhythmia induction protocol using these techniques (6). Because ventricular tachyarrhythmia induction is usually accomplished with propagated right ventricular extrastimuli and because it is often facilitated by minimizing the extrastimulus coupling interval, study of the determinants of the minimal coupling interval (ventricular functional refractory period) should provide information relevant to the design of ventricular tachyarrhythmia induction protocols.

The purpose of this investigation was to identify those procedural factors that determine ventricular functional refractoriness, to assess the relation between functional refractoriness and tachycardia induction and to use this information to devise a rational ventricular tachyarrhythmia induction protocol.

Methods

Study patients. Patients undergoing a clinically indicated transvenous catheter electrophysiologic study participated in the first phase of this investigation. Patients with documented, symptomatic, sustained ventricular tachycardia participated in the second phase. These individuals were otherwise unselected.
Twenty-one patients participated in the study; 10 in phase I and 11 in phase II. The mean age of phase I patients was 51 ± 16 years. Four of these 10 patients had a history of prior myocardial infarction and 6 had no identifiable structural heart disease. The mean age of phase II patients was 54 ± 15 years and all were referred for the management of documented symptomatic ventricular tachycardia. Ten of these 11 patients had a history of prior myocardial infarction and 1 patient had congestive cardiomyopathy.

**Phase I procedures.** After informed consent was obtained and all electrophysiologically active medications had been withdrawn for at least four half-lives, an electrophysiologic study was performed in each of the 10 patients. In addition to the clinical study, two quadripolar electrode catheters with a 1 cm interelectrode distance were positioned in close proximity at the right ventricular apex. The distal pair of electrodes of one catheter, designated the pacing catheter, was used for bipolar right ventricular stimulation with a constant current programmable stimulator (Bloom Associates). The three remaining electrode pairs (the proximal pair of the pacing catheter, the proximal pair of the extra catheter and the distal pair of the extra catheter) recorded bipolar ventricular electrograms (Fig. 1). Radiographs were obtained in two orthogonal views (30° right anterior oblique and 60° left anterior oblique) to permit calculation, by trigonometric analysis, of the minimal distance from the distal electrode of the pacing catheter to the midpoint of each recording electrode pair (Fig 1). Surface electrocardiographic leads I, aVF and V₁ were recorded simultaneously with bipolar intracardiac electrograms filtered between 30 and 500 Hz on an Electronics for Medicine VR-16 recorder at a paper speed of 100 mm/s.

**The extrastimulus protocol is presented in Table 1.** The initial stimulator settings were a pulse width of 2 ms, a stimulus intensity equal to the late diastolic excitability threshold, an eight beat drive train with a basic cycle length of 600 ms and a single extrastimulus that scanned diastole at 10 ms decrements to the ventricular effective refractory period. The process was then repeated with stepwise variation of stimulus intensity, pulse width, basic drive cycle length and number of extrastimuli as indicated in Table 1. For double extrastimuli the coupling interval between the first extrastimulus and the last train stimulus was set 10 ms above the ventricular effective refractory period and a second extrastimulus scanned diastole at 10 ms decrements to its effective refractory period. Thus, right ventricular refractory curves (Fig. 2) from three right ventricular recording sites were obtained under 14 conditions, including two duplicate applications with identical stimulator settings which served as time controls.

**Phase II Procedures**

A second group of 11 patients with documented symptomatic ventricular tachycardia was examined with the extrastimulus induction protocol developed during the first

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**Table 1. Study Ventricular Extrastimulus Protocol (phase I)**

<table>
<thead>
<tr>
<th>Step</th>
<th>SI</th>
<th>Pulse Width (ms)</th>
<th>BCL (ms)</th>
<th>No. of Extrastimuli</th>
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<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>600</td>
<td>1</td>
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<tr>
<td>2</td>
<td>2</td>
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</table>

Stimulator settings for each step of the phase I study protocol. The two time control pairs of stimulator settings are steps 2 and 7 and steps 4 and 10. BCL = basic pacing cycle length; SI = stimulus intensity (multiples of threshold).
To provide recording site-specific information, latency is defined as the apparent pause between the time of the stimulus artifact and the time of local ventricular activation at each recording site rather than as the apparent pause between the time of the stimulus artifact and the time of the first evidence of ventricular activation at any site. The intrinsic latency ($L_1$) at each recording site was defined as the $S_1 V_1$ interval. Maximal latency due to the first extrastimulus ($L_2$) was defined as the $S_2 V_2$ interval at the functional refractory period of $S_2$. The difference between $L_2$ and $L_1$ was termed the change in latency of $S_2$ ($ΔL_2$) (Fig. 3). Maximal latency of the second extrastimulus ($L_3$) was defined as the $S_3 V_3$ interval at the functional refractory period of $S_3$. The difference between $L_2$ and $L_3$ was termed the change in latency of $S_3$ ($ΔL_3$).

The effective refractory period, functional refractory period and change in latency of $S_4$ could be similarly defined. However, because the $S_4$ technique usually induced ventricular tachycardia in the study group, these data were infrequently obtained and will not be reported.

Sustained, inducible ventricular tachycardia was defined as the induction, by the extrastimulus technique, of a rhythm, of consecutive ventricular depolarizations with a cycle length of less than 500 ms persisting for at least 30 seconds or requiring premature termination because of serious hemodynamic compromise.

Statistical analysis. Continuous data are presented as mean ± 1 SD and significant differences ($p < 0.05$) were determined by two-way analysis of variance and Duncan's multiple range test. The significance of the correlation of distance between the recording site and the pacing site and $ΔL_2$ was examined by linear regression. Chi-square analysis was used to determine the significance of changes in dichotomous data.

### Table 2. Ventricular Extrastimulation Protocol for Clinical Induction Studies (phase II)

<table>
<thead>
<tr>
<th>Step</th>
<th>Extrastimulation</th>
<th>Cycle Length (ms)</th>
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<tr>
<td>1</td>
<td>$S_1 S_2$</td>
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<td>8</td>
<td>$S_1 S_2 S_3 S_4$</td>
<td>500</td>
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<tr>
<td>9</td>
<td>$S_1 S_2 S_3 S_4$</td>
<td>400</td>
</tr>
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</table>

Using a stimulus intensity of twice diastolic threshold and a pulse width of 2 ms delivered at the right ventricular apex; repeated, if necessary, from a second right ventricular site or left ventricle, or both. $S_1 S_2$ = single extrastimulus; $S_1 S_2 S_3$ = double extrastimuli; $S_1 S_2 S_3 S_4$ = triple extrastimuli.
Results

Phase I

Effects of recording site. Refractory curves obtained under all conditions were qualitatively similar to the typical right ventricular refractory curve shown in Figure 2. In each instance, the minimal, intermediate and longest functional refractory periods, were recorded from the electrode pairs closest to, intermediate from and most distant from the pacing site, respectively. Linear regression revealed a weak ($r = 0.42$) but significant ($p < 0.05$) correlation between $\Delta L_2$ and the calculated distance between that recording site and the pacing site. Variations in other potential determinants of the functional refractory period did not alter this relation. For clarity, subsequent results consider only the functional refractory period recorded from the proximal electrode pair of the pacing catheter.

Effects of stimulus intensity. Figure 4 illustrates the effects of varying stimulus intensity on the effective and functional refractory periods. The right ventricular effective refractory period shortened progressively as stimulus intensity was increased. The effective refractory period was $276 \pm 18$ when the stimulus intensity was equal to late diastolic threshold and it decreased to $236 \pm 14$ ms ($p < 0.05$) at a stimulus intensity of 16 times late diastolic threshold. A significant decrease in effective refractory period occurred as the stimulus intensity was increased from threshold to 2 times threshold, from 2 to 4 times threshold and from 8 to 16 times threshold. In contrast, although the functional refractory period was significantly decreased by increasing the stimulus intensity from threshold to twice threshold ($292 \pm 17$ to $282 \pm 14$ ms, $p < 0.05$), further increments in stimulus intensity did not further reduce functional refractoriness. As shown in Figure 3, the different responses of the effective and functional refractory periods to increases in stimulus intensity result from a gradual increment in the $\Delta L_2$.

Effects of pulse width. The pattern of change in the effective and functional refractory periods with variations in the stimulus pulse width (Fig. 5) was similar to that observed with changes in stimulus intensity. With a pulse width of 1 and 5 ms the effective refractory period was...
Effects of pacing cycle length. Figure 6 illustrates the effects of varying basic ventricular pacing cycle length on effective and functional refractory periods. The right ventricular effective refractory period shortened progressively as ventricular pacing cycle length decreased. With a pacing cycle length of 600 and 400 ms the effective refractory period was 244 ± 15 and 218 ± 9 ms, respectively (p < 0.05). A significant decrease in effective refractory period was observed as pacing cycle length was decreased from 600 to 500 ms and from 500 to 400 ms (p < 0.05). In this instance, the change in right ventricular functional refractory period paralleled changes in effective refractory period. With a pacing cycle length of 600 and 400 ms the functional refractory period was 281 ± 12 and 260 ± 14 ms, respectively (p < 0.05). No significant change in ΔL₂ accompanied these changes in pacing cycle length.

Effects of multiple extrastimuli. The effects of a single extrastimulus and double extrastimuli on effective and functional refractory periods are shown in Figure 7. Both the effective and functional refractory periods were markedly reduced when two ventricular extrastimuli were used. The effective refractory period was 244 ± 17 ms with a single extrastimulus and was 188 ± 23 (p < 0.05) with double extrastimuli. The functional refractory period was 279 ± 16 ms with a single extrastimulus and was 214 ± 16 ms (p < 0.05) with double extrastimuli. There was no significant difference between ΔL₂ and ΔL₃.

Figure 5. Effects of varying pulse width (PW) on the effective refractory period (ERP), the functional refractory period (FRP) and ΔL₂. Format and abbreviations as in Figure 4.
tachycardia was not altered by changes in the stimulus intensity, there was variability in the number of extrastimuli required to induce tachycardia in some patients. The number of extrastimuli required to induce ventricular tachycardia at a stimulus intensity of twice threshold decreased in one patient and increased in two patients compared with that required at a stimulus intensity of 10 times diastolic threshold. The remaining seven patients had ventricular tachycardia induced by the same number of extrastimuli at 2 and 10 times threshold. The variability in these results is compared with that observed with duplicate applications of the stimulation protocol at a fixed stimulus intensity of 10 times diastolic threshold in Figure 8. The proportions of patients with inducible tachycardia using the same number of or more or fewer extrastimuli were not different.

Coupling intervals and induced tachycardia. The 10 phase II patients with inducible ventricular tachycardia each had their tachycardia induced three times with varying stimulus intensities in a random sequence. At the point of tachycardia induction, the coupling intervals and induced tachycardia were compared.

Figure 7. Effects of one ($S_1\rightarrow S_2$) versus two ($S_1\rightarrow S_2\rightarrow S_3$) extrastimuli on the effective refractory period (ERP), functional refractory period (FRP) and change in latency ($\Delta L$). Format as in Figures 4, 5 and 6.

Phase II

Stimulus intensity and induced tachycardia. Variations in the stimulus intensity above twice late diastolic threshold had no effect on the inducibility of ventricular tachycardia. Ten of the 11 phase II patients had sustained monomorphic ventricular tachycardia induced at some point during the first application of the stimulation protocol using a stimulus intensity of 10 times diastolic threshold. The same 10 patients also had monomorphic ventricular tachycardia induced during all other applications of the stimulation protocol regardless of the stimulus intensity used.

Number of extrastimuli and induced tachycardia. Although the presence or absence of inducible ventricular...
Figure 8. Phase of extrastimulus protocol inducing ventricular tachycardia in 11 phase II patients with a stimulus intensity of twice threshold (2T), the randomized application using a stimulus intensity of 10 times threshold (10T*2) and the initial application using a stimulus intensity of 10 times threshold (10T*1). NI = no ventricular tachycardia induced, S2 = single extrastimulus at drive cycle lengths of 600, 500 and 400 ms, S3 = double extrastimuli; S4 = triple extrastimuli.

cardia induction, the coupling interval between the terminal stimulus artifacts and between the terminal propagated ventricular electrograms observed at 2 and 5 times threshold were compared with those observed at 10 times threshold. Thus, 20 comparisons were available for each coupling interval. The coupling intervals were reproducible within 10 ms on 8 of 20 stimulus coupling interval comparisons and on 17 of 20 electrogram coupling interval comparisons (p < 0.05). Similarly, the coupling intervals were reproducible within 20 ms on 9 of 20 stimulus coupling interval comparisons and on 19 of 20 electrogram coupling interval comparisons (p < 0.05). Therefore, at the point of ventricular tachycardia induction the coupling interval between the terminal ventricular electrograms (analogous to the functional refractory period) was more consistent than the coupling interval between the terminal stimulus artifacts (analogous to the effective refractory period).

**Ventricular refractory periods.** The effects of stimulus intensity, pacing cycle length and number of extrastimuli on right ventricular effective and functional refractory periods observed in phase II patients were similar to those reported for phase I patients.

**Discussion**

**Determinants of the functional refractory period.** The ventricular functional refractory period is the minimal coupling interval between two propagated ventricular depolarizations and has at least two components: 1) the minimal ventricular capture interval, and 2) the difference in subsequent arrival times at the ventricular recording site. The former is estimated by the ventricular effective refractory period and the latter by the change in local latency. The effects of extrastimulus conditions on effective refractory periods have been reported (8,9). However, the effects of extrastimulus conditions on changes in local latency and, therefore, on functional refractory periods have not been systematically examined in humans. The data of this study indicate that changes in local latency and functional refractoriness are determined by at least five procedural factors.

The functional refractory period is reduced by minimizing the distance between the pacing and recording sites. The effective refractory period is not affected by the site of ventricular recording. Despite recording from sites in close proximity to the pacing site, no evidence of local ventricular capture without propagation was found. The progressive increase in functional refractory period with more distant recording sites is the result of a greater change in local latency. Like the effective refractory period, the functional refractory period is decreased by shortening the basic pacing cycle length or by the addition of more than one extrastimulus. The effect of the latter exceeds that of the former.

However, changes in pacing cycle length and number of extrastimuli alter effective and functional refractory periods in parallel without significant changes in local latency. Unlike the effective refractory period, the functional refractory period is not affected by increasing the stimulus intensity above twice diastolic threshold or by increasing the pulse width above 2 ms. Further increments in these determinants decreased the effective refractory period but increased the change in latency such that the functional refractory period did not change. Therefore, the different effects of extrastimulus conditions on the effective and functional refractory periods are due to the contribution of the change in local latency to the functional refractory period.

**The electrophysiologic property described by the change in local latency is affected by the distance between the recording site and the pacing site.** Therefore, this measurement includes a conduction phenomenon. Although the data from this study cannot further refine the physiologic mechanisms of the effects of extrastimulus conditions on the change in latency, they are consistent with in vitro observation of the slowed conduction velocity of extrastimuli applied during the period of partial repolarization (phase III) of a preceding action potential (10). It follows that maneuvers such as increasing stimulus intensity or pulse width which permit extrastimulus capture earlier during phase III of a preceding action potential, would further slow conduction velocity and, therefore, increase the change in latency. However, maneuvers such as shortening basic drive cycle length or the use of multiple extrastimuli, which also shorten the preceding action potential duration, should have less or no effect on the conduction velocity or the change in latency of an extrastimulus.

**Implications for the design of extrastimulation protocols.** In general, the aim of clinical ventricular extrastimulation protocols in patients with ventricular tachyarrhythmias is to maximize the probability of reproducing the patient's clinical tachyarrhythmia while minimizing the probability of the induction of nonclinical ventricular tach-
yarrhythmias. Nonclinical tachyarrhythmias are more frequently induced when closely coupled propagated extrasimuli are used (11, 12). Because the minimal coupling interval of propagated extrasimuli is measured by the functional refractory period, definition of the determinants of functional refractoriness is important for the rational design of a ventricular tachyarrhythmia induction protocol. Such a protocol should include manipulation of the determinants of the functional refractory period to produce a stepwise reduction of this minimal coupling interval. The data of this study indicate that this aim can conveniently be accomplished by a protocol similar to that outlined in Table 2.

The functional refractory period is decreased less by shortening the basic pacing cycle length within the physiologic rate range than by the use of multiple extrasimuli. Therefore, progressive shortening of this minimal coupling interval may be obtained by first shortening the basic pacing cycle length and then using multiple extrasimuli. The data of this study show that the shortest functional refractory period is recorded closest to the site of stimulation. Therefore, if this extrasimulus protocol fails to induce ventricular tachycardia when applied at the right ventricular apex, the protocol should be repeated from a site closer to the area of myocardium presumed essential to tachycardia induction to achieve a shorter coupling interval at that critical site. Because increasing stimulus intensity above twice threshold or increasing pulse width above 2 ms does not shorten the functional refractory period, these maneuvers should not increase the yield of ventricular tachycardia induction. With respect to stimulus intensity, the foregoing hypothesis was tested in phase II of this study. Increasing stimulus intensity from 2 to 10 times diastolic threshold had no significant effect on ventricular tachycardia induction in these patients with documented spontaneous ventricular tachycardia. Although the phase II study group is small, the results are consistent with previous observations that increasing stimulus intensity above twice threshold has little, if any, effect on the induction of clinical ventricular tachycardia (13). However, increasing stimulus intensity has been noted to increase the likelihood of inducing ventricular fibrillation (14, 15).

These considerations indicate that the determinants of ventricular tachycardia and ventricular fibrillation induction by programmed stimulation are different, and suggest an optimal stimulus intensity of twice threshold for ventricular tachycardia induction. Although increasing stimulus intensity above twice diastolic threshold did not shorten the functional refractory period, we have shown, as have others (9), that this maneuver does shorten the effective refractory period. Because this maneuver does not influence ventricular tachyarrhythmia induction, the determinants of effective refractoriness are less important to ventricular tachyarrhythmia induction than are the determinants of functional refractoriness.

The data from the present study were obtained by applying the extrastimulus protocol at ventricular sites with normal diastolic thresholds. Michelson et al. (16) demonstrated that a stimulus intensity of five times threshold increases the yield of ventricular tachyarrhythmia induction over that observed with a stimulus intensity of twice threshold when the extrastimulus protocol is applied to areas within a myocardial infarction in a canine model (16). Therefore, if the clinical extrastimulus protocol is applied to an area of myocardium with a high diastolic threshold, the yield of ventricular tachycardia induction may be increased by using a stimulus intensity of five times threshold.

Conclusions. Determinants of the functional refractory period include five procedural factors. These factors are stimulus intensity, pulse width, basic cycle length, number of extrasimuli and the proximity of the pacing and recording sites. The data obtained support the use of an extrastimulus protocol using a stimulus intensity of twice late diastolic threshold and a pulse width of 2 ms, gradually shortening the functional refractory period first by shortening the basic pacing cycle length, second by using multiple extrasimuli and finally by repositioning the pacing catheter.

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References


