THERAPY AND PREVENTION

VENTRICULAR ARRHYTHMIAS

Summation and inhibition by ultrarapid train pacing in the human ventricle

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ABSTRACT Trains of ultrarapid stimuli that begin late in the refractory period have been reported both to produce early single captures to terminate tachyarrhythmias and to inhibit the response to subsequent threshold stimuli. To determine which characteristics of trains facilitate capture and which enhance inhibition, we compared the right ventricular strength interval relationship for single extrastimuli (S$_2$) with that for 100 Hz trains with a duration of 100 msec in 29 patients. Pulse frequency was varied in 12 patients (50, 100, and 200 Hz) and train duration (50, 100, and 150 msec) was varied in 11 patients; the effect of procainamide (10.1 ± 2.3 µg/ml) was assessed in 10 patients. Relative to S$_2$, 100 Hz trains with a duration of 100 msec prolonged the effective refractory period (ERP) at low current strength (inhibition), but shortened the ERP at high-current strength (summation): at 0.5 mA, the train ERP was 47 ± 6 (SEM) msec longer than the S$_2$ ERP (p < .001); at 16 mA it was 12 ± 1 msec shorter (p < .001). Trains prolonged the functional refractory period (FRP) slightly at low currents (13 ± 3 msec, p = .001 at .05 mA), but did not shorten FRP significantly at high currents (2 ± 2 msec, p = NS at 16 mA) because of increased stimulus-response latency. Inhibition increased with increasing pulse frequency (p < .001), increasing train duration (p < .001), and procainamide (p < .01). Summation increased with increasing pulse frequency (p < .001), but not increasing train duration or procainamide, suggesting that inhibition and summation depend on different electrophysiologic mechanisms. We then compared trains and S$_2$ during hemodynamically stable, monomorphic ventricular tachycardia at current strengths of twice threshold (20 tachycardias) and 10 mA (15 tachycardias). At twice threshold, trains prolonged the ERP by 55 ± 5 msec (p < .001) and the FRP by 25 ± 5 msec (p < .001). At 10 mA, they shortened the ERP by 13 ± 2 (p < .001), but did not alter the FRP. At twice threshold, inhibition prevented trains from terminating two tachycardias that could be terminated by S$_2$. Our findings indicate that high-current, low-frequency trains are best for single-capture termination of ventricular tachycardia.


SUBTHRESHOLD STIMULI during the refractory period have been reported both to inhibit and to facilitate the response to subsequent stimuli.1–8 In dogs, short trains of ultrarapid, subthreshold stimuli produce more inhibition than a single stimulus.3 In contrast, a train of three subthreshold stimuli, which did not produce depolarization when delivered alone or in pairs, has been reported to depolarize the human ventricle (summation).1

A systemic investigation of the effects of repetitive stimulation during the refractory period on myocardial excitability has not been reported. The results of such a study are not only of basic interest but also have important clinical implications. Trains can cause single, earliest captures to terminate supraventricular or ventricular tachycardia without the time-consuming diastolic scanning necessary with single extrastimuli.9,10 Alternatively, subthreshold trains that inhibit local activation have been reported to terminate ventricular tachycardia.11

In this study, we first investigated the effects of train stimulation on inhibition and summation in the human right ventricle during ventricular pacing. We studied the effect of varying current strength, train duration, and pulse frequency and the effect of procainamide. Then we applied our findings to termination of ventricular tachycardia.

Methods

Patients. Sixty-four patients undergoing clinically indicated electrophysiologic testing were enrolled in this study after they gave written, informed consent. Group I consisted of 40 patients
in whom the effects of trains were studied during ventricular pacing. In this group, patients were excluded if the pacing threshold exceeded 0.25 mA (four patients), threshold varied by more than 0.05 mA during the study (six patients), or a single ventricular extrastimulus induced six or more repetitive ventricular responses (one patient). Thus, data are reported for 29 group I patients (24 men and five women, age range 20 to 73 years). Fifteen patients had coronary artery disease and previous myocardial infarction, five had dilated cardiomyopathy, three had rheumatic valvular disease, and six had no identifiable structural heart disease. The indications for electrophysiologic study were sustained ventricular tachycardia or ventricular fibrillation in 17 patients, nonsustained ventricular tachycardia in five patients, syncope in four patients, and supraventricular tachyarrhythmias in three patients.

Group II consisted of 22 patients in whom the effects of trains were studied during sustained hemodynamically stable, monomorphic ventricular tachycardia. Patients were excluded because single ventricular extrastimuli or trains caused acceleration of ventricular tachycardia (two patients), the cycle length of ventricular tachycardia varied by more than 20 msec during the study (two patients), or morphologically identical tachycardias could not be induced reproducibly (two patients). Thus, data are presented for 16 patients (14 men and two women, age range 43 to 72 years) who had coronary artery disease and a previous myocardial infarction and were studied because of clinical sustained ventricular tachycardia.

**Electrophysiologic study.** In group I, all antiarrhythmic drugs, including digoxin and β-blockers, were discontinued for five half-lives. Quadrupolar catheters with a 5 mm interelectrode distance were positioned in the right ventricular apex and outflow tract. Pacing was performed through the distal bipolar of the catheter at the apex; the diastolic pacing threshold was less than 0.25 mA in all patients (0.21 ± 0.03 mA). Electrograms were recorded from the proximal bipolar of both catheters and filtered at 50 to 400 Hz. Six surface electrocardiographic (ECG) leads and intracardiac electrograms were recorded simultaneously on magnetic tape and on a multichannel recorder at a paper speed of 250 mm/sec. A custom-built programmed stimulator (Bloom Associates) was used for extrastimulus and train pacing. Pacing was performed with square-wave constant-current pulses 1 msec in duration.

In group II, data were collected during 20 morphologically distinct ventricular tachycardias. Pacing and recording techniques identical to those in group I patients were used during hemodynamically stable, reproducibly inducible, monomorphic ventricular tachycardia (cycle lengths 399 ± 62 msec). Femoral arterial pressure was monitored continuously, and mean arterial pressure was stable within 10 mm Hg. The pacing threshold was 0.22 ± 0.07 mA during sinus rhythm. Six tachycardias were initiated in the control state and 14 during antiarrhythmic therapy with a type 1A antiarrhythmic drug (five tachycardias), a type 1A drug combined with mexiletine (five tachycardias), encaïnide (two tachycardias), and amiodarone (two tachycardias).

**Pacing protocol: group I.** The strength-interval relationship was determined at a pacing cycle length of 500 msec for single extrastimuli (S₂) and ultrarrapid single-capture trains after eight consecutive pacing impulses (S₁), which resulted in ventricular capture. First, S₂ was introduced with an S₁/S₂ interval of 350 msec and a current strength of 0.5 mA, and the S₁/S₂ interval was shortened by decrements of 5 msec until S₂ failed to depolarize the ventricle. The current strength for S₁ and S₂ was then increased and the process was repeated. In the first five patients, the increments for current strength were 0.5 mA between current strengths of 0.5 and 2.0 mA, 1.0 mA between current strengths of 2.0 and 8.0 mA, and 2.0 mA between current strengths of 8.0 and 16.0 mA. In the last 24 patients, measurements were made only at current strengths of 0.5, 1.0, 2.0, 4.0, 8.0, and 16.0 mA. The current strength was then decreased to 0.5 mA, and S₂ was replaced by a train, with the initial train stimulus introduced 350 msec after the last S₁. The interval between S₁ and the initial train stimulus was then shortened by decrements of 5 msec until the train failed to depolarize the ventricle. The process was repeated with the use of trains at each current strength used for S₂.

All patients were tested with 100 Hz trains (interval between pulses 10 msec) with duration of 100 msec (11 pulses). We varied the pulse frequency in 12 patients who were tested with 50, 100 and 200 Hz trains with duration of 100 msec. We varied the train duration in 11 patients who were tested with 100 Hz trains with duration of 50, 100, and 150 msec. In 10 patients, we determined the strength-interval relationship for S₂ and 100 Hz trains with duration of 100 msec before and after administration of intravenous procainamide. Procainamide was administered as a loading dose of 15 mg/kg at 50 mg/min followed by an infusion at 6 mg/min (plasma concentration 10.1 ± 2.3 μg/ml).

To avoid systemic errors of data collection, pulse frequency and train duration were varied in random order; the late diastolic threshold was measured after each strength-interval curve and remained stable within ±0.03 mA during each study. We checked reproducibility of measurements as follows: (1) the S₂ effective refractory period (ERP) and functional refractory period (FRP) was measured at 0.5 and 16 mA after each strength-interval curve, and (2) one complete strength-interval curve for S₂ (five patients) or trains (10 patients) was repeated after one or more intervening curves. All measurements of reproducibility were stable to within ±5 msec, except for measurements in patients who were excluded because of changes in threshold of 0.05 mA or more.

**Pacing protocol: group II.** Pacing was performed during ventricular tachycardia only at twice diastolic threshold and 10 mA. First, S₂ was introduced in late diastole after every 12 tachycardia beats and scanned progressively earlier in 5 msec decrements until it failed to depolarize the ventricle or the tachycardia terminated. S₁ was coupled to the local electrogram at the right ventricular apex with an initial coupling interval of 100 msec less than the tachycardia cycle length. If tachycardia terminated, it was reinduced. Two induced arrhythmias were judged to be the same arrhythmia if the QRS morphology was the identical in all six recorded surface electrocardiographic leads and the cycle lengths varied by 20 msec or less. S₂ was then introduced with a coupling interval of 100 msec (within the ERP), and the coupling interval was increased in 5 msec increments until capture occurred. S₁ was then replaced by a 100 Hz train with duration of 100 msec. The initial train stimulus had a coupling interval of 100 msec less than the tachycardia cycle length, so that the train ended at the subsequent local electrogram. The process used for S₁ was then repeated for trains. The current strength was increased to 10.0 mA and measurements for both S₁ and trains were performed. Data were recorded during 20 distinct tachycardias at a current strength of twice threshold and during 15 tachycardias at a current strength of 10 mA.

**Definitions.** We used standard definitions for the ERP and FRP of S₂. We used Fisher’s definition for train ERP and FRP. The ERP for trains was the longest interval between S₁ and the final train stimulus (Sₙ) that did not depolarize the ventricle; the FRP for trains was the shortest interval between V₁, the electrogram resulting from S₁, and Vₙ, the electrogram resulting from the train. The coupling interval for trains was defined as the interval between S₁ and Sₙ.

Inhibition was assumed if a train failed to capture the ventricle when delivered with a coupling interval at which S₂ captured the ventricle. Summation was assumed if the train produced a response while S₂ with the same coupling interval was ineffec-
Results

S2 vs trains. In group I, the V1V2 interval resulting from late diastolic trains was similar to that resulting from an S2 with a coupling interval equal to that of the initial train stimulus. However, as the train coupling interval shortened, the train electrogram was recorded later during the train interval. Figure 1 shows the ERP and FRP strength-interval relationships for S2 and 100 Hz trains with duration of 100 msec in a single group I patient together with selected analog recordings. At a current strength of 0.5 mA, the S2 FRP and the train FRP were equal. The train electrogram resulted from one of the initial train stimuli and fell within the train interval. When the train coupling interval was decreased by 5 msec, the train did not capture the ventricle, despite the fact that train pulses continued for 100 msec beyond the S2 ERP. This indicates that pulses early in the train inhibit the response to subsequent pulses. The result at 1.0 mA was similar to the result at 0.5 mA. When the current strength was increased to 2.0 mA, the train and S2 ERPs were equal, indicating that inhibition was no longer present. The result at 4.0 mA was similar to that at 2.0 mA. At 8.0 and 16 mA, the train ERPs were slightly shorter than the S2 ERPs, suggesting that summation occurs. In this patient, the train and S2 FRPs were similar at all current strengths.

Figure 2, A, compares the ERP strength-interval relationships in all 29 group I patients for S2 and 100 Hz trains with duration of 100 msec. Inhibition was significant at current strengths of 2.0 mA or less (p < .01); summation was significant at current strengths of 8.0 mA or more (p < .01). The train ERP exceeded the S2 ERP at 0.5 mA by 47 ± 6 msec and was shorter than the S2 ERP at 16 mA by 12 ± 1 msec. The train ERP strength-interval relationship for pooled patient data was a smooth curve despite abrupt transitions in individual patient data. Inhibition occurred in all 29 patients. Summation occurred above a critical current

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

**FIGURE 1.** Strength-interval relation in one patient for S2 and 100 Hz trains with duration of 100 msec. The relationship for ERP is shown in the upper graph and the relationship for FRP in the lower graph. Selected analog recordings for S2 (left column) and trains (right column) are also shown. The upper recording in each pair shows the ERP; the lower recording shows the FRP. Recordings are shown for current strengths 0.5, 2.0, and 8.0 mA. The train ERP is longer than the S2 ERP at low current strengths (inhibition) and shorter at high current strengths (summation). In this patient, the train and S2 FRPs are equal at all current strengths. Stimulus-response latency increases at high currents to limit FRP shortening. See text for discussion. S1 = last of eight consecutive pacing stimuli at cycle length 500 msec; S2 = extrastimulus; Sf = last train stimulus.
strength in 26 patients (90%); in three patients (10%) the S2 and train ERPs were equal at high current strengths.

Figure 2, B, shows the corresponding FRP strength-interval relationships. At current strengths of 1.0 mA or less, the train FRP was significantly longer than the S2 FRP (p < .001), but the difference was much less than that for ERP (13 ± 3 msec at 0.5 mA). At 0.5 mA the train ERP exceeded the S2 ERP in 20 patients (69%). At higher current strengths, the train FRP did not differ significantly from the S2 FRP. Although the train ERPs shortened relative to the S2 ERPs with increasing current strength, the stimulus-response latency for trains increased relative to latency for S2 in a smoothly progressive fashion, resulting in similar train and S2 FRPs. Local ventricular capture without global ventricular capture did not occur in any patient. The FRP for S2 and trains always occurred at a coupling interval 5 msec greater than the corresponding ERP.

Effect of varying pulse frequency. Figures 3 and 4 show the effect of varying pulse frequency (50, 100, and 200 Hz) for trains with duration of 100 msec in group I patients. Figure 3 shows analog recordings from a single patient for the lowest and highest current strengths used, 0.5 and 16 mA. Both inhibition at 0.5 mA and summation at 16 mA increased with increasing pulse frequency. Figure 4, A, shows that for the group of 12 patients, inhibition increased with increasing pulse frequency at current strengths of 2.0 mA or less (p < .001); summation increased with increasing pulse frequency at current strengths of 8.0 mA or more (p < .001). However, the ERPs for S2 and 50 Hz trains did not differ significantly at any current strength, indicating that inhibition and summation were minimal or absent at this frequency. In each patient, the ERP curves for 100 and 200 Hz trains crossed the curves for 50 Hz trains and S2 between 2.0 and 8.0 mA. Figure 4, B, shows that at low current strengths, the dependence of FRP on pulse frequency was weaker than the dependence of ERP. FRP increased with increasing pulse frequency only at current strengths of 1.0. mA or less (p < .01). At high current strengths, the FRPs for S2 and trains with each frequency did not differ significantly.

Effect of varying train duration. Figures 5 and 6 show the effect of varying train duration (50, 100, and 150 msec for 10 Hz trains in group I patients. The analog


FIGURE 3. Analog recordings show effect of varying pulse frequency for S2 and trains with duration of 100 msec in one patient. Recordings are shown for current strengths of 0.5 mA (left) and 16 mA (right). ERP lengthening at 0.5 mA (inhibition) and ERP shortening at 16 mA (summation) are frequency dependent. 50 Hz trains have only a minimal effect. The FRP is not altered by train frequency. At 0.5 mA it falls progressively earlier in higher frequency trains as the ERP increases. See figure 1 for abbreviations.
recordings from one patient in figure 5 show that inhibition at 0.5 mA increased with increasing train duration, but summation at 16 mA did not. Figure 6, A, shows that for the group of 11 patients, inhibition increased with increasing train duration at current strengths of 2.0 mA or less (p < .001). At 16 mA, the S2 ERP was significantly longer than the ERP for trains of each duration (p < .01), but the amount of summation for trains with all three durations was similar. At 16 mA, the probability of missing a true difference in ERPs of 5 msec between trains with duration 50 and 150 msec was less than .02; the probability of missing an 8 msec difference, i.e., the difference between ERPs for S2 and 50 msec trains, was less than 0.001. Figure 6, B, shows that the FRPs followed a similar, but weaker, trend at low current strengths. FRP increased with increasing train duration only at current strengths of 1.0 mA or less (p < .01). At current strengths, the S2 and train FRPs did not differ significantly.

Effect of procainamide. Figure 7, A, shows ERP strength-interval relationships before and after administration of procainamide in 10 group I patients. Data are shown for S2 and 100 Hz trains with duration of 100 msec. The curves for S2 and trains both shift to the right after procainamide, but the curves for trains shifts by a greater amount at low current strengths. This is seen more clearly in figure 7, C, which shows the change in ERP caused by procainamide as a function of current strength. The effect of procainamide on train ERPs is significantly greater than the effect of S2 ERPs for current strengths of 2.0 mA or less (p < .01) and similar for higher current strengths. Thus, procainamide enhanced inhibition but did not alter summation. Figure 7, B, shows that the FRP curves for S2 and trains after procainamide were both shifted to the right. The train FRP exceeded the S2 FRP slightly at all current strengths, but this difference was not significant at any current strength.

Effect during ventricular tachycardia. Table 1 summarizes results of pacing with S2 and trains during ventricular tachycardia. The train ERP exceeded the S2 ERP by 55 ± 5 msec (p < .001) at twice threshold and was shorter than the S2 ERP by 13 ± 2 msec (p < .001) at 10.0 mA. The train ERP exceeded the S2 FRP by 25 ± 5 msec (p < .001) at twice threshold, but was not significantly different at 10 mA. At twice threshold, the responses to trains and S2 were concordant in 19 tachycardias (termination in four and no termination in 15)

and discordant in one (termination only by S2). At this current strength, only late diastolic trains terminated ventricular tachycardia, with the resulting V2 falling early in the train interval. Inhibition frequently prevented ventricular capture by early diastolic trains that began within the S2 ERP, as shown in figure 8. In the one patient with a discordant response, the electrogram resulting from the effective S2 fell within the train FRP. At 10 mA, S2 and trains each terminated six of 15 tachycardias and accelerated one tachycardia.

Discussion

The principal findings of this study are that ultrarapid trains produce inhibition at low current strengths and summation at high current strengths. The maximum prolongation of ERP was approximately five times the maximum shortening. Increased stimulus-response latency for trains resulted in equal S2 and train FRPs at high current strengths despite summation. Inhibition increased with increasing pulse frequency, but did not depend on train duration. Procainamide enhanced inhibition, but did not alter summation.

Previous studies of inhibition and summation. Subthreshold stimulation during the refractory period has been reported to inhibit the response to subsequent threshold stimuli in frog and canine preparations4-6 and in humans.1,2 Windle et al.2 reported that a single subthreshold stimulus prolongs the human ventricular ERP. Skale et al3 reported that 250 to 500 Hz trains delivered during the refractory period produced greater inhibition than a single subthreshold stimulus in the canine heart in situ.

Tamargo et al.7 reported that sequential stimuli delivered within the refractory period for a single stimulus could at times evoke a propagated response in the canine ventricle. In the only previous study of sum-

FIGURE 7. Effect of procainamide on strength-interval relationship for S2 and 100 Hz trains with duration of 100 msec in 10 patients. A, ERP strength-interval relationship. B, FRP strength-interval relationship. C, The difference between S2 and train ERPs (\(\Delta ERP\)) is plotted on the ordinate and current strength is plotted on the abscissa for data shown in A. \(\Delta ERP\) for trains is significantly greater than that for S2 at current strengths of 2.0 mA or less (p ≤ 1.01).
TABLE 1
Effect of trains during ventricular tachycardia

<table>
<thead>
<tr>
<th>Current</th>
<th>n^a</th>
<th>S_2</th>
<th>Train</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Two × threshold</td>
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<td>248±8</td>
<td>304±11</td>
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<tr>
<td>10 mA</td>
<td>15</td>
<td>209±11</td>
<td>197±11</td>
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<tr>
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<td>263±9</td>
<td>288±12</td>
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<tr>
<td>10 mA</td>
<td>15</td>
<td>246±11</td>
<td>243±11</td>
<td>NS</td>
</tr>
</tbody>
</table>

^aNumber of patients.

formation in the human heart in situ, Prystowsky and Zipes\(^1\) reported that a train of three pulses produced summation in only one of six patients tested. They measured the effect of a subthreshold conditioning stimulus or train on the response to a subsequent test stimulus. We selected a different design, which was more suitable for measuring summation by trains in addition to inhibition, but did not allow us to determine which specific stimulus in the train was inhibited. Because we varied the current strength of S_1 in parallel with that of S_2 or the train, our S_2 and train refractory periods may be influenced by electrotonic effects from S_1. These electrotonic influences should be equal for S_2 and trains.

**FRP strength-interval relationships.** Less attention has been paid to the FRP strength-interval relationships than to the ERP strength-interval relationships. Our finding that the FRP for S_2 and trains had a much weaker dependence on current strength than the ERP is similar to that of Mitchell et al.,\(^14\) who analyzed the strength-interval relationship for the S_2 FRP. We found that low current trains prolonged the FRP significantly, but less than the ERP, because capture frequently occurred during the train interval. In previous studies in which impulses were delivered during the refractory period,\(^1,7\) temporal summation was measured by the ability of sequential stimuli to evoke a response when a single stimulus did not. The issue of functional refractoriness was not addressed. We found that when high current trains were delivered within the S_2 ERP, local stimulus-response latency\(^15\) increased so that high-current trains did not shorten excitability as measured by the S_2 FRP. Antzelevitch and Moe\(^6\) reported that temporal summation of impulses conducted across a sucrose gap in mammalian Purkinje fibers could shorten the FRP of this system in vitro, but they delivered conditioning pulses after full membrane repolarization, rather than during the action potential as we did.

**Mechanism of inhibition.** Windle et al.\(^6\) studied the effects of subthreshold stimulation during the refractory period on action potential duration and refractoriness in canine Purkinje fibers. They found that subthreshold stimuli produced low-amplitude, local responses that prolonged the action potential and ERP. Either electrotonic effects or reactivation of ionic currents could explain our observation: electrotonic prolongation of the action potential could delay voltage-dependent recovery of sodium channel excitability. Alternatively, activation of an insufficient number of sodium channels to generate action potential would initiate a new cycle of refractoriness in these prematurely excited channels.

Inhibition in the human heart may result from similar electrotonic or ionic effects or refractoriness in adjacent tissues, which limits propagation of a local response. The greater inhibitory effect of higher frequency or longer trains in our study may be due to a cumulative effect of repeated stimulation, regardless of the mechanism.

![FIGURE 8](http://circ.ahajournals.org/)

**FIGURE 8.** Analog recordings demonstrate inhibition by 100 Hz train with duration of 100 msec at a current strength of 0.34 mA (twice threshold) during a single episode of sustained ventricular tachycardia. Surface electrocardiographic leads I, aVF, and V_1 are shown with intracardiac electrograms recorded from the right ventricular apex (RVA) and right ventricular outflow tract (RVOT). **Top,** The S_2 ERP of 225 msec. Decreasing the S_1/S_2 by 5 msec to 210 msec produced the S_2 ERP. **Bottom,** The train ERP of 305 msec, 95 msec longer than the S_2 ERP. The coupling interval of the initial train stimulus is only 10 msec shorter than the coupling interval of S_2 at top. The corresponding train FRP was 225 msec, with the train electrogram falling within the train interval.
Mechanism of summation. Antzelevitch and Moe \(^8\) also found that two closely coupled subthreshold stimuli could produce activation through temporal summation of electrotonic potentials. Our findings may be explained by temporal summation of electrotonic potentials or subthreshold ionic currents activated by each train pulse. The dependence of summation on pulse frequency is consistent with temporal summation of either type. Summation's independence from train duration suggests that the membrane can produce a cumulative, propagated response to repetitive, subthreshold stimuli only over a time interval less than the shortest train used in this study, 50 msec. In contrast, inhibition, which depends on train duration, requires only that all voltage and channel-state conditions for a propagated response not be met simultaneously.

Effect of procainamide. Procainamide has been reported to shift the strength-interval relationship for the human right ventricular S\(_2\) ERP to the right without altering its shape.\(^{16}\) We found that procainamide shifted the steep portion of the S\(_2\) and train curves by a similar amount, leaving the magnitude of summation unaltered. However, it caused a greater shift for low-current trains than for S\(_2\), resulting in a significant increase in inhibition. Procainamide could enhance inhibition by delaying recovery of prematurely activated sodium channels, prolonging refractoriness in adjacent tissues, or altering passive membrane properties.\(^{17}\) The discordant responses of inhibition and summation to procainamide are additional evidence that the electrophysiologic mechanisms responsible for these phenomena differ qualitatively or quantitatively.

Clinical implications. Ultrarapid single-capture trains have been used to terminate supraventricular and ventricular tachycardia.\(^{10}\) Fisher et al.\(^{10}\) reported that trains and S\(_2\) had comparable efficacy for termination of well-tolerated ventricular tachycardia; they used current strengths that varied from four times threshold to 14 mA.\(^{10}\) These authors found that the mean refractory period for trains exceeded the mean refractory period for S\(_2\) by 11 msec during matched episodes of ventricular tachycardia. In this analysis, they pooled data for ERPs and FRPs as well as for trains with different frequencies and current strengths above four times threshold.

Our data during ventricular pacing indicate that single-capture trains with a 1 msec pulse width can be delivered at frequencies up to 50 Hz without producing inhibition. Trains with a frequency of 100 Hz or more require current strengths of 10 to 20 times threshold to overcome inhibition reliably. During ventricular tachycardia, our protocol minimized the effects of inhibition on single-capture termination by delivering the initial train in late diastole and scanning it progressively earlier. However, this approach obviates the advantage of trains, which is to avoid time-consuming diastolic scanning. Had we limited the train coupling intervals to bracket the most reliable tachycardia termination zone around the S\(_2\) ERP, inhibition would have been a greater problem. Despite this, our data demonstrate that inhibition by low-current, 100 Hz trains may prevent single-capture termination of some tachycardias.

Enhancement of inhibition by procainamide or other antiarrhythmic drugs might further diminish the efficacy of low-current trains with frequencies of 100 Hz or more. Because the current strengths required to overcome inhibition reliably are inefficient for implanted devices and have been reported to induce non-clinical ventricular tachyarrhythmias,\(^{18}\) we suggest that trains used for single-capture termination of tachycardias should be limited to frequencies below 100 Hz.

We are not aware of a clinical application for summation caused by high-current trains in this study. The magnitude of summation was small, and marked local stimulus-response latency prevented shortening of functional refractoriness, which is critical for termination of tachycardias. Furthermore, such high currents may be proarrhythmic.

Subthreshold extrastimuli\(^{19}\) and trains\(^{11}\) have been reported to terminate ventricular tachycardia, and subthreshold trains have been reported to interrupt reciprocating tachycardia in one patient with Wolff-Parkinson-White syndrome.\(^{11}\) If the mechanism for this effect is prolongation of refractoriness in a localized region of a reentry circuit, our data from ventricular pacing suggest that subthreshold trains should be more effective than single stimuli; that low-current, high-frequency, long-duration trains should be most effective; and that procainamide or other antiarrhythmic drugs may enhance this effect. However, inhibition with single pulses has been reported to occur only over a very limited distance,\(^1\) limiting the possible clinical application of subthreshold pacing for termination of tachycardias.

We thank Lincoln Moses, Ph.D, and Ian Johnson, Ph.D, for statistical assistance.

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Summation and inhibition by ultrarapid train pacing in the human ventricle.
C D Swerdlow, L B Liem and M R Franz

_Circulation_. 1987;76:1101-1109
doi: 10.1161/01.CIR.76.5.1101
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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