Repellent Responses to Single Ventricular Extrastimuli in Patients with Serious Ventricular Arrhythmias: Incidence and Clinical Significance

JEREMY N. RUSKIN, M.D., JOHN P. DIMARCO, M.D., AND HASAN GARAN, M.D.

SUMMARY Electrophysiologic studies were carried out in 85 patients with serious ventricular arrhythmias: 44 with recurrent sustained ventricular tachycardia (group A), 16 with recurrent nonsustained ventricular tachycardia (group B), and 25 with recent prehospital ventricular fibrillation not associated with acute myocardial infarction (group C). Programmed ventricular stimulation from the right ventricular apex included premature stimulation during normal sinus rhythm, atrial pacing, and ventricular pacing, as well as brief bursts of rapid ventricular pacing (RVP). A repetitive ventricular response (RVR) was defined as one or more nonstimulated premature ventricular depolarizations in response to a single paced premature ventricular depolarization during normal sinus rhythm or atrial pacing. RVRs were observed in seven of 44 (16%) group A patients, one of 16 (6%) group B patients, and three of 25 (12%) group C patients. In contrast, single and double premature ventricular stimuli during ventricular pacing and/or bursts of RVP resulted in the reproducible initiation of ventricular tachycardia in 40 of 44 (91%) group A patients, 10 of 16 (63%) group B patients, and 19 of 25 (76%) group C patients. We conclude that RVRs to single ventricular extrastimuli during normal sinus rhythm or atrial pacing are rare, and therefore are an insensitive index of susceptibility to serious ventricular arrhythmias in these patients.

THE INCIDENCE and clinical significance of repetitive ventricular responses (RVR) to single ventricular extrastimuli during normal sinus rhythm (NSR) or atrial pacing has stimulated considerable interest and debate.1-4 Recently, Greene and co-workers reported a high (> 85%) incidence of RVR in patients with a history of recurrent ventricular tachycardia (VT).1 Their findings suggested that the suppression of RVR might constitute a useful end point to guide the selection of long-term prophylactic antiarrhythmic drug therapy.2 The purpose of this study was to assess the incidence of RVR and to compare the sensitivity of this finding with that of electrically stimulated VT in three populations of patients with serious ventricular arrhythmias.

From the Cardiac Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts.

Address for correspondence: Jeremy N. Ruskin, M.D., Cardiac Unit, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts 02114.

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Methods

Electrophysiologic studies were carried out in 85 patients who were referred for the management of serious ventricular arrhythmias. Sixty-four males and 21 females, mean age 56 years (range 19–75 years), were studied. Sixty-three patients had coronary artery disease, 10 had valvular heart disease, and eight had primary myocardial disease. Four patients had no detectable evidence of structural heart disease. The patients were divided into three groups, based on the rhythm disturbance for which they were referred. Group A included 44 patients with a history of recurrent (two to 80) episodes of symptomatic sustained VT that required drug therapy or cardioversion for termination. VT was associated with loss of consciousness in 21 patients and with presyncope, congestive heart failure or angina pectoris in 23. Group B included 16 patients with recurrent episodes of symptomatic nonsustained VT (≥ 5 beats) that were associated with syncope in seven patients and presyncope or palpitations in nine patients. Group C
that delivered rectangular 2-msec pulses. All ventricular stimulation was carried out from the right ventricular apex at twice diastolic threshold (< 2 mA).

The following stimulation protocol was used in all 85 patients: (1) Atrial pacing at rates of 100–300 beats/min. (2) Premature atrial stimulation during atrial pacing at one or more basic cycle lengths. (3) Ventricular pacing at rates of 60–150 beats/min (30-second bursts). (4) Premature ventricular stimulation with single (S1) and double (S2S3) extrastimuli during sinus rhythm and during fixed-rate atrial pacing at a cycle length of 600 msec. Premature stimuli were introduced after every eighth sinus or atrially paced beat. (5) Premature ventricular stimulation with single (S1) and double (S2S3) extrastimuli during ventricular pacing at multiple basic cycle lengths (S2S1). Premature stimuli were introduced after every eighth paced beat. (6) Rapid ventricular pacing (RVP) at rates of 150–280 beats/min. Pacing was delivered in brief bursts of two to five beats.

An RVR was defined as one or more nonstimulated premature ventricular depolarizations not caused by His-Purkinje reentry and occurring reproducibly in response to a single stimulated premature ventricular depolarization during sinus rhythm or atrial pacing (fig. 1). A nonstimulated (wide QRS complex) ventricular response was defined as His-Purkinje reentry if it was associated with a critical degree of retrograde His-Purkinje conduction delay and an HV interval with a duration equal to or greater than that observed during spontaneous sinus rhythm. Sustained VT was defined as VT that required pacing or external countershock for termination. Non-sustained VT was defined as VT that persisted for at

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

**Figure 1.** Repetitive ventricular response (RVR) in a patient with recurrent sustained ventricular tachycardia. Tracings from top to bottom represent surface ECG leads 1, 2, and V1, a His bundle electrogram (HBE), a right ventricular apical electrogram (RVA) and time lines generated at 50-msec intervals. The last in a series of eight spontaneous sinus beats is followed by a single paced premature ventricular depolarization (PVD) from the right ventricular apex. S represents the stimulus artifact. The paced PVD is followed by a single RVR. The RVR is not preceded by a His bundle deflection and the QRS complex morphology and axis orientation of the RVR differ markedly from those of the paced PVD.
least five beats and reverted spontaneously within 100 beats to sinus rhythm.

**Results**

The responses to programmed ventricular stimulation are summarized in Table 1.

**Incidence of RVR**

RVRs to single ventricular extrastimuli delivered during NSR or atrial pacing were observed in seven of 44 (16%) patients with recurrent sustained VT, in one of 16 (6%) patients with recurrent nonsustained VT, and in three of 25 (12%) patients with prehospital VF (fig. 1).

RVR in response to two sequential premature ventricular extrastimuli delivered during NSR or atrial pacing were present in 18 of 44 (41%) patients with sustained VT, three of 16 (19%) patients with nonsustained VT, and in five of 25 (20%) patients with prehospital VF.

**Incidence of Inducible VT**

Single ventricular extrastimuli delivered during NSR or atrial pacing resulted in the initiation of sustained VT in one of 44 patients with a history of sustained VT and in none of the patients with a history of nonsustained VT or prehospital VF. The use of two sequential premature ventricular extrastimuli during NSR or atrial pacing resulted in the initiation of sustained VT in eight and nonsustained VT in two of 44 patients with a history of sustained VT. This mode of ventricular stimulation resulted in the initiation of nonsustained VT in one of 16 patients with a history of nonsustained VT and sustained VT in two of 25 patients with a history of prehospital VF.

Single and double premature ventricular extrastimuli delivered during ventricular pacing, as well as brief bursts of rapid ventricular pacing, resulted in the initiation of sustained VT in 34 and nonsustained VT in six of the 44 patients with recurrent sustained VT (fig. 2). These modes of programmed ventricular stimulation resulted in the initiation of nonsustained VT in 10 of 16 patients with a history of nonsustained VT (fig. 3), and sustained VT in 10 and nonsustained VT in nine of 25 patients with a history of prehospital VF. The difference between the incidence of RVR to single ventricular extrastimuli during NSR or atrial pacing and the incidence of inducible VT with more aggressive modes of programmed ventricular stimulation was significant at the \( p < 0.0001 \) level for groups A and C and at the \( p < 0.001 \) level for group B.

**Discussion**

The incidence and clinical significance of the RVR as defined in this and previous studies are of considerable interest and debate. The initiation of RVR after a single premature ventricular stimulus has been used as an index of ventricular electrical instability in experimental animals. Recently, Greene and co-workers reported RVR in 66 of 77 patients (86%) with a history of recurrent VT, in 22 of 61 patients (36%) with recent myocardial infarction and in none of 22 normal control patients. In an earlier study, they observed symptomatic VT or sudden death within 1 year in 15 of 19 post-myocardial infarction patients with RVR and in only four of 29 post–myocardial infarction patients without RVR. These initial observations suggested that RVR was a sensitive indicator of ventricular electrical instability and a predictor of risk for subsequent sudden death. Schaeffer et al. proposed that the acute suppression of RVR by antiarrhythmic drugs might be a useful indicator of long-term antiarrhythmic efficacy in patients with VT. In contrast, in this study, we found evidence of RVR, as defined by Greene and co-workers, in only 16% of patients with recurrent sustained VT, 6% of patients with recurrent nonsustained VT, and 12% of patients with recent prehospital VF. This low incidence of RVR in patients with recurrent VT has been confirmed by other investigators.

**Table 1. Incidence of Repetitive Ventricular Responses and Ventricular Tachycardia in Response to Various Modes of Programmed Ventricular Stimulation**

<table>
<thead>
<tr>
<th></th>
<th>Group A VT (n = 44)</th>
<th>Group B NSVT (n = 16)</th>
<th>Group C VF (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RVR</td>
<td>VT</td>
<td>RVR</td>
</tr>
<tr>
<td>1 VPD</td>
<td>7</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>NSR/AP</td>
<td>(16%)</td>
<td>(2%)</td>
<td>(6%)</td>
</tr>
<tr>
<td>2 VPD</td>
<td>18</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>NSR/AP</td>
<td>(41%)</td>
<td>(23%)</td>
<td>(19%)</td>
</tr>
<tr>
<td>1 + 2 VPD</td>
<td>40</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>VP/RVP</td>
<td>(91%)</td>
<td></td>
<td>(63%)</td>
</tr>
</tbody>
</table>

Abbreviations: AP = atrial pacing; NSR = normal sinus rhythm; NSVT = nonsustained ventricular tachycardia; RVP = rapid ventricular pacing; RVR = repetitive ventricular responses; VF = ventricular fibrillation; VP = ventricular pacing; VPD = ventricular premature depolarization; VT = ventricular tachycardia.
These disparate observations probably cannot be explained on the basis of differences in the stimulation protocols. In our study, all programmed stimulation was performed from the right ventricular apex, because we have found that other catheter positions within the right ventricle lack sufficient stability and reproducibility for serial antiarrhythmic drug testing. Greene and co-workers carried out programmed stimulation from a second site, usually the right ventricular outflow tract, if RVR did not occur during right ventricular apical stimulation. However, only 13 of the 92 patients (14%) with RVR in their study required testing from a second right ventricular site to elicit the RVR. Both studies employed constant current stimulation at twice diastolic threshold. Furthermore, electrophysiologic studies were performed in the absence of antiarrhythmic drug therapy in all 85 patients in our series and in 196 of 221 patients in the series reported by Greene and co-workers. Differences in the patient populations are also unlikely to account for the disparate observations on the incidence of RVR in the two series. Of the 85 patients in our series, 44 had a history of symptomatic sustained VT, 16 had symptomatic nonsustained VT,
and 25 patients had survived at least one episode of out-of-hospital ventricular fibrillation. Of the patients studied by Greene and co-workers, the largest group included 102 patients with symptomatic ventricular tachycardia.\(^9\) The clinical characteristics of the patients with VT in both studies were quite similar.\(^9\)

During RVR testing, we encountered several types of wide QRS-complex responses that might lead to an overestimation of the true incidence of RVR as defined in this and earlier studies (i.e., intraventricular reentry). Patients with frequent spontaneous ventricular premature complexes often manifest random ectopy after a paced premature beat, although this is rarely reproducible on repeat stimulation at the same or similar coupling intervals. Catheter-induced ventricular ectopy, which may mimic local reentry, is another source of error in RVR testing, and can be avoided only by highly stable catheter placement. In addition, two other forms of wide QRS-complex responses to premature ventricular stimuli that may be confused with RVR are retrograde atrioventricular nodal reentry (echo) beats with aberrant ventricular conduction and reentry within the His-Purkinje system.\(^8,9\) Both forms of reentry constitute normal physiologic responses and are uniformly associated with the occurrence of a His bundle deflection before the onset of the local septal ventricular electrogram and an HV interval with a duration equal to or greater than that observed during supraventricular rhythm.\(^8,9\)

An even more common finding in our experience is the occurrence of aberrant ventricular conduction of the sinus beat immediately after a paced premature ventricular depolarization. This occurs as a result of retrograde ventriculoatrial conduction of the premature impulse within the His-Purkinje system, but failure of the impulse to reach and reset the sinoatrial node. This latter response is uniformly associated with a high-to-low atrial activation sequence and an HV interval equal to or greater than that observed during supraventricular rhythm. Thus, true RVR may be diagnosed with certainty only in the presence of a stable His bundle electrogram recording; the absence of a His bundle recording may result in a significant overestimation of the true incidence of RVR. Because of the problems associated with distinguishing true RVR from other wide QRS-complex responses, as well as the lack of diagnostic sensitivity of RVR, we believe that the initiation of clinical VT should be used as the primary diagnostic and therapeutic end point in the management of this group of patients.

The incidence of ventricular repetitions in response to ventricular extrastimuli delivered during ventricular pacing far exceeds that observed during supraventricular rhythm.\(^10\) Farshidi and co-workers observed single or multiple ventricular repetitions due to local (intraventricular) reentry in 76% of patients with a history of VT or VF and in only 9.1% of patients without a history of serious ventricular arrhythmias. Of 41 patients in whom clinical VT could be induced by programmed cardiac stimulation, 38 (92.7%) manifested single or multiple repetitive responses resulting from intraventricular reentry.\(^10\) In addition to ventricular drive, however, these in-
vestigators used both single and double premature ventricular extrastimuli. Furthermore, the predictive value of single repetitive responses with regard to the risk of subsequent arrhythmias or sudden death, as well as their value as an end point for the selection of long-term antiarrhythmic drug therapy, has yet to be assessed. Multiple (> 5) repetitive responses, which we have defined as nonsustained VT, are common in response to single and double extrastimuli delivered during ventricular pacing in patients with serious ventricular arrhythmias. Furthermore, the suppression of these responses (nonsustained VT) with antiarrhythmic drugs has, in our experience, been an extremely useful therapeutic end point.

Clinical Implications

We conclude from our own observations in 85 patients, and those of others in comparable numbers of patients, that RVRs after single ventricular extrastimuli delivered during normal sinus rhythm or atrial pacing are present in approximately 15% of patients with a history of VT or VF unassociated with acute myocardial infarction. Thus, although the specificity of these responses must be studied, RVR testing as defined in this and previous studies is an extremely insensitive index of susceptibility to serious ventricular arrhythmias. In contrast, programmed premature ventricular stimulation during ventricular pacing, as well as brief bursts of rapid ventricular pacing, results in the reproducible initiation of sustained or nonsustained ventricular tachycardia in 75–90% of patients with a history of VT or VF. Furthermore, the suppression of electrically inducible VT with antiarrhythmic drugs is highly predictive of a successful clinical response at 1–2 years of follow-up in these patients. Thus, we believe that the suppression of inducible VT is the most sensitive and reliable therapeutic end point.

References

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J N Ruskin, J P DiMarco and H Garan

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