Comparison of Coupling Intervals That Induce Clinical and Nonclinical Forms of Ventricular Tachycardia During Programmed Stimulation

FRED MORADY, MD, LORENZO A. DiCARLO, Jr., MD, JEFFREY M. BAERMAN, MD, and MICHAEL de BUITLEIR, MB

Coupling intervals of extrastimuli that induced 57 previously documented unimorphic ventricular tachycardias (VTs) were compared with coupling intervals that induced 57 episodes of polymorphic VT or ventricular fibrillation (VF) in patients without a documented or suspected history of polymorphic VT or VF. Programmed stimulation was performed with the patient in the drug-free state, with 1 to 3 extrastimuli and 2 basic drive cycle lengths (600 or 500 ms, and 400 ms) at 2 right ventricular sites; stimuli were twice diastolic threshold. The mean coupling intervals of the first, second and third extrastimuli that induced nonclinical VT/VF (241 ± 19, 185 ± 19 and 173 ± 24 ms, respectively, mean ± standard deviation) were significantly shorter than the corresponding coupling intervals that induced the clinical VTs (266 ± 25, 228 ± 32 and 214 ± 27 ms, respectively, p <0.001 for each). Regardless of the basic drive cycle length, the shortest coupling interval required to induce a clinical VT was 180 ms. Depending on the drive cycle length, 29 to 70% of nonclinical VT/VF induced by 3 extrastimuli required a coupling interval of less than 180 ms to induce. Therefore, a lower limit of coupling intervals may be identified below which only nonclinical VT/VF is induced by programmed stimulation. Restriction of coupling intervals to this lower limit may allow for significant improvement in specificity without compromise in the sensitivity of programmed ventricular stimulation protocols.

(Am J Cardiol 1986;57:1269–1273)

Unimorphic ventricular tachycardia (VT) that occurs spontaneously can often be induced by programmed ventricular stimulation. The yield of clinically significant forms of VT progressively increases as the number of extrastimuli in the stimulation protocol increases.[1-5] However, programmed ventricular stimulation may also induce ventricular fibrillation (VF) or rapid, polymorphic VT, which often represent laboratory artifacts of no clinical significance.[6] The yield of these nonclinical arrhythmias also increases as the number of extrastimuli used during programmed stimulation increases.[1-4,7,8] Because nonclinical forms of polymorphic VT or VF often require countershock to terminate, it is desirable to minimize the induction of these arrhythmias.

Coupling intervals that induce polymorphic VT or VF may be shorter than the coupling intervals that induce unimorphic VT.[9] It is therefore possible that a limitation of coupling intervals without a decrease in the number of extrastimuli might improve the specificity of programmed ventricular stimulation without impairing sensitivity. However, no studies have critically analyzed or compared the coupling intervals that induce clinical and nonclinical forms of VT/VF. This study compares the coupling intervals that induced clinical forms of unimorphic VT and nonclinical forms of polymorphic VT or VF, using a stimulation protocol that includes up to 3 ventricular extrastimuli. Our aim was to evaluate whether there is a lower limit of coupling intervals below which only nonclinical forms of VT are induced.

From the Division of Cardiology, Department of Internal Medicine, University Hospitals, University of Michigan Medical Center, Ann Arbor, Michigan. Manuscript received December 6, 1985; revised manuscript received January 21, 1986, accepted January 22, 1986.

Address for reprints: Fred Morady, MD, Division of Cardiology, University Hospital, 1500 East Medical Center Drive, Ann Arbor, Michigan 48109.

TABLE I Characteristics of Clinical and Nonclinical Forms of Ventricular Tachycardia Induced by Programmed Ventricular Stimulation

	Clinical VTs	Nonclinical VTs
n	57	57
Cycle length (ms) (mean ± SD)	309 ± 60	192 ± 18*
Duration		
Nonsustained	0	29
Sustained	57	28
Configuration of VT		
Right bundle branch block	39	0
Left bundle branch block	18	0
Polymorphic	0	44
Ventricular fibrillation	0	13
Induction technique		
One extrastimulus	10 (18%)	0
Two extrastimuli	31 (54%)	14 (24%)
Three extrastimuli	16 (28%)	43 (76%)

* $p < 0.001$ vs cycle length of clinical VT.
SD = standard deviation; VT = ventricular tachycardia.

Methods

Definitions: VT induced by programmed ventricular stimulation was categorized as clinical if it was unimorphic and similar in configuration to a patient's spontaneous episode of VT, as determined by a 12-lead electrocardiogram.

A ventricular arrhythmia induced by programmed ventricular stimulation was categorized as nonclinical if it was polymorphic VT or VF and if it was induced in a patient who did not have a history of polymorphic VT or VF. All patients had had at least 24 hours of continuous electrocardiographic monitoring demonstrating the absence of polymorphic VT, and no patient had a history of out-of-hospital cardiac arrest or VF. The nonclinical polymorphic VT/VFs included in this study were induced in patients with documented sustained or nonsustained unimorphic VT, supraventricular tachycardia, sick sinus syndrome, carotid hypersensitivity or atrioventricular conduction disturbances who underwent programmed ventricular stimulation in the course of a complete electrophysiologic study, or in patients with unexplained syncope. Polymorphic VT and VF induced in patients with unexplained syncope do not have clinical significance.[6,10-12] However, polymorphic VT or VF induced in patients with a history of cardiac arrest was not included in this study, because the clinical significance of polymorphic VT or VF in such patients is unclear.[6]

Sustained VT was defined as VT at least 30 seconds in duration or that required countershock for termination. Nonsustained VT was defined as VT at least 6 beats in duration that terminated spontaneously within 30 seconds.

Clinical ventricular tachycardias: Fifty-seven clinical VTs were induced in 52 patients who had a history of documented, sustained, unimorphic VT. The characteristics of these VTs are described in Table I. The patients in whom these VTs were induced consisted of 44 men and 9 women, mean age 57 ± 12 years (± standard deviation). Forty-three patients had coronary artery disease (with a history of myocardial infarction in 36), 2 idiopathic dilated cardiomyopathy, 2 mitral valve prolapse and 5 no identifiable structural heart disease.

Nonclinical ventricular tachycardias: Nonclinical polymorphic VT or VF was induced in 57 patients. The characteristics of these episodes of induced VT or VF are described in Table I. Patients in whom these tachycardias were induced consisted of 37 men and 20 women, mean age 62 ± 9 years. Thirty-five patients had coronary artery disease (with a history of myocardial infarction in 28), 10 idiopathic dilated cardiomyopathy, 3 mitral valve prolapse and 9 no identifiable structural heart disease.

Electrophysiologic study protocol: Patients underwent electrophysiologic study in the fasting, unsedated state after they gave informed consent. All studies were performed at least 4 half-lives after all antiarrhythmic drug treatment had been discontinued. Two quadripolar electrode catheters were inserted percutaneously into a femoral vein. Whenever indicated, atrial stimulation was performed; then the catheters were positioned against the apex of the right ventricle and the right ventricular outflow tract or septum. Electrocardiographic leads V_1, I and III, and the intracardiac electrograms were displayed on an oscilloscope and recorded on an Electronics for Medicine VR 16 recorder at a paper speed of 25 mm/s. In addition, whenever sustained unimorphic VT was induced, a 12-lead electrocardiogram was recorded. Stimulation was performed using a programmable stimulator (Bloom Associates, Ltd.) with stimuli that were 2 ms in duration and twice diastolic threshold. In all patients, the diastolic threshold was 0.8 mA or less.

Programmed stimulation was performed using 6- to 8-beat drive trains at 2 basic drive cycle lengths, either 600 or 500 ms, and 400 ms. Coupling intervals of the first, second and third extrastimuli were designated as 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 450 ms, depending on the basic drive cycle length. Coupling intervals were decreased in steps of 10 ms. Programmed stimulation with double extrastimuli was performed starting with an S_1S_2 30 ms beyond the effective refractory period and with an S_2S_3 of 300 ms. When the second extrastimulus (S_3) reached refractoriness, S_1S_2 was decreased by 10-ms 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 again decreased by 10 ms steps until S_3 again evoked a response. This process was continued until the first extrastimulus (S_2) no longer evoked a response. After programmed stimulation at 2 basic drive cycle lengths with 1 and 2 extrastimuli was completed at the right ventricular apex, these same steps were performed at the second right ventricular site. Programmed ventricular stimulation with 3 extrastimuli was then performed at the right ventricular apex, with S_2 and S_3 positioned 30 ms beyond their respective points of refractoriness, and with an initial S_3S_4 of 300 ms. When the third extrastimulus (S_4) no longer evoked a response, the S_2S_3 interval was decreased in

TABLE II Comparison of the Mean Coupling Intervals that Induced 57 Episodes of Clinical Ventricular Tachycardia and 57 Episodes of Nonclinical Ventricular Tachycardia or Ventricular Fibrillation

	Clinical VTs	Nonclinical VT/VFs	p Value
S_1S_2 (ms)	266 ± 25*	241 ± 19	<0.001
S_2S_3 (ms)	228 ± 32	185 ± 19	<0.001
S_3S_4 (ms)	214 ± 27	173 ± 24	<0.001

*Mean ± standard deviation.

S_1S_2, S_2S_3 and S_3S_4 = coupling intervals of first, second and third extrastimuli, respectively; VF = ventricular fibrillation; VT = ventricular tachycardia.

TABLE III Comparison of Mean Coupling Intervals that Induced Nonclinical Ventricular Tachycardia or Ventricular Fibrillation at a Basic Drive Cycle Length of 600 and 500 ms vs 400 ms

	Basic Drive Cycle Length (ms)		
	600/500*	400	p Value
S_1S_2 (ms)	248 ± 17†	233 ± 18	<0.01
S_2S_3 (ms)	194 ± 19	175 ± 16	<0.001
S_2S_4 (ms)	182 ± 24	162 ± 19	<0.01

*Mean coupling intervals at a basic drive cycle length of 600 and 500 ms were not significantly different and have been pooled.

† Values are mean ± standard deviation.

Abbreviations as in Table II.

10-ms steps until S_4 again evoked a response. This process was continued until S_3 no longer evoked a response, at which point the S_1S_2 interval was decreased by 10-ms steps until S_3 again evoked a response. This was continued until S_2 no longer evoked a response. After programmed stimulation with 3 extrastimuli at 2 basic drive cycle lengths at the right ventricular apex, 3 extrastimuli were then introduced at the second right ventricular site.

The endpoint of the stimulation protocol in patients who had a history of VT was the induction of each patient's clinical VT. In patients without a history of VT, the endpoint was induction of VT requiring countershock for termination. Reproducibility of an induced VT was assessed except when countershock was necessary to terminate the VT. In many patients VT was reproducibly inducible, but the coupling intervals that induced the VT were variable. In these cases, the coupling intervals that induced the first episode of VT were noted.

Statistical analysis: Statistical comparisons were performed with Student t test or by analysis of variance. A p value <0.05 was considered significant.

Results

The mean S_1S_2, S_2S_3 and S_3S_4 intervals that induced the clinical and nonclinical VTs are listed in Table II. The mean S_1S_2, S_2S_3 and S_3S_4 intervals that induced the nonclinical VTs were each significantly shorter than the corresponding mean coupling intervals of the extrastimuli that induced the clinical VTs ($p < 0.001$).

Among the clinical VTs there was no significant difference in the mean of the coupling intervals that induced VT at a basic drive cycle length of 600, 500 or 400 ms. Among the nonclinical VTs, mean coupling intervals of the extrastimuli that induced VT/VF at a basic drive cycle length of 600 and 500 ms were not significantly different. However, at a basic drive cycle length of 400 ms, the mean coupling intervals that resulted in the induction of nonclinical VT or VF were significantly shorter than the corresponding coupling intervals at a basic drive cycle length of 600 and 500 ms (Table III). There was no significant difference in the mean S_1S_2, S_2S_3 or S_3S_4 intervals that induced the 29 episodes of nonsustained nonclinical VT and the 28 episodes of sustained nonclinical VT or VF.

The actual coupling intervals that induced the 114 episodes of VT/VF are shown in Figure 1. The shortest S_2S_3 or S_3S_4 interval required to induce a clinical VT was 180 ms. Among the 14 episodes of nonclinical VT or VF induced by 2 extrastimuli, 2 (14%) were induced by an S_2S_3 interval of less than 180 ms. Among the 43 episodes of nonclinical VT or VF induced by 3 extrastimuli, 23 (53%) were induced by an S_2S_3 or S_3S_4 interval of less than 180 ms. At a basic drive cycle length of 600 or 500 ms, 23 episodes of nonclinical VT

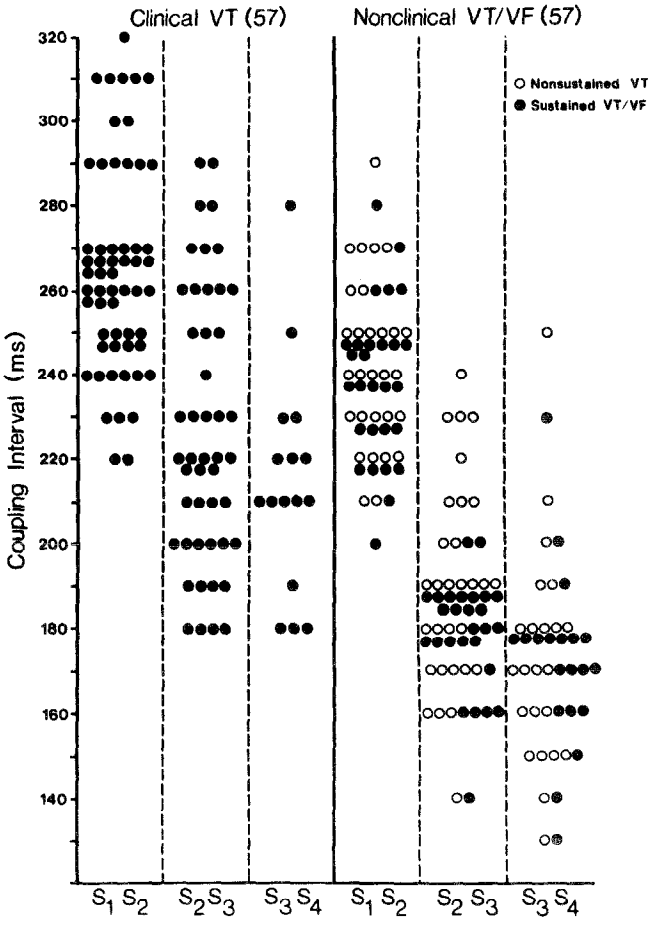

FIGURE 1. Coupling intervals that induced 57 episodes of clinical ventricular tachycardia (VT) and 57 episodes of nonclinical VT or ventricular fibrillation (VF). Coupling intervals at basic drive cycle lengths of 600, 500 and 400 ms have been pooled. S_1S_2, S_2S_3 and S_3S_4 = coupling intervals of first, second and third extrastimuli, respectively.

or VF were induced by 3 extrastimuli, of which 9 (39%) required an S_2S_3 and/or S_3S_4 interval of less than 180 ms. At a basic drive cycle length of 400 ms, 20 episodes of nonclinical VT or VF were induced by triple extrastimuli, of which 14 (70%) required an S_2S_3 or S_3S_4 interval of less than 180 ms.

Discussion

The results of this study demonstrate that the coupling intervals required to induce nonclinical forms of VT or VF are often shorter than the coupling intervals required to induce clinical VTs during programmed ventricular stimulation. The shortest S_2S_3 or S_3S_4 coupling interval that resulted in the induction of clinical VT was 180 ms, whereas a large proportion of nonclinical forms of VT or VF (up to 70% at a basic drive cycle length of 400 ms) were induced with an S_2S_3 or S_3S_4 interval of less than 180 ms.

These results have important implications regarding the sensitivity and specificity of programmed ventricular stimulation protocols. The yield of nonclinical VT or VF may be significantly decreased without compromising the yield of clinical VT by use of a programmed ventricular stimulation protocol in which the S_2S_3 and S_3S_4 intervals are limited to 180 ms each (at basic drive cycle lengths of 600, 500 and 400 ms).

In this study, 28% of clinical VTs required 3 extrastimuli to induce. Similarly, previous studies have reported that the use of 3 extrastimuli during programmed ventricular stimulation increases the yield of clinical VT by approximately 25%.[1-4] However, in the present and in previous studies, the use of 3 extrastimuli was responsible for the induction of most of the nonclinical forms of VT or VF that were induced by programmed ventricular stimulation.[1-4,7,8] Therefore, while needed to induce a significant proportion of clinically relevant VTs, 3 extrastimuli may also result in induction of a clinically irrelevant form of polymorphic VT or VF that may require direct-current countershock to terminate. Our results indicate that limiting the S_2S_3 and S_3S_4 intervals to 180 ms, while not completely eliminating the possibility of inducing a nonclinical arrhythmia with 3 extrastimuli, will significantly decrease the yield of nonclinical VT or VF without decreasing the yield of clinical VTs. The degree by which the yield of nonclinical arrhythmias is diminished is dependent on the basic drive cycle length (39% at a basic drive cycle length of 600 or 500 ms and 70% at a basic drive cycle length of 400 ms).

Whereas the concept that specificity of a programmed ventricular stimulation protocol can be improved without compromising sensitivity may be generally applicable, the specific recommendation that the S_2S_3 and S_3S_4 intervals be limited to 180 ms clearly applies only to stimulation protocols similar to that used in the present study. The minimum S_2S_3 or S_3S_4 intervals needed to induce a clinical form of VT may be longer or shorter than 180 ms, with current strengths more than 2 times threshold, basic drive cycle lengths of more than 600 ms or less than 400 ms, use of isoproterenol to facilitate induction of VT or with left ventricular stimulation. Further, because all episodes of VT and VF were induced in the absence of antiarrhythmic drug therapy, the results of this study cannot be applied to programmed stimulation during electropharmacologic testing.

None of the nonclinical VTs in this study were unimorphic. Although some forms of unimorphic VT that have never been documented may be induced in patients who have a documented history of a particular form of unimorphic VT, these forms of VT were not included in the present study because of uncertainty as to whether they are truly nonclinical or clinical but undocumented.[4]

Conversely, none of the clinical VTs in this study were polymorphic VT or VF. Although polymorphic VT or VF is often the documented arrhythmia at the time of resuscitation in patients with out-of-hospital cardiac arrest, the initiating arrhythmia in such patients may frequently be unimorphic VT.[13,14] Because the clinical significance of polymorphic VT or ventricular fibrillation induced by programmed stimulation in patients with a history of out-of-hospital cardiac arrest is unclear,[6] such patients were excluded from this study.

Approximately 50% of the nonclinical arrhythmias included in this study were sustained and required direct-current countershock to terminate. Because none of the patients with induced sustained polymorphic VT or VF had a history of a cardiac arrest or had received countershocks in the past, these sustained arrhythmias were clearly nonclinical in these patients. However, it may be argued that some of the nonsustained episodes of polymorphic VT induced in this study may have also occurred spontaneously, but may have been asymptomatic and undocumented. This possibility cannot be ruled out and is a limitation of the study. However, the means and distributions of the coupling intervals that induced the sustained and nonsustained forms of the nonclinical arrhythmias did not differ, and therefore the results would have been similar even if the nonclinical arrhythmias had been restricted to those that were sustained.

Acknowledgment: We are grateful to Lisa Hackbarth for her excellent secretarial assistance.

References

1. Mann DE, Luck JC, Griffin JC, Herre JM, Limacher MC, Magro SA, Robertson NW, Wyndham CRC. *Induction of clinical ventricular tachycardia using programmed stimulation: value of third and fourth extrastimuli. Am J Cardiol 1983;52:501-506.*
2. Brugada P, Green M, Abdollah H, Wellens HJJ. *Significance of ventricular arrhythmias initiated by programmed ventricular stimulations: the importance of the type of ventricular arrhythmia induced and the number of premature stimuli required. Circulation 1984;69:87-92.*
3. Buxton AE, Waxman HL, Marchlinski FE, Untereker WJ, Waspe LE, Josephson ME. *Role of triple extrastimuli during electrophysiologic study of patients with documented sustained ventricular tachyarrhythmias. Circulation 1984;69:532-540.*
4. Morady F, DiCarlo L, Winston S, Davis JC, Scheinman MM. *A prospective comparison of triple extrastimuli and left ventricular stimulation in studies of ventricular tachycardia induction. Circulation 1984;70:52-57.*
5. Brugada P, Wellens HJJ. *Comparison in the same patient of two programmed ventricular stimulation protocols to induce ventricular tachycardia.*

Am J Cardiol 1985;55:380–383.
6. Wellens HJJ, Brugada P, Stevenson WG. *Programmed electrical stimulation of the heart in patients with life-threatening ventricular arrhythmias: what is the significance of induced arrhythmias and what is the correct stimulation protocol? Circulation 1985;72:1–7.*
7. Morady F, Shapiro W, Shen E, Sung RJ, Scheinman MM. *Programmed ventricular stimulation in patients without spontaneous ventricular tachycardia. Am Heart J 1984;107:875–882.*
8. Brugada P, Abdollah H, Heddle B, Wellens HJJ. *Results of a ventricular stimulation protocol using a maximum of 4 premature stimuli in patients without documented or suspected ventricular arrhythmias. Am J Cardiol 1983;52:1214–1218.*
9. Morady F, DiCarlo LA, Liem LB, Krol RB, Baerman JM. *Effects of high stimulation current on the induction of ventricular tachycardia. Am J Cardiol 1985;56:73–78.*
10. Morady F, Shen E, Schwartz A, Hess D, Bhandari A, Sung RJ, Scheinman MM. *Long-term follow-up of patients with recurrent unexplained syncope evaluated by electrophysiologic testing. JACC 1983;2:1053–1059.*
11. DiCarlo LA Jr, Morady F, Schwartz AB, Shen EN, Baerman JM, Krol RB, Scheinman MM, Sung RJ. *Clinical significance of ventricular fibrillation-flutter induced by ventricular programmed stimulation. Am Heart J 1985; 109:959–963.*
12. Doherty JU, Pembrook-Rogers D, Grogan EW, Falcone RA, Buxton AE, Marchlinski FE, Cassidy DM, Kienzle MC, Almendral JM, Josephson ME. *Electrophysiologic evaluation and follow-up characteristics of patients with recurrent unexplained syncope and presyncope. Am J Cardiol 1985;55:703–708.*
13. Kempf FC Jr, Josephson ME. *Cardiac arrest recorded on ambulatory electrocardiograms. Am J Cardiol 1984;53:1577–1582.*
14. Milner PG, Platia EV, Reid PR, Griffith LSC. *Ambulatory electrocardiographic recordings at the time of fatal cardiac arrest. Am J Cardiol 1985; 56:588–592.*