EXPERIMENTAL STUDIES

Importance of the Pacing Mode in the Initiation of Ventricular Tachyarrhythmia in a Canine Model of Chronic Myocardial Infarction

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The use of unipolar anodal or bipolar pacing, as compared with unipolar cathodal pacing, purportedly increases the likelihood of inducing inadvertent ventricular fibrillation in susceptible patients. In this study, the ability to initiate sustained ventricular tachycardia or fibrillation with unipolar cathodal, unipolar anodal and bipolar pacing modes was compared using programmed ventricular stimulation at 82 subendocardial perinfarction sites in 11 dogs with chronic myocardial infarction.

The late diastolic excitability threshold was significantly higher and the ventricular refractory period was significantly shorter (p < 0.001) with anodal pacing (mean 0.62 mA, 156 ms, respectively) than with pacing in either the cathodal (0.12 mA, 174 ms) or the bipolar (0.13 mA, 173 ms) mode. At a current intensity twice that of the excitability threshold, the introduction of one or two extrastimuli induced ventricular tachycardia and ventricular fibrillation comparably among the three pacing modes. However, when three extrastimuli were used, ventricular fibrillation was induced with anodal pacing twice as frequently (50 [61%] of 82 sites) as with either of the other two pacing modes (each 15 [18%] of 82 sites, p < 0.001), whereas the induction of ventricular tachycardia remained comparable with anodal pacing (15 [18%] of 82 sites) and cathodal and bipolar pacing (each 14 [17%] of 82 sites). Furthermore, a similarly high incidence of inducibility of ventricular fibrillation was observed with both cathodal pacing (56 [68%] of 82 sites) and bipolar pacing (40 [49%] of 82 sites) when an increased current equal to twice the anodal excitability threshold (1.23 mA) was used. This high incidence was related to the ability to introduce extrastimuli earlier in ventricular diastole.

Thus, at comparably high levels of pacing current, the initiation of ventricular fibrillation was just as likely with unipolar cathodal or bipolar pacing as with unipolar anodal stimulation. Shortening of refractoriness with increasingly higher currents appeared to be an important contributory mechanism. Conversely, pacing from normal sites with low excitability thresholds using either cathodal or bipolar stimulation minimized the risk of inadvertent ventricular fibrillation.

(J Am Coll Cardiol 1985;6:99–103)

Methods

Experimental preparation. Studies were done in 11 healthy adult mongrel dogs weighing 14.1 to 18.3 kg (mean 15.9). Four to 8 days before the study, the dogs underwent two-stage occlusion of the mid left anterior descending coronary artery, followed by reperfusion after 2 hours of com-
complete occlusion, using aseptic techniques as previously described (10).

The electrophysiologic study was performed under pentobarbital anesthesia (30 mg/kg body weight, intravenously) with the heart exposed through a midline sternal thoracotomy. The lead II scalar electrocardiogram and intraaortic blood pressure were monitored continuously. Bipolar Teflon-coated stainless steel plunge (hook) wire electrodes, which were insulated except for the tips, were used for stimulation. Ten pairs of subendocardial electrodes were placed in normal myocardium in the distribution of non-occluded vessels approximately 1 to 2 cm from the infarct margins (3). Data were recorded from a total of 110 sites in these 11 dogs. A site was excluded from the analysis if unstable capture or an unstable excitability threshold was observed in any of the pacing modes. Programmed electrical stimulation was performed using a custom-designed digital stimulator (Bloom Associates, Ltd.) and a constant-current source providing rectangular current pulses 2 ms in duration. One of the pair of stimulating subendocardial electrodes served alternately as the cathode (unipolar cathodal stimulation) and anode (unipolar anodal stimulation) so that unipolar stimulation was always from the same pole of the pair. A stainless steel rib spreader having a surface of approximately 8 cm² in contact with the chest wall served as an indifferent electrode. For bipolar stimulation, the same pole used for unipolar stimulation served as the cathode and the other pole as the anode with an interelectrode distance of approximately 1 mm. The diastolic excitability threshold was determined at each test site and defined as the stimulus of minimal strength (mA) that consistently resulted in a propagated ventricular response when delivered in late diastole.

Study protocol. To evaluate the inducibility of sustained ventricular tachyarrhythmias (of at least 15 seconds’ duration), ventricular extrastimuli were introduced during ventricular pacing. Both the drive and extrastimuli were applied at the same ventricular site using two protocols.

In Protocol I, each site underwent unipolar cathodal stimulation at twice the excitability threshold for cathodal pacing, unipolar anodal stimulation at twice the excitability threshold for anodal pacing and bipolar stimulation at twice the excitability threshold for bipolar pacing. Protocol II was utilized when Protocol I failed to initiate sustained ventricular tachyarrhythmias. Protocol II consisted of unipolar cathodal stimulation with current increased to twice the excitability threshold for anodal pacing and bipolar stimulation at twice the excitability threshold for anodal pacing.

After eight ventricular drive beats (S₁) at a cycle length of 300 ms, an extrastimulus (S₂) was introduced, beginning late in diastole. Simultaneous atrial drive pacing was used in animals with less than 1:1 ventriculoatrial conduction to avoid inadvertent capture beats and interruption of the stimulation protocol. The coupling interval was gradually decreased, moving S₂ initially in steps of 10 ms, and then in steps of 2 ms within 10 ms of refractoriness. The end point was the initiation of either a sustained ventricular tachycardia lasting for more than 15 seconds or ventricular fibrillation before the ventricular refractory period was reached. The ventricular refractory period was defined as the longest S₁S₂ coupling interval failing to elicit a ventricular response. If a sustained ventricular tachyarrhythmia was not elicited, the S₂ interval was increased to 50 ms greater than the ventricular refractory period, and two extrastimuli (S₂,S₃) were introduced with the S₂S₃ interval equal to the S₁S₂ interval. The S₂S₁ coupling interval was shortened until refractoriness for S₁ appeared, and then the S₁S₂ coupling interval was shortened until capture for S₂ again occurred. This tandem method was used until refractoriness for S₂ was reached. If two extrastimuli failed to elicit a sustained arrhythmia, three extrastimuli were introduced and the coupling intervals were shortened progressively in a similar way until a sustained arrhythmia was initiated or refractoriness for S₂ was reached.

The ventricular arrhythmia had to be reproduced at least two times at each pacing site. The order of pacing mode was always initially cathodal, then either anodal or bipolar; finally, a second trial was made of cathodal stimulation to confirm the reproducibility of the results and stability of the preparation. In animals with ventricular tachyarrhythmia causing rapid hemodynamic deterioration, direct-current countershock (10 to 40 watt-seconds) was applied if rapid ventricular pacing was not successful in terminating the arrhythmia. At least 5 minutes were allowed for recovery after countershock. All experiments conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and the Lankenau Animal Care Policy.

Statistical methods. The significance of differences in excitability thresholds and ventricular refractory periods obtained by different stimulation protocols was determined using repeated-measures analysis of variance. To isolate differences in repeated-measures analysis of variance, multiple comparisons with paired t tests using the residual mean square and the Bonferroni correction were made. Comparison of inducibility of sustained ventricular tachyarrhythmias among different stimulation protocols was performed using Cochran’s test, and pairwise comparisons with McNemar’s test were done using the Bonferroni correction.

Results

Excitability thresholds and ventricular refractory periods (Table 1). The electrophysiologic variables were evaluated at 82 sites in which all stimulation protocols were completed. The excitability thresholds were similar for both unipolar cathodal and bipolar pacing modes (mean 0.12 and 0.13 mA, respectively), but the excitability threshold for
Table 1. Excitability and Refractoriness With Different Pacing Modes

<table>
<thead>
<tr>
<th></th>
<th>Unipolar Cathodal</th>
<th>Unipolar Anodal</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET (mA) (n = 82)</td>
<td>0.12 ± 0.05</td>
<td>0.62 ± 0.27*</td>
<td>0.13 ± 0.07</td>
</tr>
<tr>
<td>VRP using current twice ET (ms) of respective pacing mode (n = 82)</td>
<td>173.6 ± 21.4</td>
<td>156.4 ± 20.8*</td>
<td>172.9 ± 22.2</td>
</tr>
<tr>
<td>VRP using current twice anodal ET intensity (ms) (n = 37)</td>
<td>145.1 ± 10.4</td>
<td>146.6 ± 11.8</td>
<td>156.3 ± 8.8*</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. *p < 0.001 versus cathodal and bipolar pacing; †p < 0.001 versus cathodal and anodal pacing. ET = excitability threshold; VRP = ventricular refractory period.

Table 2. Effect of Pacing Mode, Current Intensity and Number of Ventricular Extrastimuli on Ventricular Tachyarrhythmia

<table>
<thead>
<tr>
<th>Mode and Current (n = 82 pacing sites)</th>
<th>VT</th>
<th>VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,2 VES</td>
<td>3 VES</td>
</tr>
<tr>
<td>Cathodal</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>2 × C-ET</td>
<td>3 (4)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>2 × A-ET</td>
<td>3 (4)</td>
<td>13 (16)</td>
</tr>
<tr>
<td>Anodal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 × A-ET</td>
<td>4 (5)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>2 × B-ET</td>
<td>3 (4)</td>
<td>9 (11)</td>
</tr>
<tr>
<td>2 × A-ET</td>
<td>3 (4)</td>
<td>9 (11)</td>
</tr>
</tbody>
</table>

2 × A-ET = twice the anodal excitability threshold; 2 × B-ET = twice the bipolar excitability threshold; 2 × C-ET = twice the cathodal excitability threshold; n = number of sites of inducible tachyarrhythmias; VES = ventricular extrastimuli; VF = ventricular fibrillation; VT = sustained ventricular tachycardia.

Table 2. Effect of Pacing Mode. Current Intensity and Number of Ventricular Extrastimuli on Ventricular Tachyarrhythmia

Initiation: Number and Percent of Sites of Inducible Arrhythmia

anodal pacing was considerably higher (0.62 mA) (p < 0.001) (Table 1). Measurements of ventricular refractory periods using a current intensity of twice the excitability threshold for each pacing mode revealed that anodal pacing resulted in consistently shorter ventricular refractory periods (mean difference 17 ms) than those obtained with the other two pacing modes. The cathodal and bipolar ventricular refractory periods were similar.

Ventricular refractory periods were also measured in the unipolar cathodal and bipolar pacing modes using current increased to twice the intensity of the anodal excitability threshold in a subset of 37 sites at which this was possible without inducing sustained tachyarrhythmias. As described, ventricular refractory periods during cathodal and bipolar pacing using a current intensity of twice the excitability threshold for anodal pacing were significantly shorter than the refractory periods using either cathodal pacing at twice the excitability threshold for cathodal pacing or bipolar pacing at twice the excitability threshold for bipolar pacing. Ventricular refractory periods were similar for cathodal and anodal pacing using the same current intensity of twice the excitability threshold for anodal pacing, but were significantly longer for bipolar pacing at this current intensity (Table 1).

Initiation of ventricular tachyarrhythmia (Table 2). Programmed ventricular stimulation using a current intensity twice the excitability threshold for each respective pacing mode induced sustained ventricular tachyarrhythmia in 9 (82%) of the 11 study dogs with cathodal pacing, in 11 dogs (100%) with anodal stimulation and in 8 dogs (73%) with bipolar pacing. The relative frequency with which sustained ventricular tachycardia or fibrillation was initiated in these animals was similar using unipolar cathodal, anodal or bipolar pacing at twice the threshold current for the respective mode. Overall, 3 (27%) of the 11 dogs had sustained ventricular tachycardia initiated in all three modes; in the remaining 8 dogs ventricular fibrillation was initiated in one or more modes.

In contrast, there were significant differences in the inducibility of ventricular tachyarrhythmias with the different pacing modes with respect to the use of one or two versus three ventricular extrastimuli. When only one or two ventricular extrastimuli were introduced, the inducibility of both ventricular tachycardia and ventricular fibrillation was comparable among the three stimulation modes using a current intensity of twice the excitability threshold for the cathodal, anodal and bipolar pacing modes (mean 0.24, 1.24 and 0.26 mA, respectively) (Tables 1 and 2). When a third extrastimulus was introduced, the inducibility of ventricular tachycardia was increased but still comparable among these three modes. In contrast, the inducibility of ventricular fibrillation was twice as frequent with anodal stimulation (61 versus 28%, p < 0.001) as with the other two pacing modes when three extrastimuli were utilized. Importantly, ventricular fibrillation induced by either the cathodal or the bipolar pacing mode was always reproduced by anodal stimulation. Conversely, reproduction of the high incidence of ventricular
fibrillation observed with anodal stimulation using either two or three extrastimuli was only possible with cathodal stimulation when the current used was increased to twice the excitability threshold of the anodal pacing mode (mean 1.23 mA), but without significantly increasing the inducibility of ventricular tachycardia. Although bipolar stimulation at twice the excitability threshold of the anodal pacing mode also increased the inducibility of ventricular fibrillation, the incidence was not as frequent as with the other modes (p < 0.001). The increased inducibility of ventricular fibrillation with cathodal or bipolar stimulation using a current intensity of twice the anodal excitability threshold was closely related to the ability to introduce extrastimuli earlier in diastole, as evidenced by the changes in ventricular refractoriness shown in Table 1.

**Discussion**

**Clinical background.** Our study demonstrates the importance of the pacing mode in initiating ventricular tachyarrhythmias. As suggested by clinical reports, unipolar anodal stimulation using a current intensity of twice the excitability threshold initiated ventricular arrhythmia more frequently than did either unipolar cathodal or bipolar stimulation. Preston (9) initially brought clinical attention to anodal stimulation as a possible cause of pacemaker-induced ventricular fibrillation. He reported, after reviewing earlier studies, a frequent association of pacemaker-induced ventricular fibrillation with bipolar electrodes in the human subject. The possibility could not be excluded that the relatively small-surfaced anode of the bipolar system in use at the time, placed on or within the heart, permitted anodal stimulation. Subsequently, there was concern that a premature electrical stimulation during fixed rate continuous pacing could become a potential trigger for ventricular fibrillation irrespective of the pacing mode. In fact, there are a few reported cases (11–13) of unipolar cathodal stimulation inadvertently inducing ventricular tachyarrhythmia.

At present, bipolar lead systems with small surface area anodes are used routinely for electrophysiologic studies and cardiac pacing as well as in postoperative patients with temporary plunge wire electrodes inserted during open heart surgery. Bipolar leads are also often utilized in emergency settings such as acute myocardial infarction at a time when the myocardium is especially vulnerable to ventricular fibrillation.

**Experimental background.** In previous studies comparing different pacing modes, experimental evidence consistently demonstrated an increased vulnerability to ventricular arrhythmias from unipolar anodal (hyperpolarizing) or bipolar stimulation as compared with unipolar cathodal (depolarizing) stimulation (14–17). The current required to induce ventricular fibrillation in healthy canine hearts (14) and acutely ischemic canine hearts (15) by cathodal stimulation was reported to be, respectively, 2.5 and 1.5 times higher than required for anodal or bipolar stimulation.

It has been known that the strength-interval curve depicting anodal thresholds has a characteristic abrupt drop to a minimal value called "anodal supernormality" or "the anodal dip" (18, 19). This dip during phase 3 of the ventricular action potential was thought to allow excitation during early diastole at relatively low current intensity, thus increasing susceptibility to ventricular fibrillation with anodal stimulation (11, 20–23). With anodal stimulation, hyperpolarization occurs, and subsequent depolarization results from the "break" or termination of the anodal stimulation pulse. van Dam et al. (18) speculated that the bipolar strength-interval curve would be a composite of the lower portions of the superimposed anodal and cathodal curves, after demonstrating the simultaneous spread of two excitation waves from the poles of the bipolar electrode pair when the current applied exceeded the excitability thresholds of both the cathode and anode.

**Initiation of ventricular tachycardia versus fibrillation.** An important finding in our study was that inducibility of ventricular tachyarrhythmia was not affected by the pacing mode when 1) the arrhythmia of interest was ventricular tachycardia rather than ventricular fibrillation, or 2) only one or two ventricular extrastimuli were introduced. Although the inducibility of ventricular tachycardia with two or three extrastimuli was similar in all three pacing modes using a current intensity of twice the excitability threshold of that mode, the initiation of ventricular fibrillation was considerably more frequent in all three pacing modes using three extrastimuli and a current intensity of twice the anodal excitability threshold.

Previously reported experimental and clinical studies (4, 24–28) have provided strong evidence suggesting a reentrant mechanism of most programmed pacing-induced ventricular tachyarrhythmias. However, the significance of each subtype of ventricular tachyarrhythmia (namely, ventricular tachycardia and ventricular fibrillation) has not been well described. Vandepol et al. (1) and Spielman et al. (29) found that a single ventricular extrastimulus induced sustained ventricular tachycardia in about one-third of susceptible patients, but ventricular fibrillation was never induced by a single extrastimulus. Although ventricular fibrillation was occasionally induced with a single ventricular extrastimulus in our model of chronic myocardial infarction, its initiation generally required a greater number of extrastimuli than did the initiation of ventricular tachycardia. This was probably not the result of a greater distance between the stimulating site and the reentrant circuit in dogs with inducible ventricular fibrillation because electrodes were always placed within 2 cm of the infarction zone.

**The introduction of multiple extrastimuli shortens the minimal achievable coupling intervals.** Since the temporal dispersion of recovery is greater after premature beats with short rather than long coupling intervals (30), the requirement of multiple extrastimuli for initiation of ventricular fibrillation might indicate differences in patterns of
inhomogeneous conduction in cardiac tissue in the anatomic substrate of ventricular fibrillation compared with that of ventricular tachycardia. If this hypothesis is correct, it would be reasonable to assume that anodal stimulation, particularly when combined with the use of three extrastimuli, has a propensity to induce ventricular fibrillation because of the ability to achieve relatively shorter coupling intervals. Notably, this effect of anodal stimulation could be reproduced by increasing the intensity of cathodal current, which not only shortened the refractory period, but also could increase temporal dispersion even when the coupling interval was not altered (18).

Clinical implications. Our study suggests that the stimulus mode, current intensity and number of extrastimuli can influence the results of programmed pacing. Using one or two ventricular extrastimuli and twice the threshold current, the frequency of initiation of ventricular tachyarrhythmia was comparable in this model using unipolar cathodal, anodal or bipolar pacing. However, using three extrastimuli, particularly with anodal pacing, there was a disproportionate increase in inducibility of ventricular fibrillation. These results indicate that inadvertent initiation of ventricular fibrillation is minimized by pacing from sites with low excitability thresholds using either unipolar cathodal or bipolar stimulation and only one or two ventricular extrastimuli. Moreover, the data suggest that initiation of ventricular fibrillation is at least no more likely with bipolar pacing than with the other pacing modes.

We gratefully acknowledge the biomedical assistance of John Nielands, and the technical assistance of Mark Schaffenburg, Sydney Vail and Rohn Price. We also thank Rose Marie Wells for secretarial assistance in the preparation of this manuscript.

References