A prospective comparison of programmed ventricular stimulation with triple extrastimuli versus single and double extrastimuli during infusion of isoproterenol

This prospective study compared the yield of programmed ventricular stimulation with single and double extrastimuli during an infusion of isoproterenol with that of programmed stimulation with triple extrastimuli. The subjects of this study were 58 patients who underwent programmed stimulation and did not have inducible ventricular tachycardia (VT) with single or double extrastimuli at two basic drive cycle lengths and at two right ventricular sites; 17 patients had a history of uniform VT unrelated to exercise, and 41 had no history of documented or suspected VT or ventricular fibrillation (VF). Programmed stimulation was performed with triple extrastimuli at both right ventricular sites. Isoproterenol was infused as a dose titrated to increase the sinus rate by 25% or to a rate of 100 beats/min, whichever was greater, and stimulation then was repeated with single and double extrastimuli. Among the 17 patients with a history of uniform VT, the clinical VT was induced by three extrastimuli in five patients (29%) and by two extrastimuli during isoproterenol infusion in six patients (35%, $p > 0.05$). Among the total study population of 58 patients, nonclinical multiform VT or VF was induced by three extrastimuli in 29 patients (50%), and by two extrastimuli during isoproterenol infusion in 15 patients (26%, $p < 0.05$). Therefore stimulation with two extrastimuli during isoproterenol infusion has the same probability of inducing a clinical form of VT as does stimulation with extrastimuli, but the former has a significantly lower probability of inducing nonclinical multiform VT and VF. (Am Heart J 1989;117:342.)

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The yield of clinical forms of ventricular tachycardia during programmed ventricular stimulation is increased by the use of triple extrastimuli,[1-6] and also by the infusion of isoproterenol.[7,8] Several studies[1-4] have determined that the use of triple extrastimuli increases the yield of sustained uniform ventricular tachycardia by 12% to 28%. Isoproterenol has been reported[8] to facilitate the induction of ventricular tachycardia in 50% of patients with a history of sustained ventricular tachycardia in whom programmed ventricular stimulation alone failed to reproducibly induce sustained ventricular tachycardia. However, the effect of isoproterenol on the yield of uniform ventricular tachycardia during programmed ventricular stimulation to date has not been determined in prospective fashion. In addition, whereas several studies[1-6,9,10] have established that triple ventricular extrastimuli increase the yield of nonclinical forms of multiform ventricular tachycardia and ventricular fibrillation, the effect of isoproterenol on the specificity of programmed ventricular stimulation has not been examined. Therefore data are not available on the yield of programmed ventricular stimulation with single and double extrastimuli during an infusion of isoproterenol relative to the yield of programmed ventricular stimulation with triple extrastimuli.

The purpose of this prospective study was to compare the sensitivity and specificity of programmed ventricular stimulation with single and double extrastimuli during an infusion of isoproterenol with that of programmed ventricular stimulation with triple extrastimuli.

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METHODS

Patients studied. Fifty-eight patients who underwent programmed ventricular stimulation and who did not have inducible ventricular tachycardia with either single or double extrastimuli were entered prospectively into this study.

Seventeen patients with a mean age of 58 ± 13 years (± standard deviation) had a history of uniform ventricular tachycardia not precipitated by exercise. The ventricular tachycardia was sustained in 15 patients and nonsustained in two. Eleven patients had coronary artery disease (10 with a history of myocardial infarction), two had hypertensive heart disease, two had a dilated cardiomyopathy, and two had no identifiable structural heart disease.

Forty-one patients with a mean age of 50 ± 15 years had no history of documented or suspected ventricular tachycardia. Twenty-two of these patients had no identifiable structural heart disease, nine patients had coronary artery disease (six with a history of myocardial infarction), six had mitral valve prolapse or valvular heart disease, and two patients each had a dilated cardiomyopathy or hypertensive heart disease. These patients underwent an electrophysiology study for evaluation of unexplained syncope, paroxysmal supraventricular tachycardia, or ventricular premature complexes. None of these patients had ventricular tachycardia during at least 24 hours of electrocardiographic monitoring and none had a history of cardiac arrest.

Electrophysiology study protocol. Patients were studied in the fasting, unsedated state after providing informed consent, and at least 4 half-lives after discontinuation of antiarrhythmic drugs. Two quadripolar electrode catheters were inserted percutaneously through a femoral vein and were positioned against the right ventricular apex and either the right ventricular outflow tract or septum. Electrocardiographic leads V_1, I, and III, and the intracardiac electrograms were recorded on a Siemens-Elema Mingograf 7 recorder (Siemens Elema AB, Solna, Sweden) at a paper speed of 25 mm/sec. If sustained unimorphic ventricular tachycardia was induced, a 12-lead electrocardiogram (ECG) was also obtained, whenever possible. Stimulation was performed with a programmable stimulator (Bloom Associates, Ltd., Narberth, Pa.) with stimuli that were 2 msec in duration and twice the diastolic threshold.

Programmed stimulation was performed using six- to eight-beat drive trains and basic drive cycle lengths of 500 and 400 msec. The coupling intervals of the first, second, and third extrastimuli were designated S_1S_2, S_2S_3, and S_3S_4, respectively. Programmed stimulation was initiated at the right ventricular apex with an S_1S_2 of 350 to 400 msec, depending on the basic drive cycle length. Coupling intervals were decreased in 10 msec steps. Programmed stimulation with double extrastimuli was performed starting with an S_1S_2 30 msec beyond the effective refractory period, and with an initial S_2S_3 of 300 msec. When S_3 reached refractoriness, S_1S_2 was decreased in 10 msec steps until S_3 again evoked a response. S_2S_3 was then decreased until S_3 again reached refractoriness, and S_1S_2 was decreased in 10 msec steps until S_3 evoked a response. This process was continued until S_2 reached refractoriness. After stimulation at two basic drive cycle lengths with S_2 and S_3 was completed at the right ventricular apex, these steps were repeated at the second right ventricular site. In each of the patients in this study, neither uniform nor polymorphic ventricular tachycardia or ventricular fibrillation was induced by programmed stimulation with one or two extrastimuli.

Programmed stimulation with triple extrastimuli was then performed at the right ventricular apex with S_2 and S_3 set 30 msec beyond their respective points of refractoriness, and with an initial S_3S_4 of 300 msec. When S_4 no longer evoked a response, the S_2S_3 interval was decreased in 10 msec steps until S_4 again evoked a response. This process was continued until S_3 no longer evoked a response, at which point S_1S_2 was decreased in 10 msec steps until S_3 again evoked a response. After stimulation with triple extrastimuli at two basic drive cycle lengths at the right ventricular apex, this process was repeated at the second right ventricular site.

Infusion of isoproterenol. After completion of stimulation with triple extrastimuli at two basic drive cycle lengths and at two right ventricular sites, isoproterenol was infused intravenously at an initial rate of 2 μg/min. If direct-current countershock was necessary during stimulation with triple extrastimuli, the isoproterenol infusion was started after a 10-minute rest period. The dose of isoproterenol was titrated to achieve a steady-state increase in heart rate of 25%, or a heart rate of 100 beats/min, whichever was greater. The range of isoproterenol doses was 0.7 to 4.0 μg/min. The mean heart rate after infusion of isoproterenol was 106 ± 8 beats/min. Programmed ventricular stimulation with single and double extrastimuli was then repeated in the manner described above.

In patients who had a history of unimorphic ventricular tachycardia, the end point of programmed stimulation with either triple extrastimuli or single and double extrastimuli during an infusion of isoproterenol was the induction of the clinical tachycardia (same bundle branch block configuration and axis as the documented ventricular tachycardia), or completion of the stimulation protocol. In patients without a history of documented ventricular tachycardia/ventricular fibrillation, the end point of programmed stimulation was the induction of sustained polymorphic ventricular tachycardia or ventricular fibrillation, or completion of the stimulation protocol. However, during programmed stimulation with triple extrastimuli in four patients and during stimulation with double extrastimuli during infusion of isoproterenol in two patients, the stimulation protocol was stopped after the induction of several seconds of nonsustained polymorphic ventricular tachycardia, in order to avoid inducing sustained polymorphic ventricular tachycardia or ventricular fibrillation requiring direct-current countershock.

Nonsustained ventricular tachycardia was defined as ventricular tachycardia lasting six beats to 30 seconds.

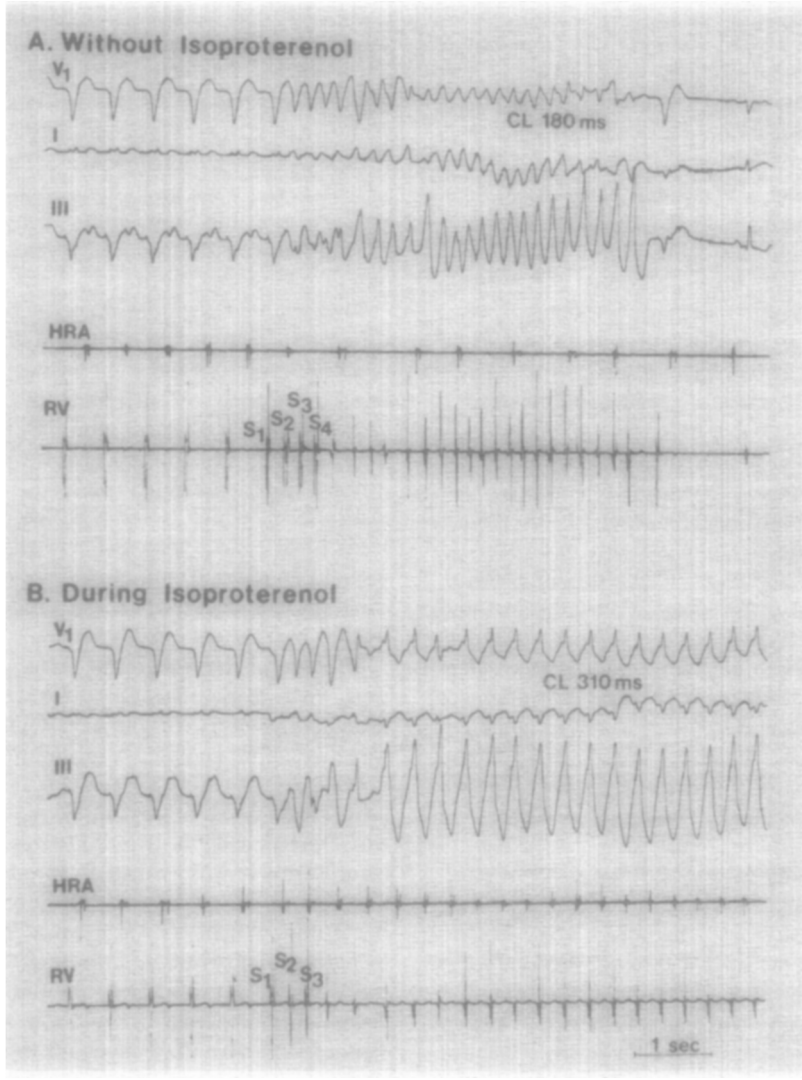

Fig. 1. Programmed stimulation with triple extrastimuli **(A)**, then with double extrastimuli during an infusion of isoproterenol **(B)**, in a patient with a history of sustained unimorphic ventricular tachycardia (VT). VT was not induced by single or double extrastimuli at two basic drive cycle lengths and at two right ventricular sites before isoproterenol infusion. From *top to bottom* are leads V_1, I, and III, and intracardiac electrograms recorded at the high atrium *(HRA)* and right ventricular apex *(RV)*. The drive cycle length is 500 msec. Triple extrastimuli ($S_2S_3S_4$, coupling intervals 220/200/180 msec) resulted in the induction of 21 beats of polymorphic nonsustained VT (mean cycle length 180 msec), whereas double extrastimuli (S_2S_3, coupling intervals 230/200 msec) during isoproterenol induced sustained unimorphic VT (mean cycle length 310 msec); the configuration of this induced VT was the same as that of the patient's spontaneous VT.

Sustained ventricular tachycardia was defined as ventricular tachycardia lasting more than 30 seconds or requiring direct-current countershock to terminate. Induced polymorphic ventricular tachycardia and ventricular fibrillation were defined as "nonclinical" because no patient had a history of documented polymorphic ventricular tachycardia, ventricular fibrillation, or cardiac arrest.

Statistical analysis. The yield of clinical and nonclinical arrhythmias induced by triple extrastimuli versus single and double extrastimuli during isoproterenol infusion was compared by chi square analysis or by Fisher's exact test. Other comparisons were performed with a *t* test for matched pairs. A p value <0.05 was considered to be statistically significant.

RESULTS

Induction of clinical ventricular tachycardia. Among the 17 patients who had a history of uniform ventricular tachycardia, the clinical ventricular tachycardia was induced by triple extrastimuli in five patients (29%) and by double extrastimuli during an infu-

Table I. Effect of isoproterenol on the shortest attainable coupling intervals

Site	DCL (msec)	*Shortest attainable S_1S_2 (msec)*		*Shortest attainable S_2S_3 (msec)*	
		Before isoproterenol	*During isoproterenol†*	*Before isoproterenol*	*During isoproterenol†*
RVA	500	248 ± 24*	228 ± 21	193 ± 25	176 ± 26
RVA	400	235 ± 24	216 ± 22	183 ± 27	167 ± 28
RVOT/S	500	252 ± 25	229 ± 27	202 ± 31	179 ± 29
RVOT/S	400	237 ± 27	216 ± 24	187 ± 32	168 ± 30

DCL, Drive cycle length; RVA, right ventricular apex; RVOT/S, right ventricular outflow tract or septum
*Mean ± standard deviation.
†All of the intervals measured during isoproterenol infusion are significantly shorter than before isoproterenol infusion ($p < 0.001$).

sion of isoproterenol in six patients (35%). These induction rates were not significantly different ($p > 0.05$). In no patient was ventricular tachycardia induced by a single extrastimulus during isoproterenol infusion.

In three patients, clinical ventricular tachycardia was induced both by triple extrastimuli and by double extrastimuli during infusion of isoproterenol. In two patients, the clinical ventricular tachycardia was induced by triple extrastimuli but not by single or double extrastimuli during isoproterenol infusion. In three patients, clinical ventricular tachycardia was induced by double extrastimuli during infusion of isoproterenol but not by triple extrastimuli (Fig. 1).

Among the three patients in whom clinical ventricular tachycardia was induced both by triple extrastimuli and by double extrastimuli during isoproterenol infusion, the mean cycle length of the ventricular tachycardia was 277 ± 19 msec when induced by triple extrastimuli, and 257 ± 9 msec when induced by double extrastimuli during isoproterenol infusion. This difference was not statistically significant ($p > 0.05$).

Induction of nonclinical ventricular tachycardia/ventricular fibrillation. Among the total study population of 58 patients, nonclinical multiform ventricular tachycardia or ventricular fibrillation was induced by triple extrastimuli in 29 patients (50%), and by double extrastimuli during isoproterenol infusion in 15 patients (26%). The 26% induction rate of nonclinical arrhythmias with double extrastimuli during isoproterenol infusion was significantly lower than the 50% induction rate that occurred with triple extrastimuli ($p < 0.05$). In no patient was polymorphic ventricular tachycardia or ventricular fibrillation induced by a single extrastimulus during isoproterenol infusion.

Among the 17 patients with a history of uniform ventricular tachycardia, polymorphic ventricular tachycardia or ventricular fibrillation was induced by triple extrastimuli in five patients and by double extrastimuli during isoproterenol infusion in two patients.

Direct-current countershock was required to terminate sustained polymorphic ventricular tachycardia or ventricular fibrillation in 19% of patients during stimulation with triple extrastimuli, and in 5% of patients during stimulation with double extrastimuli during isoproterenol infusion ($p < 0.05$). Each of the three patients who required countershock during the isoproterenol infusion also required countershock during stimulation with triple extrastimuli.

Among the patients in whom the polymorphic ventricular tachycardia was nonsustained, the mean duration of the ventricular tachycardia was 15 ± 16 beats when induced by triple extrastimuli, and 12 ± 12 beats when induced by double extrastimuli during isoproterenol infusion ($p > 0.05$).

Effect of isoproterenol on shortest attainable coupling intervals (Table I). At both right ventricular stimulation sites and at both basic drive cycle lengths, isoproterenol significantly reduced the shortest attainable S_1S_2 interval ($p < 0.001$). During isoproterenol infusion, there was also a significant reduction in the shortest attainable S_2S_3 interval ($p < 0.001$).

Coupling intervals that induced ventricular tachycardia. In a total of 21 patients, stimulation with double extrastimuli during isoproterenol infusion resulted in the induction of a clinical or nonclinical arrhythmia. In each patient, the S_1S_2 interval that induced ventricular tachycardia/ventricular fibrillation during stimulation with double extrastimuli was shorter (by a mean of 28 ± 13 msec) than the shortest S_1S_2 before isoproterenol infusion. The S_2S_3 interval that induced ventricular tachycardia/ventricular fibrillation during isoproterenol infusion was shorter than the shortest S_2S_3 interval attainable before isoproterenol infusion in 9 of 21 patients.

Safety of isoproterenol infusion. No adverse reac-

tions were noted during the infusion of isoproterenol. No patient complained of chest pain during the isoproterenol infusion. The sustained arrhythmias induced by double extrastimuli during isoproterenol infusion were not more difficult to terminate than when induced by triple extrastimuli in the absence of isoproterenol.

DISCUSSION

This study has demonstrated that among patients in whom ventricular tachycardia is not induced by programmed stimulation with single or double extrastimuli at two basic drive cycle lengths and at two right ventricular sites, the yield of clinical forms of ventricular tachycardia is similar with both double extrastimuli during isoproterenol infusion and with triple extrastimuli. However, stimulation with double extrastimuli during isoproterenol infusion results in fewer nonclinical forms of polymorphic ventricular tachycardia and ventricular fibrillation as compared to stimulation with triple extrastimuli. Therefore in patients in whom programmed stimulation with single and double extrastimuli has not yielded a clinical tachycardia, it may be preferable to next infuse isoproterenol and restimulate with single and double extrastimuli before proceeding to triple extrastimuli. Stimulation with double extrastimuli during an infusion of isoproterenol has the same probability of inducing a clinical form of ventricular tachycardia as does stimulation with triple extrastimuli, but a significantly lower probability of inducing a nonclinical arrhythmia.

Although the overall yield of clinical ventricular tachycardia was the same with double extrastimuli during isoproterenol infusion as with triple extrastimuli, there were some patients in whom one technique but not the other induced ventricular tachycardia. Therefore if stimulation with double extrastimuli during an infusion of isoproterenol does not yield a clinical ventricular tachycardia, stimulation with triple extrastimuli after discontinuation of the isoproterenol infusion would be appropriate.

Mechanism of facilitation of ventricular tachycardia induction during isoproterenol infusion. In this study, isoproterenol facilitated the induction of ventricular tachycardia with double extrastimuli by consistently decreasing ventricular refractoriness and allowing stimulation with S_1S_2 coupling intervals that were shorter than the shortest coupling intervals attainable before isoproterenol infusion. However, in a previous study,[8] the coupling intervals that induced ventricular tachycardia during isoproterenol infusion were sometimes equal to or longer than the shortest attainable coupling intervals before isoproterenol infusion.[8] This implies that isoproterenol may facilitate the induction of ventricular tachycardia not only by allowing stimulation with shorter coupling intervals, but also by altering the conduction properties of the myocardium.

Limitations. Nonsustained polymorphic ventricular tachycardia induced by programmed stimulation was characterized as a nonclinical arrhythmia because continuous ECG monitoring in the patients in this study had not demonstrated any episodes of polymorphic ventricular tachycardia. Nevertheless, we cannot rule out the possibility that some patients may have had spontaneous episodes of asymptomatic, nonsustained multiform ventricular tachycardia when they were not being monitored. However, because no patient had a history of cardiac arrest, the episodes of sustained polymorphic ventricular tachycardia and ventricular fibrillation induced during programmed stimulation were clearly nonclinical. Of note is that the yield of nonclinical arrhythmias with double extrastimuli during isoproterenol infusion remains significantly lower than that with triple extrastimuli, even if the analysis is restricted to the nonclinical arrhythmias that were sustained. To avoid the need for additional countershocks, the reproducibility of induction of nonclinical arrhythmias was not tested.

Although no difference was found in this study in the yield of clinical ventricular tachycardia with double extrastimuli during isoproterenol infusion as compared to triple extrastimuli, it is possible that a significant difference would emerge with an increase in sample size. Also, the induction of a nonclinical arrhythmia requiring countershock in patients with a history of uniform ventricular tachycardia may have resulted in an underestimate of the yield of uniform ventricular tachycardia.

Graded isoproterenol infusions have been shown[11] to have progressively greater effects on conduction and refractoriness. However, in the present study, time constraints did not allow evaluation of more than one dose of isoproterenol. Therefore we cannot evaluate whether the dose of isoproterenol used in this study was the optimal dose. Although they were not observed in this study, isoproterenol may have adverse effects; for example, isoproterenol may precipitate myocardial ischemia in patients who have coronary artery disease. Therefore close clinical observation is indicated when isoproterenol is infused.

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