Comparative effects of single- and linear triple-site rapid bipolar pacing on atrial activation in canine models

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Ryu, Kyungmoo, Raja N. Ghanem, Ceelen M. Khrestian, Naomichi Matsumoto, Robert N. Goldstein, Jayakumar Sahadevan, Parvin C. Dorostkar, and Albert L. Waldo. Comparative effects of single- and linear triple-site rapid bipolar pacing on atrial activation in canine models. Am J Physiol Heart Circ Physiol 289: H374–H384, 2005. First published February 11, 2005; doi:10.1152/ajpheart.01265.2004.—Nonuniform conduction may cause block and/or delay, thereby providing a substrate for the onset and maintenance of reentrant atrial arrhythmias. We tested the hypothesis that linear triple-site, bipolar, rapid pacing (LTSBRP) of the right atrium generates more uniform wave-front propagation compared with single-site, bipolar, rapid pacing (SSBRP), thereby reducing and/or eliminating conduction block and delay that is otherwise present. Five dogs with pericarditis and three normal dogs were studied. Three plunge-wire electrode pairs were placed 5–7 mm apart in both perpendicular and parallel configurations at the superior aspect of the crista terminals and were used to pace at 200- and 300-ms cycle lengths for ≤6 s. During pacing, 380 electrograms were recorded simultaneously from electrode arrays placed epicardially on the atria, which produced activation sequence maps for each pacing episode. Local conduction-velocity vectors were computed for each site during each episode. Histograms of absolute velocity vector angles from the x-axis (of the crista terminals) were plotted to assess uniformity of wave-front propagation, and the magnitude of each vector was computed to assess the local speed. LTSBRP showed 1) more uniform linear activation wave fronts compared with SSBRP, 2) velocity vectors with a more uniform magnitude and direction compared with SSBRP, 3) a predominant absolute velocity vector angle vs. a scattered angle distribution with SSBRP, and 4) shorter right atrial activation time and faster mean epicardial speed than SSBRP for each pacing cycle length. LTSBRP created a more uniform wave-front propagation with less or no conduction block and/or delay compared with SSBRP.

ANATOMICAL DISCONTINUITIES and nonuniformities in the right atrium (RA) are recognized as important factors for inhomogeneous propagation of atrial activation (18). In such anisotrophic tissue, inhomogeneous conduction may cause conduction block, conduction delay, and/or formation of a functional line of block due to fiber-orientation anisotropy (18) or spatial dispersion of electrophysiological properties such as repolarization (17, 20), excitability (6), and local conduction velocity (7, 16). Such occurrences may provide a substrate for the onset and maintenance of reentrant atrial arrhythmias and thereby increase atrial arrhythmia vulnerability especially at rapid rates and in the presence of atrial substrate abnormalities such as pericarditis.

To terminate atrial reentrant rhythms, rapid atrial pacing from a single site (19) or dual sites (8, 14) is used clinically. However, rapid pacing of the atria may be associated with proarrhythmic effects (19), e.g., conversion of supraventricular tachyrhythmias to atrial fibrillation (19). Moreover, the nature of propagation during rapid atrial pacing is not completely understood. In this study, we tested the hypothesis that in canine RA, bipolar, linear, triple-site rapid pacing creates more uniform propagation than bipolar, single-site rapid pacing and thereby minimizes or eliminates conduction block or delay (potential proarrhythmic effects that might otherwise be present due to rapid pacing). Using simultaneous multisite mapping and local velocity-vector estimation analysis, we studied the epicardial atrial activation patterns in vivo generated by rapid, bipolar, single-site pacing and rapid, bipolar, linear, triple-site pacing of the RA in dogs with normal and abnormal atria.

METHODS

We studied five dogs with sterile pericarditis and three normal mongrel dogs (17–23 kg body wt). The canine sterile pericarditis model was created as previously described (11, 13) 4 days before an open-chest mapping study. Two of five dogs with pericarditis were treated with oral prednisone (2 mg/kg twice a day) starting 2 days preoperatively until the day of the open-chest mapping study. We have shown previously (10) that prednisone significantly attenuates the inflammatory response associated with pericarditis, eliminates inducibility of atrial flutter, and affects all electrophysiological parameters including refractoriness and total right atrial activation time. This provided us with the opportunity to study normal, abnormal, and treated atria. All studies were performed in accordance with guidelines specified by the Institutional Animal Care and Use Committee of Case Western Reserve University, the American Heart Association Policy on Research Animal Use, the National Institutes of Health’s “Public Health Service Policy on Humane Care and Use of Laboratory Animals,” and “Guiding Principles in the Care and Use of Animals” of the American Physiological Society.

Studies of dogs in open-chest state. The heart was exposed while the dog was under general anesthesia and mechanically ventilated as previously described (11, 13). Thin (0.2-mm diameter) wire (80% nickel-20% chromium) electrode pairs were placed at selected epicardial right atrial sites using the plunge-wire technique (26-gauge needle) and were used for pacing. Three plunge-wire electrode pairs were placed in a linear fashion perpendicular to the superior aspect of the crista terminals (CT; Fig. 1A) and were used to pace simultaneously during triple-site pacing perpendicular to the CT. For triple-
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Fig. 1. A: diagram of the epicardial right atrium (RA). Locations of the pericardial reflection (dashed line) and the right atrial electrode recording array (gray area), which contains 188 unipolar electrodes arranged in a bipolar configuration (see B), are shown. Superior, caudocranial direction; inferior, craniocaudal direction; anterior, ventral; posterior, dorsal; AV, atroventricular; CT, crista terminalis; IVC, inferior vena cava; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RSPV, right superior pulmonary vein; SVC, superior vena cava; , bipolar stimulation site (interelectrode distance, 2 mm; distance between centers of each electrode pair, 5–7 mm). B: enlarged area from electrode array diagram shows arrangement of neighboring electrode pairs. Interelectrode distance, 0.7 mm; distance between center of electrode pair, 4.2 mm diagonally and 6 mm perpendicularly. See text for discussion.

RESULTS

Atrial activation patterns during three different pacing configurations. With the use of the simultaneous multisite mapping technique, atrial activation patterns generated during linear perpendicular triple-site pacing, linear parallel triple-site pacing, and single-site pacing of the RA were analyzed and compared using classic sequence-of-activation mapping techniques. Figure 3 illustrates a representative example of pacing at a 200-ms CL in a normal dog including the right atrial activation sequence maps of three different pacing configurations (Fig. 3A) and representative AEGs from the same sites (sites a–e) that are shown on the maps (Fig. 3B). During site simultaneous pacing parallel to the CT, two electrode pairs at each end of the triple-site perpendicular pacing arrangement were removed and placed superiorly and inferiorly to the center pair in a linear fashion parallel to the CT (Fig. 1A). The center electrode pair, which remained in the same position for both triple-site linear pacing configurations, was also used for single-site pacing. The interelectrode distance of each pacing electrode pair was 2 mm, and the distance between the centers of each pacing electrode pair was 5–7 mm (Fig. 1B). With the use of the three different electrode pacing configurations, rapid pacing (model DTU; Bloom Electrophysiology; Fischer Imaging) was performed for 6 s at cycle lengths (CLs) of 200 and 300 ms using twice-threshold stimuli.

Data acquisition. During all pacing, 380 unipolar atrial electrograms (AEGs) arranged in pairs were recorded simultaneously from electrode arrays placed epicardially on both atria using two cardiac mapping systems (9, 11). The interelectrode distance of each bipolar recording electrode in the array was 0.7 mm, and the distance between the center of a bipolar electrode pair and its neighbor was 4.2 mm diagonally and 6 mm perpendicularly. For time alignment of the two mapping systems, a common marker channel was used manually at deliberate intervals throughout the study. AEGs were individually amplified (at 1,000 gain), band-pass filtered (at 1–500 Hz), sampled (at 1 kHz), and digitized (at 12 bits, analog to digital). Data were transferred to a personal computer for offline analysis.

Data analysis: activation sequence analysis. Data were analyzed as previously described (9, 11). This permitted selection of activation times and computation of isochronous maps with a maximum resolution of 1 ms. Raw AEGs acquired in both unipolar and bipolar formats (obtained by subtracting two raw unipolar AEGs) were available to assist in the selection of activation times. During a steady-state response to the pacing (i.e., 3–4 s after the initiation of pacing), the atrial activation sequence was analyzed. Activation sequence maps were drawn at 5-ms intervals. Total right atrial activation time was noted by the latest recorded activation on the RA for each beat in each episode. In all dogs, three consecutive beats were analyzed to assess the consistency of pacing effects on the atrial activation pattern. The locations of the pacing electrode pairs in relation to the mapping array were visually confirmed at the end of each study.

Data analysis: local velocity-estimation analysis. Local velocity vectors were estimated for all dogs using an automated algorithm described by Bayly et al. (1) and implemented in Matlab (MathWorks). This algorithm uses the fitting of polynomials \( T(x,y) \) to a set of “active” points in \((x, y, t)\) space. The active points are defined as activation times in each recorded electrode location. Local velocity vectors are then estimated from the partial derivatives of these polynomials for one beat during each pacing episode. These local velocity vectors were plotted in a “spatial” velocity vector field. A histogram of absolute velocity vector angles (\(\alpha\)-values) with respect to the x-axis (i.e., along the CT) was plotted to assess uniformity of wave-front propagation in all directions (Fig. 2A). For each pacing episode in each dog, a mean overall epicardial speed was computed from the absolute magnitude (M, in units of cm/s) of each velocity vector (Fig. 2A).

Data analysis: local activation time-difference analysis. Local activation time differences were calculated for each of four neighboring bipolar recording sites arranged in a perfect square (Fig. 2B) using a method described by Lammers et al. (12). In all recording areas, the largest activation time difference was calculated from each set of four bipolar electrode pairs.

Statistical analysis. Data are expressed as means ± SD. A paired t-test was used, and a value of \( P < 0.05 \) was considered statistically significant. All statistical tests were done for both 200- and 300-ms pacing CLs between single-site pacing vs. triple-site perpendicular pacing groups and between single-site pacing vs. triple-site parallel pacing groups.

RESULTS

Atrial activation patterns during three different pacing configurations. With the use of the simultaneous multisite mapping technique, atrial activation patterns generated during linear perpendicular triple-site pacing, linear parallel triple-site pacing, and single-site pacing of the RA were analyzed and compared using classic sequence-of-activation mapping techniques. Figure 3 illustrates a representative example of pacing at a 200-ms CL in a normal dog including the right atrial activation sequence maps of three different pacing configurations (Fig. 3A) and representative AEGs from the same sites (sites a–e) that are shown on the maps (Fig. 3B). During
single-site pacing (Fig. 3, left), slow conduction and conduction block were found near the pacing site (site b) and at the superior region of the CT (sites d and e). Slow conduction near the pacing site was eliminated by both perpendicular (Fig. 3, middle) and parallel (Fig. 3, right) triple-site pacing. However, slow conduction and conduction block at the right atrial border were only eliminated by parallel triple-site pacing (Fig. 3, right). The activation sequence map during parallel triple-site pacing (Fig. 3, right) demonstrated that the activation wave front initially propagated anteriorly toward the atrioventricular groove within 15 ms and subsequently propagated simultaneously caudocranially and craniocaudally in the right atrial free wall. In addition, the activation pattern produced by the triple-site pacing configurations showed a more linear and uniform propagation in all directions in the RA (Fig. 3A). The activation pattern during 300-ms CL pacing in the same dog illustrated similar findings for all three pacing configurations.

The local velocity vector analysis of this same episode is shown (Fig. 3C). The velocity vector field map demonstrated a distribution of velocity vectors with more uniform magnitude and direction in triple-site pacing compared with single-site pacing. Triple-site pacing revealed a predominant absolute velocity vector angle distribution in the histogram (Fig. 3D) in contrast with single-site pacing, which showed a scattered absolute velocity vector angle distribution (i.e., a wide range of absolute velocity vector angle distributions without any predominant angle). Triple-site pacing perpendicular to the CT and triple-site pacing parallel to the CT demonstrated predominant absolute local velocity vector angle distributions of 40–50° and 10–30°, respectively.

Figure 4 demonstrates the consistency of right atrial activation of all pacing configurations. Two consecutive beats after the activation shown in Fig. 3 demonstrate a consistent activation pattern with minimal beat-to-beat variation pacing at 200-ms CL in all three pacing configurations.

A representative example of the sequence of right atrial activation in a prednisone-treated dog with pericarditis during pacing at a 300-ms CL is shown in Fig. 5. Figure 5A shows the activation sequence maps during each of three different pacing configurations, and Fig. 5B shows representative AEGs recorded from sites a to d shown on the maps. During single-site pacing (Fig. 5, left), relatively slow conduction, denoted by relative crowding of isochrones, was found in the region of the superior CT (sites c and d), and the activation pattern that occurred during the first 20 ms caused by the pacing stimuli was nonuniform and irregular in all directions in the RA. When compared with the activation pattern during perpendicular (Fig. 5, middle) and parallel (Fig. 5, right) triple-site pacing, the activation pattern during single-site pacing also showed a more convex type of propagation with different degrees of wave-front curvature (i.e., the negative reciprocal of the local radius of wave front) throughout the RA. During both linear perpendicular and parallel triple-site pacing, the activation pattern became more homogeneous and uniform in all directions with elimination (in perpendicular pacing) and minimization (in parallel pacing) of an area of relatively slow conduction at the superior CT region that was present during single-site pacing. Isochronous lines demonstrated smoother activation compared with that of single-site pacing. These representative examples also revealed the presence of relatively slow conduction as the activation took 20 ms to travel from sites b to c during single-site pacing (compare Fig. 5, left with Fig. 5, middle and right). However, this delay was eliminated or minimized during triple-site pacing (perpendicular pacing, 9 ms; parallel pacing, 14 ms). The activation patterns during 200-ms CL pacing in the same dog demonstrated similar findings in all three pacing configurations.

Figure 5C illustrates the local velocity vector field of this episode. Linear triple-site pacing resulted in more uniform distribution of velocity vectors (magnitude and direction) than single-site pacing. Figure 5D shows the histogram of the absolute local velocity vector angle from the x-axis of all vectors. Triple parallel pacing had a predominant angle (70–90°) compared with single-site pacing, which showed no predominant angle. This is explained by the conduction pattern generated by the parallel pacing configuration. When the three bipolar sites placed parallel to the CT were simultaneously stimulated, the activation propagated posterior and anterior to the CT in a linear fashion instead of in a radial fashion as seen in the activation sequence map for single-site pacing (Fig. 5A). Triple perpendicular pacing also had a predominant angle (20–40°) compared with single-site pacing, which showed no predominant angle. This is explained by the conduction pattern generated by the perpendicular configuration. When the three bipolar sites placed perpendicular to the CT were simultaneously stimulated, the activation propagated superior and inferior to the pacing sites instead of in a radial fashion as seen in the activation sequence map for single-site pacing (Fig. 5A).
Fig. 3. A representative example of 200-ms cycle length (CL) pacing episodes in a normal dog (dog no. 2). A: activation sequence maps. B: representative atrial electrograms (AEGs) from sites a to e. C: velocity vector field maps. D: histograms of absolute local velocity vector angles with respect to the x-axis of the CT. Isochrones are drawn at 5-ms intervals. T, conduction block; S, pacing stimulus. See text for discussion.
Computed local velocity vectors will have a predominant angle, because the wave front is linear and traveling predominantly in two opposite directions from the pacing region. Therefore, the conduction generated by linear triple-site pacing travels in a relatively uniform or homogeneous fashion to all parts of the RA. In contrast, the histogram of single-site pacing shows a scattered angle (i.e., a wide range of local velocity-vector angles) distribution, which suggests that the wave fronts generated by single-site pacing travel in all directions with no dominant directional pattern.

Figure 6 shows right atrial activation maps from another representative example during 300-ms CL pacing in an untreated dog with pericarditis. Figure 6A shows the activation sequence maps during three different pacing configurations, and Fig. 6B shows representative AEGs recorded from selected sites a to h. Atrial conduction was notably different during pacing compared with normal and prednisone-treated hearts with sterile pericarditis in Figs. 3 and 5; this was presumably secondary to inflammation from the pericarditis. Conduction block was present near the sinus node and near the right superior pulmonary vein-pericardial attachment, and relatively slow conduction was found in the lateral right atrial free wall (Fig. 6A, left). Slow conduction was present in the low right atrial free wall (sites g and h) and near the atrioventricular groove close to the mid-right atrial free wall. These conduction abnormalities were minimized or eliminated by linear triple-site pacing (Fig. 6A, middle and right). Linear triple-site pacing produced more uniform and linear propagation of the wave fronts in all directions from the pacing area even in the presence of pericarditis. The activation pattern during pacing at 200-ms CL in the same dog demonstrated similar findings in all three pacing configurations. The local velocity-vector analysis of this same episode is shown in Fig. 6C. The velocity-vector field map shows a distribution of velocity vectors with more uniform magnitude and direction during triple-site pacing compared with single-site pacing. Triple-site pacing showed a predominant absolute velocity vector angle in the histogram (Fig. 6D) in contrast with single-site pacing, which showed a scattered absolute velocity vector angle distribution. Triple-site pacing perpendicular and parallel to the CT demonstrated a predominant absolute velocity vector angle distributions of 20–50° and 70–90°, respectively.
Fig. 5. A representative example of 300-ms CL pacing episodes in a prednisone-treated dog with sterile pericarditis (SP, dog no. 4). A: activation sequence maps. B: representative AEGs from sites a to d. C: velocity vector field maps. D: histograms of absolute local velocity vector angles with respect to the x-axis of the CT. See text for discussion.
Fig. 6. A representative example of 300-ms CL pacing episodes in a dog with pericarditis (dog no. 6). A: activation sequence maps. B: representative AEGs from sites a to h. C: velocity vector field maps. D: histograms of absolute local velocity vector angles with respect to the x-axis of the CT. See text for discussion.
Activation patterns in the left atrium (LA) during three different pacing configurations were similar in all dogs studied. Figure 7 shows activation maps from a representative example during 200-ms pacing (dog no. 8). The activation sequence maps were obtained during single-site pacing (Fig. 7A) and during triple-site pacing placed perpendicular (Fig. 7B) and parallel (Fig. 7C) to the CT. In all pacing configurations, activation wave fronts from the pacing site traveled to the LA across the Bachmann’s bundle pathway and down the left atrial free wall, across a pathway inferior to the inferior vena cava, to the left atrial free wall, across the CT, and then between the inferior vena cava and the right inferior pulmonary vein. The latest activation in the LA was found in the free wall where the wave fronts from the RA collided. Also, in this example, prominent slow conduction and conduction block were seen in the RA during single-site pacing. However, these conduction abnormalities were eliminated with both types of triple-site pacing.

Of interest, atrial activation time to the LA was shorter using either triple-site pacing method compared with single-site pacing; times were 14 and 32 ms for triple-site pacing parallel and perpendicular to the CT, respectively, in this episode. In all dogs, triple-site pacing shortened the total atrial activation time by 6–32 ms compared with single-site pacing. In addition, triple-site pacing parallel to the CT shortened the total atrial activation time compared with triple-site pacing perpendicular to the CT in the majority of dogs (300-ms pacing: 6/8 dogs, 7.8 ± 4.1 ms mean difference; 200-ms pacing: 7/8 dogs, 9.3 ± 4.8 ms mean difference). When triple-site pacing perpendicular to the CT had a shorter atrial activation time than during triple-site pacing parallel to the CT (300-ms pacing, 2/8 dogs; 200-ms pacing, 1/8 dogs), the difference was only 2–3 ms.

Total right atrial activation time, local activation time difference, and vector magnitude. Total right atrial activation times from all pacing episodes in all dogs are shown in Table 1. There was a statistically significant decrease in the total right atrial activation time between single-site pacing and both parallel and perpendicular linear triple-site pacing at all CLs. Parallel triple-site pacing had the shortest total right atrial activation time at both 200 ms (35 ± 4.9 ms) and 300 ms (36 ± 4.1 ms) compared with the others and was significantly different from single-site pacing (P < 0.05; Table 1). Perpendicular triple-site pacing also showed a significant decrease in total right atrial activation time at both 200 ms (40 ± 3.7 ms) and 300 ms (41 ± 5.2 ms) compared with single-site pacing (51 ± 11.8 and 49 ± 9.9 ms, respectively; P < 0.05).

Mean local activation time differences from all recorded sites for all pacing episodes in all dogs are shown in Table 2. These also reveal a statistically significant decrease in the local activation time between single-site pacing and both parallel and perpendicular linear triple-site pacing at both CLs. Parallel triple-site pacing had the shortest mean local activation time difference at both 200 ms (4.7 ± 0.7 ms) and 300 ms (4.9 ± 0.5 ms) compared with the others and was significantly different from single-site pacing (P < 0.05; Table 2). Perpendicular triple-site pacing also showed a significant decrease in mean local activation time at both 200 ms (5.1 ± 0.7 ms) and 300 ms (5.0 ± 0.8 ms) compared with single-site pacing (6.3 ± 1.2 and 6.1 ± 1.2 ms, respectively; P < 0.05).

The mean velocity vector magnitudes from all pacing episodes in all dogs are shown in Table 3. These demonstrate a statistically significant increase in the mean velocity vector magnitude between single-site pacing and both parallel and perpendicular linear triple-site pacing at both CLs. Parallel triple-site pacing had the largest velocity vector magnitude at both 200 ms (86 ± 6.9 cm/s) and 300 ms (86 ± 9.6 cm/s) compared with the others and was significantly different from single-site pacing (P < 0.05; Table 3). Perpendicular triple-site
pacing also showed a significant increase in the velocity vector magnitude at both 200 ms (84 ± 7.5 cm/s) and 300 ms (83 ± 6.7 cm/s) compared with single-site pacing (73 ± 8.1 and 73 ± 9.6 cm/s, respectively; P < 0.05).

**DISCUSSION**

The data presented in this study show that bipolar linear triple-site pacing at rapid rates produces a more uniform and linear atrial activation pattern than single-site pacing. The wave front created by linear triple-site pacing propagated in a more homogeneous and uniform fashion in all directions in the RA from the pacing region with less or no conduction block and/or conduction delay compared with the wave front created by single-site pacing.

The basic mechanisms relating activation pattern to conduction velocity in excitable tissue are well described (7). In an excitable medium, the wave-front patterns are generally described as three types: flat, convex, and concave. Among the three, the concave (i.e., curving inward) wave-front pattern creates a more rapid depolarization in front of the advancing wave front compared with the flat wave-front pattern. This is because the local excitatory current of the concave wave-front pattern is larger than that of the flat wave-front pattern. When the wave front is convex (i.e., curving outward), the wave front will travel more slowly than the flat wave front, because the local excitatory current is distributed over a larger membrane area in front of the wave front than the flat wave front. As a result, conduction velocity of the concave wave front is faster than other wave-front types.

Comparison of single- vs. triple-site pacing. As we showed in this pacing study, single-site pacing creates a more heterogeneous activation pattern; furthermore, it also causes nonuniform conduction, which is denoted by conduction delay, conduction block, and nonuniform curvature. This nonuniform conduction pattern in the RA is known to be influenced by the complex anatomical structures of the RA such as the CT and the pectinate muscles (2, 16, 18, 21). However, all abnormal conduction was eliminated or decreased in the same tissue medium by perpendicular and parallel triple-site pacing even in the presence of an abnormal substrate (pericarditis). This suggests that despite the potential conduction abnormalities inherent in both the gross anatomical structure of the RA and the abnormalities associated with pericarditis, linear triple-site pacing provides more uniform propagation by producing a linear and uniform activation wave front. Linear triple-site pacing also significantly shortens total right atrial activation time, which indicates that the conduction velocity of the wave front produced by linear triple-site pacing is faster than that of single-site pacing. The mean local activation difference was significantly decreased, and the mean local velocity vector magnitude was significantly increased in linear triple-site pacing compared with single-site pacing, which also indicates that conduction of the wave front produced by linear triple-site pacing is faster than that of single-site pacing. These observa-

### Table 1. Total right atrial activation times for all pacing episodes and dogs

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Treatment Group</th>
<th>Total Right Atrial Activation Time, ms</th>
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<td></td>
<td>Single Site</td>
<td>Triple Perpendicular Sites</td>
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<tr>
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<td>300 ms</td>
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<tr>
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</tr>
<tr>
<td>3</td>
<td>Normal</td>
<td>300 ms</td>
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<tr>
<td>4</td>
<td>SP-Pred</td>
<td>300 ms</td>
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<tr>
<td>5</td>
<td>SP-Pred</td>
<td>300 ms</td>
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<tr>
<td>6</td>
<td>SP</td>
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<tr>
<td>7</td>
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<tr>
<td>8</td>
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Normal, normal dog; SP, dog with sterile pericarditis; SP-Pred, dog with sterile pericarditis that received oral prednisone. P < 0.05, values between single-site pacings at 300 ms vs. each of triple-site pacings at 300 ms and between single-site pacings at 200 ms vs. each of triple-site pacings at 200 ms.

### Table 2. Mean local activation time differences for all pacing episodes and dogs

<table>
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<th>Dog No.</th>
<th>Treatment Group</th>
<th>Mean Local Activation Time Difference, ms</th>
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<td>3</td>
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<td>300 ms</td>
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<tr>
<td>4</td>
<td>SP-Pred</td>
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<tr>
<td>5</td>
<td>SP-Pred</td>
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<tr>
<td>6</td>
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<td>7</td>
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<tr>
<td>8</td>
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Mean ± SD: 6.1 ± 2.7 / 6.3 ± 2.7 / 5.0 ± 0.8 / 5.1 ± 0.7 / 4.9 ± 0.5 / 4.7 ± 0.7

See Table 1 for treatment groups. P < 0.05, between single-site pacings at 300 ms vs. each of triple-site pacings at 300 ms and between single-site pacings at 200 ms vs. each of triple-site pacings at 200 ms.
tions further suggest that the wave front created by linear triple-site pacing is close to the flat wave-front type, which has the most favorable activation properties (i.e., uniform and rapid conduction) when considering flat, concave, or convex types of activation (7).

Effects of anatomical structures. The effects of anatomical structures of the RA, especially the pectinate muscles, on the direction of impulse propagation are also well demonstrated in this study. The pectinate muscles have a netlike distribution on the endocardium of the RA anterior from the CT with many muscle bundles, some of which form bridges (5, 21). When three bipolar sites placed parallel to the CT are simultaneously stimulated, the activation should propagate superiorly and inferiorly from the pacing sites (see Fig. 5A, right). A histogram of absolute velocity vector angle computed in this episode demonstrates predominant absolute velocity vector angle distributions of 80–90° (see Fig. 5D, right), which suggest that the activation wave fronts are traveling predominately perpendicular to the CT. However, the activation sequence map from one other dog demonstrates that the same pacing configuration can cause a different conduction pattern due to anatomical structure. In this dog, as the activation sequence map demonstrates (see Fig. 3A, right), the activation initially propagates anterior and posterior to the CT and then superior and inferior to the CT. Activation from the pacing sites travels anterior from the CT very rapidly, presumably via the pectinate muscle bundles. Activation superior and inferior to the CT takes a longer period of time. Thus resulting activation due to triple-site pacing travels caudocranially and craniodacrally in a planar manner. A histogram of absolute velocity vector angle computed in this case demonstrates predominant absolute velocity vector angle distributions of 10–30° (see Fig. 3D, right), which also suggests that the activation wave fronts are traveling predominantly caudocranially and craniodacrally relative to the CT. These two cases demonstrate that regardless of the presence of the pectinate muscles, the triple-site bipolar pacing always generates more uniform propagation, and the impulse propagation created by the triple-site bipolar pacing overcomes the structural complexity compared with the single-site pacing.

Comparison with previous studies. Recent studies have demonstrated that dual-site right atrial pacing (8, 14) decreases the recurrence of atrial fibrillation and that dual-site atrial pacing decreases the inducibility of atrial fibrillation (22) in patients. Becker et al. (4) showed that multisite pacing is effective in suppression of atrial fibrillation in an animal model by producing less functional conduction block with multidirectional excitation and a reduction in total activation time (3). However, these previous studies used multisite pacing from two or more locations far from one another (high RA, low RA, high LA, and low LA in animal studies; one site on high RA and the other site on ostium or distal site of coronary sinus in clinical studies) with each location being as a single-site pacing. Our study is not comparable to these previous studies, because in our triple-site pacing, the pacing electrodes were very close to one another in a linear configuration. Also, the clinical studies only paced at clinically acceptable (i.e., <100 beats/min) rates. Becker et al. (3) suggested that shortening of atrial activation time and multidirectional excitation, which prevents functional conduction block, may increase efficacy in atrial fibrillation suppression. Therefore, it is possible that the decrease in biatrial activation time and minimization and/or elimination of conduction block demonstrated in our study with triple-site pacing may have similar effects if applied in patients. However, chronic dual-site atrial pacing alone has proven disappointing in long-term clinical trials (15).

Limitations. We studied only three normal dogs and five dogs with pericarditis, two of which were treated with prednisone. Although the number of dogs in each group was relatively low, total right atrial activation time, mean velocity vector magnitude, absolute velocity vector angles, and mean local activation time differences appear to be fairly homogeneous within each group. Thus because the data appear to be homogeneous, this limitation is minimized. We have not studied atrial activation patterns during pacing at CLs shorter than 200 ms.

Clinical implications. Anti-tachycardia pacing is a standard treatment option to terminate most reentrant tachycardias, but it may instead precipitate other tachycardias (e.g., AFL → atrial fibrillation). Overdrive pacing techniques to interrupt reentrant tachycardias virtually always are performed by pacing from a single-site. However, conduction pattern during rapid pacing is not clear. Our study demonstrates that single-site rapid atrial pacing can be associated with production or enhancement of conduction abnormalities not present during triple-site pacing (especially the linear type). This in turn suggests that the latter type of pacing may be more effective and even less pro-arrhythmic than single-site anti-tachycardia pacing when used clinically.
In conclusion, this study provides a detailed understanding of the activation pattern during rapid atrial pacing in three different pacing configurations. We have shown in vivo that at rapid atrial pacing rates, both parallel and perpendicular linear triple-site pacing create more uniform linear impulse propagation, and single-site pacing creates heterogeneous propagation with the presence of conduction abnormalities. Linear propagation of the wave front generated by triple-site pacing in the RA minimizes or eliminates conduction block or delay, which are important components for the onset and maintenance of atrial arrhythmias. Abnormalities of conduction (delay and/or block) are related to both abnormal substrates and pacing rates, but at the same pacing rate, these abnormalities are also related to the types of pacing performed. Additional studies are required to test the potential clinical significance of the linear triple-site pacing technique.

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REFERENCES