Termination of Sustained Ventricular Tachycardia by Ultrarapid Subthreshold Stimulation in Humans

Mohammad Shenasa, MD, PhD, René Cardinal, PhD, Teresa Kus, MD, PhD,
Pierre Savard, PhD, Martin Fromer, MD, and Pierre Pagé, MD

Our purpose was to investigate the efficacy, safety, and electrophysiological mechanism of ultrarapid subthreshold electrical stimulation in terminating sustained ventricular tachycardia (VT) in humans. Fifteen patients with inducible sustained hemodynamically stable VT and whose VT cycle length ranged between 295 and 440 msec (337 ± 60 msec) were included in this study. The stimulation threshold and ventricular myocardial effective refractory period were determined during VT, and the values ranged between 0.4 and 1.2 mA (mean, 0.7 ± 0.3 mA) and between 185 and 245 msec (mean, 225 ± 20 msec), respectively. Trains of ultrarapid subthreshold stimulation were delivered with cycle lengths of 100 to 10 msec in decremental steps of 10 msec. A 5-second pause was allowed between each step (decrement). A 2-msec pulse width was used in all patients, and a 4-msec pulse width was also tested in eight patients. Any apparent captured beat was disregarded. In eight (53%) patients, ultrarapid subthreshold stimulation terminated VT, and in the remaining seven (47%) patients, it did not. The lowest subthreshold stimulation that effectively terminated VT was 0.05 mA. In 10 patients, the site of early activity during VT was determined by endocardial catheter mapping, and subthreshold stimulation more effectively terminated VT in eight patients when it was applied close to the site of early activity. In seven patients who underwent mapping-guided arrhythmia surgery, subthreshold stimulation was applied close to the site of early activity and successfully terminated VT. In no patient did subthreshold stimulation produce acceleration of VT or induce ventricular fibrillation. We conclude that ultrarapid subthreshold stimulation, when applied appropriately, provides a safe and effective method for termination of VT in humans. Further investigations and experiences with this method are warranted. (Circulation 1988;78:1135–1143)

Subthreshold electrical stimulation delivered within the effective refractory period is reported to inhibit the response to extrastimuli that ordinarily produce a response in human heart.1 The electrophysiological mechanism of this phenomenon has recently been investigated and is thought to be due to increased local refractoriness.2–4

Different modalities of programmed electrical stimulation have been used to terminate ventricular tachycardias (VT) in humans. The use of these modalities, without the backup of an automatic defibrillator, are limited by the potential acceleration of tachycardia or its degeneration to ventricular fibrillation.5–8

Because only limited data are available on the effect of subthreshold stimulation on VT,9 we conducted this study to investigate the effectiveness and safety of ultrarapid subthreshold stimulation on termination of sustained VT in humans. In selected patients who underwent arrhythmia surgery, the mechanism of VT termination by subthreshold stimulation was investigated during computerized epicardial and endocardial mapping. The present study describes our initial experience with this method.

Patients and Methods

Fifteen patients with documented spontaneous sustained VT underwent intracardiac electrophysiological studies. There were nine men and six women aged 60 ± 11 years (range, 34–76 years). All patients had coronary artery disease and suffered remote myocardial infarction. All patients gave informed consent, and none of them were receiving antiarrhythmic drugs for at least five half-lives. Patients were included in this study only if their VT...
were reproducibly inducible by programmed ventricular stimulation, had stable cycle length (i.e., variation in the cycle length less than 20 msec) and hemodynamically were well tolerated, and could be terminated with programmed stimulation. Intracardiac electrophysiological studies were done with the technique previously reported from this laboratory.\textsuperscript{10} Programmed ventricular stimulation to induce VT was done with the previously reported protocol.\textsuperscript{10} Briefly, induction of VT was attempted with from one to three extrastimuli introduced after trains of eight beats at two cycle lengths and applied at the right ventricular apex or outflow tract. Programmed stimulation was done with twice-diastolic threshold and pulse width of 2 msec. In 10 of the 15 patients who were potential candidates for arrhythmia surgery, catheter mapping was performed with the technique described by Josephson et al.\textsuperscript{11} After the tachycardias were determined to be reproducibly inducible and hemodynamically stable, one quadripolar electrode was inserted percutaneously into the right or left femoral artery and, under fluoroscopic guidance, positioned in the left ventricle. VT was then reinduced, and left ventricular catheter mapping was done to determine the site of early activity during tachycardia. At each explored site, ultrarapid subthreshold stimuli were delivered (see “Stimulation Protocol”) during VT. After completing the endocardial mapping, the tachycardia was terminated, and the electrodes were removed. Seven patients underwent arrhythmia surgery and cryoablation of the arrhythmogenic area with intraoperative epicardial and endocardial probe mapping (in three patients) and/or computer-assisted mapping in four patients. These techniques have been previously described.\textsuperscript{12} Briefly, intraoperative epicardial and endocardial mapping was done with an on-line computer-assisted mapping procedure. During normothermic cardiopulmonary bypass, both epicardial and endocardial mapping of all morphologically distinct tachycardias were attempted. Sixty-four unipolar electrograms (referred to Wilson’s central terminal) were simultaneously recorded from the epicardial surface with a sock array of electrodes or from the endocardial surface with a balloon electrode introduced into the left ventricular cavity through the superior pulmonary vein and the mitral annulus.

Signals were amplified by programmable-gain analog amplifiers and converted to a digital format by a computer-based digital recorder at a rate of 500 samples/second.\textsuperscript{13} Several acquisition files, each containing up to 20 seconds of continuous data recording, were stored on hard disk. Selected data stored on disk were retrieved and analyzed on the PDP 11/23 and “host” computer (Digital Equipment Corporation, Maynard, Massachusetts) with custom-made software. Data were analyzed in 1-second time windows for each of the 64 recorded electrograms. Activation times were detected as the points of most rapid change in potential with a negative slope in excess of $-0.5 \text{ mV/msec}$. Whenever this criterion was not fulfilled, it was concluded that local excitation did not occur at the corresponding recording site, either as a result of inexcitability or block of conduction, as discussed in our previous reports of experimental studies.\textsuperscript{14–16} All computer-selected activation times were verified on a videoscreen by the operator. Isochronal maps were drawn automatically by the computer for selected cycles of ventricular activation with use of the point of earliest activation as the zero reference time. Isochronal lines were shown labeled with their appropriate timing value. Timing at individual sites was indicated only when it was not adequately represented by isochronal lines either because they were located at the edge of the electrode array or because they were surrounded by sites displaying inexcitability. After the early site of activity was determined, trains of subthreshold stimuli were delivered to the selected endocardial sites via the balloon electrode contacts.

**Stimulation Protocol During Ventricular Tachycardias**

Stimulation threshold was determined during both sinus rhythm and VT. Similarly, the effective refractory period of the ventricular myocardium was determined during sinus rhythm, during ventricular pacing at drive cycles of 600 and 400 msec, and during VT. During stable sustained VT, trains of subthreshold stimuli were delivered during diastole with cycle lengths beginning at 100 msec and decreasing by 10 msec at each repetition until a cycle length of 10 msec was reached (Figure 1). The values for subthreshold stimulation ranged between 10% and 90% of the stimulation threshold. In each case, at least three values of subthreshold stimulation were tested at each site. The number of cycles varied depending on the cycle length of VT. A pulse width of 2 msec was used in all patients; in selected cases, a pulse width of 4 msec duration was also tested. Stimulation was done in a bipolar mode with a positive distal contact. In addition, unipolar stimulation was tested and compared with bipolar stimulation in five patients. This protocol was tested at several endocardial sites as follows: right ventricular apex in all patients, right ventricular outflow tract in nine patients, and left ventricular pacing at multiple sites in 10 patients. In seven patients who underwent mapping-guided arrhythmia surgery for refractory VT, subthreshold stimulation was also tested in the same manner. A 5-second pause was given between each stimulation sequence. The protocol was immediately terminated if any patient developed symptoms such as chest pain, dizziness, or shortness of breath during VT.

**Definitions**

Ventricular effective refractory period was defined as the longest stimulus coupling ($S_iS_j$) interval that failed to capture the ventricle.
Sustained monomorphic VT was defined as ventricular rhythm induced by programmed electrical stimulation with rates more than 100 beats/min with consistent beat-to-beat QRS morphology and lasting longer than 30 seconds. VT that were included for this particular protocol, however, lasted for more than 1 minute and were hemodynamically stable. None of these patients required cardioversion to terminate VT.

Successful termination by subthreshold stimulation was defined as those trains that successfully immediately terminated VT without any apparent captured beats determined by isochronal maps, local electrograms, and/or surface electrocardiographic features, such as changes in QRS morphology or tachycardia cycle length. In selected cases, to further illustrate lack of capture by subthreshold stimulation that caused VT termination, subthreshold stimulation was then applied during sinus rhythm and no evoked response was seen.

Results

Stimulation threshold determined for all the sites with a pulse duration of 2 msec during sinus rhythm and VT were 0.3–1.2 mA (0.75 ± 0.3 mA) and 0.4–1.2 mA (0.7 ± 0.3 mA), respectively (p = NS). Ventricular effective refractory periods measured at the right ventricular apex during sinus rhythm, during ventricular pacing at drive cycles of 600 and 400 msec, and during VT were 190–260 (245 ± 25), 195–250 (235 ± 20), and 185–265 (225 ± 20) msec, respectively.

Effect of Subthreshold Stimulation on Ventricular Tachycardia Termination

In eight of 15 patients (53%), VT was successfully terminated at least once while varying the intensity, duration, or site of stimulation (Figure 2). In the remaining seven patients (47%), VT was not terminated during any attempt. Overall, 33 episodes of VT were tested, using all subthreshold stimulation steps, and were terminated in 17 out of 33 (51.5%). In 12 of these 17 VT episodes, reproducibility of subthreshold stimulation in terminating VT was tested twice, and nine of 12 (75%) VT were reproducibly terminated.

Effect of Cycle Length of Subthreshold Stimuli on Ventricular Tachycardia Termination

The influence of cycle length variation from 100 to 10 msec in 10-msec decrements was investigated at the same site of stimulation in 11 patients. Subthreshold stimulation at cycle lengths of 100 and 90 msec never terminated VT. Stimulation at cycle lengths of 80–30 msec were more effective (63% of all the attempts) than at cycle lengths of 20 and 10 msec (33% of the attempts). Cycle lengths of 50 and 40 msec were the most effective (85% of the attempts).

Effect of Number of Cycles of Subthreshold Stimuli

Trains of 2, 4, 6, 8, 12, 16, 20, 30, and 40 cycles were tested in six patients. At a given site, with fixed pulse duration and stimulation strength, trains with a higher number of cycles were more effective (i.e., eight to 12 cycles were more effective than two to six cycles [63% vs. 35%]), suggesting the cumulative effect of subthreshold stimuli.

Effect of Stimulation Duration (Stimulus Pulse Width)

A 2-msec pulse width was used in all patients, and a 4-msec pulse width was also used in eight patients. In four patients, subthreshold stimulation terminated VT with a pulse duration of 4 msec, whereas a 2-msec pulse duration failed (Figure 3). Unipolar subthreshold stimulation was neither more nor less effective than bipolar stimulation in terminating VT.
Effect of Ventricular Tachycardia Cycle Length

VT cycle lengths in these patients ranged between 295 and 440 msec (337 ± 60 msec). In this patient group, VT termination by subthreshold stimulation was independent of VT cycle length. For the purpose of hemodynamic stability, the majority of patients included in this study did not have very fast tachycardias. Although the train cycles were fewer in patients with faster VT (see “Patients and Methods”), the success rate of VT termination by subthreshold stimulation was constant at different VT cycle lengths.

Effect of Morphology of Ventricular Tachycardia

Successful termination of VT by subthreshold stimulation was independent of VT morphology (i.e., right vs. left bundle branch block morphology). Of the 33 VT episodes, 19 (58%) demonstrated right and 14 (42%) showed left bundle branch block morphology; VT termination among different morphologies was distributed equally.

Relation to Site of Origin of Ventricular Tachycardia

The most powerful determinant of successful VT termination by subthreshold stimulation was the proximity of the stimulation site to the site of early activity during VT. This was well documented during endocardial catheter mapping as well as during intraoperative mapping (Figure 4).

Acceleration of Ventricular Tachycardia or Induction of Ventricular Fibrillation

No apparent ventricular capture occurred during subthreshold stimulation in this patient group, and subthreshold stimulation never produced acceleration of VT by more than 20 msec or induced ventricular fibrillation.

Intraoperative Mapping

Subthreshold stimulation was performed during VT in seven patients undergoing surgery guided by epicardial and endocardial mapping. In five patients, subthreshold stimuli were delivered through endocardial electrodes located near to the origin of tachycardia; in the other two patients, it was applied through electrodes sutured at the epicardium. In the former case, the effects of subthreshold stimulation on activation patterns were unclear because of the proximity of subthreshold stimulation to the origin.
of tachycardia. Figure 5 shows the modification of the endocardial activation pattern in the latter case.

The upper traces show induction and three trials of subthreshold stimulation during VT. The third application was followed by two ventricular beats at a longer cycle length and VT termination. The isochronal map of a beat of programmed stimulation applied to the left ventricular epicardium (S3) shows an endocardial breakthrough on the lateral wall near to the apex. During tachycardia (beats 1–6), the earliest activity was recorded at the apical margin of the region of infarction. The activation patterns of beats during subthreshold stimulation that did not affect tachycardia (2) were similar to those of beats preceding stimulation (1). Acceleration of the conduction patterns was seen during subthreshold stimulation producing a transient modification of the electrocardiogram (4) or termination of tachycardia (6), by comparison to the patterns of preceding beats (3 and 5, respectively). The two final beats (7) that followed the effective trial displayed a similar activation pattern with accelerated impulse propagation. It is likely that capture did not occur during subthreshold stimulation because the patterns seen during subthreshold stimulation (2,4,6) were different from those seen during programmed stimulation (S3), although the same pair of electrodes was used for both.

Figure 6 shows four selected unipolar electrograms recorded during the response to programmed stimulation (S3) and the seven beats of VT described in Figure 5. The electrograms were recorded at the site of VT origin (Panel A, QS unipolar morphology), at sites activated midway in the VT cycle (Panels B and C, RS morphology), and at the site of terminal activity (Panel D, wider RS morphology). Note that the unipolar waveform morphologies of electrograms recorded during subthreshold stimulation (2,4,6) were similar to the morphologies of electrograms recorded during the preceding beats (1,3,5), although subthreshold stimulation accelerated the activation times of sites B, C, and D during beats 4 and 6.

Discussion

The present study demonstrates that ultrarapid subthreshold electrical stimuli, if delivered appropriately, can terminate VT in humans without apparent capture. Second, subthreshold stimulation during VT never produced faster VT or induced ventricular fibrillation. Therefore, it seems to be a safe method. Needless to say, further investigations are necessary because this study describes only a small number of patients. Of the several variables tested to determine the effectiveness of subthreshold stimulation in terminating VT, proximity to the early site of activity during the tachycardia was the most powerful determinant. This was well demonstrated during both endocardial catheter mapping and intraoperative mapping. Prystowsky and Zipes,1 Windle et al,2 and Skale et al3 demonstrated, both in humans and in dogs, that subthreshold stimuli delivered within the effective refractory period of atrium and ventricle prolonged the refractory period. These investigators called this phenomenon "inhibition." Previous studies1–4 suggested that the spatial relation of the subthreshold stimuli to the site of stimulation was critical for the phenomenon of inhibition to occur. In our study, we found that the site of delivery of subthreshold stimuli in relation to the site of early activity during VT was critical.
**FIGURE 4.** Tracings of termination of ventricular tachycardia by subthreshold stimulation: effect of site of stimulation. Subthreshold stimulation was applied at several endocardial sites during intraoperative mapping. Subthreshold stimulation at sites F₁ (anterior left ventricle) and E₁ (mid-left ventricle) did not terminate the tachycardia. Subthreshold stimulation at site D₁ (posterior midseptum) successfully terminated the tachycardia.
Other investigators have described successful termination of both supraventricular and VT by ultrarapid suprathreshold stimulation. In these studies, one stimulus of the train stimulation captured the atrium or the ventricle and caused termination of the tachycardia. Swerdlow et al recently investigated the effects of ultrarapid suprathreshold train pacing in the human ventricle during ventricular pacing or sustained VT. In the present study, we exclusively investigated the effect of subthreshold stimulation during VT. None of the trains of subthreshold stimuli produced any apparently captured beat, although it is possible that stimuli may have locally captured a critical part of the presumed reentrant circuit, without producing a QRS modification. Ruffy et al reported a patient in whom a single extrastimulus delivered during ventricular effective refractory period reproducibly terminated VT. A similar phenomenon has been observed by El-Sherif et al in an experimental model of VT. In their experiments, a single suprathreshold stimulus produced local capture but failed to propagate and, therefore, terminated VT without evoking a QRS complex. In our series, single- and double-subthreshold pulses did not terminate tachycardia.

Electrophysiological Mechanism

Termination of VT by subthreshold stimulation may be explained, in the absence of capture, by electrotonically mediated local effects. The effects of cathodal or anodal current pulses on cardiac electrical activity were reported by Weidmann in 1951. Early studies were reviewed by Hoffman and Cranefield. Because, in the present study, stimulation was done with bipolar extracellular electrodes, myocardium was exposed to both cathodal (depolarizing) and anodal (hyperpolarizing) influences.

Recently, Antzelevitch and Moe described inhibitory or facilitatory effects of subthreshold responses on excitability and conduction in Purkinje fibers. The spatial and temporal relation between the subthreshold depolarization and the next impulse determined whether the outcome would be inhibitory or facilitatory. They also demonstrated that the effects of two or multiple subthreshold responses could be additive. In the light of these experiments, it is conceivable that multiple subthreshold stimuli could break up reentrant activity either by producing local block (inhibition) or by accelerating conduction in the reentrant pathway (facilitation). In fact, Figure 5 provides evidence that conduction might have been enhanced by subthreshold stimulation that...
terminated VT. A similar effect has also been reported in a patient with accessory pathway.24

Of course, it is possible that liberation of endogenous substances as catecholamines may have played a role in VT termination by subthreshold stimulation.

Implications

The findings of this study have several implications. First, it may have mechanistic implication. Although not compared in the present study, termination by subthreshold stimuli may favor reentry mechanism opposed to other causes of VT in humans (i.e., triggered activity or enhanced automaticity) because acceleration or resetting of the tachycardias was not observed. Furthermore, it is our experience that in another group of patients subthreshold stimulation is not effective against so-called idiopathic VT, which are most probably not reentrant (personal data not included in the present study).

Second, because the proximity to the site of early activity is critical to the termination of VT by subthreshold stimulation, it may be useful to determine the site of early activity of VT. Third, this method, although preliminary, may be useful in the management of patients with sustained VT. Further studies are warranted before this method is widely
used. Gang et al\textsuperscript{25} have also recently reported promising effectiveness of subthreshold stimulation in terminating supraventricular tachycardias in patients with accessory pathways.

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\textbf{References}


\textbf{KEY WORDS} • subthreshold stimulation • ventricular tachycardia
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