EXPERIMENTAL STUDIES

Multisite Pacing for Prevention of Atrial Tachyarrhythmias: Potential Mechanisms

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OBJECTIVES To determine the effects of single-, dual-, triple- and quadruple-site atrial pacing on atrial activation and refractoriness in normal canine hearts.

BACKGROUND Multisite pacing has been suggested to be superior to single-site pacing for prevention of atrial tachyarrhythmias. However, the underlying electrophysiological mechanisms are undetermined at the moment, as is the rationale for the selection of pacing locations and the number of pacing sites.

METHODS In 13 normal beagle dogs, an epicardial multielectrode (128 bipoles) and a multiplexer mapping system were used to reconstruct epicardial atrial activation patterns obtained during simultaneous stimulation from up to four electrodes located in the high and low right and left atrium, respectively. For all pacing modes (single-, dual-, triple- and quadruple-site pacing), total activation times and local effective refractory periods at eight randomly selected sites as well as local recovery intervals were determined. In a subgroup of five dogs, total epicardial activation times were also obtained during single-site septal stimulation (septal group).

RESULTS Activation times and local recovery intervals were minimized by triple-site stimulation, whereas a fourth site did not produce further shortening. Septal stimulation produced epicardial activation times comparable to quadruple-site stimulation. Local refractory periods and their dispersion always remained unaffected. Functional conduction blocks apparent during single-site were found to resolve during multisite stimulation.

CONCLUSIONS Multisite pacing can prevent functional conduction blocks by multidirectional excitation and a reduction in total activation time. Triple-site and, possibly, septal pacing modes are expected to be most efficient because both minimize total activation times and maximize the multidirectionality of excitation. In spite of unaffected local refractory periods, the shortening of local recovery intervals might homogenize atrial repolarization and, thus, contribute to the preventive effects of multisite pacing. (J Am Coll Cardiol 2000;35:1939–46) © 2000 by the American College of Cardiology

Treatment of patients with recurrent atrial fibrillation remains a difficult issue. Due to considerable limitations of antiarrhythmic drug therapy with respect to efficacy and potential side effects, preventive pacing strategies have attracted increasing attention in recent years. Potential beneficial effects of antibradycardia pacing were primarily recognized in studies that compared conventional single-site atrial pacing with ventricular pacing in patients with sick sinus syndrome (1–4). Subsequently, multisite atrial pacing was introduced by Daubert et al. (5), demonstrating that biastral pacing from the high right atrium (HRA) and the distal coronary sinus was associated with low recurrence rates of atrial tachyarrhythmias in patients with severe interatrial conduction disturbances, as seen in hypertrophic cardiomyopathy. Recently, Saksena et al. (6,7) suggested an alternative approach using pacing electrodes positioned in the HRA and at the coronary sinus ostium (‘‘dual-site right atrial pacing’’). Prospective crossover studies in patients with drug refractory paroxysmal atrial fibrillation and coexisting bradycardia have suggested that this pacing mode significantly increases arrhythmia-free intervals as well as the proportion of patients free of atrial fibrillation recurrences (6,7). Still, these preliminary findings need to be confirmed by the results of ongoing clinical trials. Finally, studies using programmed atrial stimulation demonstrated a marked decrease in the inducibility of atrial fibrillation with multisite, as compared with conventional, HRA pacing (8,9). However, not only are current concepts on the mechanisms of these preventive effects largely speculative, there are also no data to substantiate a preference as to the number and location of specific pacing sites. Thus, in this study, activation and refractory patterns during single-,
dual-, triple- and quadruple-site stimulation in normal canine hearts were compared in an effort to elucidate potential mechanisms of preventive pacing modes and to determine the optimal number and location of pacing sites.

**METHODS**

All animal experiments conformed to the “Position of the American Heart Association on Research Animal Use” adopted November 11, 1984.

**Model preparation.** Thirteen healthy beagle dogs (16 ± 3 kg) were anesthetized with IV pentobarbital (0.5 mg/kg), intubated and ventilated with nitrous oxide and oxygen (70/30%). Electrocardiographic leads I, II and III were continuously monitored on a VR 12 recorder (Electronics for Medicine, Pleasantville, New York). The heart was exposed through an extended midsternal approach, and the pericardium was removed. During the experiments, body temperature was adjusted to 37°C with a heating lamp.

**Mapping technique.** For detailed mapping of atrial excitation in the in situ canine heart, a specially designed electrode array was placed on the epicardial surface of both atria. This multielectrode contained 128 bipoles with an interpolar distance of 1 to 2 mm and an interelectrode distance of 3 to 5 mm. Details regarding electrode design and surgical procedure have been described before (10). Data were simultaneously processed through a 256 channel multiplexer and recorded on videotape for off-line digitization (sampling rate 2,000 Hz) and computer analysis. The mapping system used was developed at the University of Limburg in Maastricht, the Netherlands (11). At each recording site, local activation time (AT) was determined automatically on the basis of the maximal first derivative, as in comparable previous studies (10,12,13). Each marking was reviewed and manually revised if necessary. In multiphasic signals lacking a sharp intrinsic deflection, the peak of the major deflection was chosen as the moment of activation. Based on these local ATs, two-dimensional isochronal activation maps were constructed manually at 10 ms intervals. Definitions of slow conduction and conduction block were adopted from previous studies (10,13).

In five dogs, a bipolar active fixation lead (Tendril 1388T, Pacesetter Inc., Sylmar, California) guided by a steerable stylet (Locator, Pacesetter Inc., Sylmar, California) was introduced into the right atrium through a 9F venous sheath in the femoral vein and screwed into the central portion of the interatrial septum under fluoroscopic guidance.

**Study protocol.** In each dog, four pacing sites located in the HRA, low right atrium (LRA), high left atrium (HLA) and low left atrium (LLA) were selected for pacing (Fig. 1, panel A). Whenever possible, sites potentially accessible with a transvenous approach, either directly or through the coronary sinus, were preferred with respect to potential future clinical applications. Constant pacing at a cycle length of 250 ms (twice diastolic threshold) was applied in all dogs using a Biotronik UHS 20 stimulator (constant voltage setting). The following combinations of electrodes were chosen in random order: HRA, HRA + LRA, HRA + LLA, HRA + LRA + LLA and HRA + LRA + HLA + LLA. For each pacing mode, activation and refractory patterns together with various parameters calculated thereof were obtained as follows:

1) Atrial activation maps were reconstructed using the criteria detailed above. The percentage of electrodes with changes in the direction of activation during multisite compared with HRA pacing was calculated.

2) Total epicardial ATs were determined on the basis of respective activation maps. During pacing from the HRA, LRA, HLA and LLA, ATs were calculated relative to the pacing artifact.

3) Local effective refractory periods (ERPs) were measured in random order at eight randomly selected sites. With constant pacing at a cycle length of 250 ms applied through one to four pacing sites, a second UHS 20 stimulator was used to introduce an extrastimulus S2 after eight locally sensed signals (S1) at each selected electrode, decreasing the S1S2 coupling interval in steps of 10 ms. The ERP was defined as the maximum S1S2 interval that failed to evoke a propagated atrial response.

4) The dispersion of ERPs was calculated, defined as maximum versus minimum ERP.

5) Furthermore, local recovery intervals were calculated, defined as local ERP plus local AT (14).

In the septal subgroup (n = 5), activation patterns and related parameters (1 and 2) were also determined during single-site septal stimulation. Since our electrode array would only allow disclosure of epicardial activation and epicardial pacing sites were compared with respect to their effect on total epicardial AT, epicardial ATs during septal pacing were not calculated relative to the pacing artifact but relative to the earliest epicardial activation.

**Statistics.** Data are presented as mean ± standard deviation. Comparative statistics were performed using analysis of variance and a Tukey Kramer HSD test for multiple comparisons (JMP software version 3.1, SAS Institute, SAS...
Figure 1. (Panel A) Posterior view of the atria with multielectrode in place. The shaded areas represent the location of pacing electrodes. (Panels B–G) Atrial activation maps obtained during different pacing modes at a cycle length of 250 ms (dog #12). See text for further details. AVR = atrioventricular ring; HLA = high left atrium; HRA = high right atrium; IVC = inferior caval vein; LA = left atrium; LAA = left atrial appendage; LLA = low left atrium; LRA = low right atrium; RA = right atrium; RAA = right atrial appendage; PV = pulmonary veins; SVC = superior caval vein; $\downarrow$ = stimulation site.
To illustrate the effects of multisite pacing on atrial pacing. Epicardial activation patterns in relation to the site(s) of pacing.

RESULTS

Campus Drive, Cary, North Carolina). A value of p < 0.05 was considered statistically significant.

RESULTS

Epicardial activation patterns in relation to the site(s) of pacing. To illustrate the effects of multisite pacing on atrial activation patterns, a set of typical activation maps has been depicted in Figure 1 (dog #12). The atria are displayed in a planar projection as if separated from the ventricles along the atrioventricular ring and incised on the inferior bodies of both appendages from the atrioventricular ring to their tips. During HRA pacing, activation spread centrifugally from the right atrial appendage (RAA) down towards the inferior vena cava (IVC) and towards the left atrium. Total epicardial AT was 78 ms, with sites of latest activation located in the LLA and in the left atrial appendage (LLA), respectively. When adding an LRA stimulation site, right atrial AT was markedly reduced due to bidirectional activation with a zone of collision about halfway between the superior vena cava (SVC) and the IVC. However, activation of the LLA was only slightly advanced. Thus, the site of latest activation during dual-site right atrial pacing was located in the lateral aspect of the left atrium, total AT being 69 ms. Bialtrial pacing from the HRA and LLA resulted in much earlier activation of the left atrium, but, due to relatively slow conduction on the way from the LLA to the LRA, excitation of the LRA was not significantly advanced compared with HRA pacing alone. Compared with dual-site right atrial pacing, bialtrial stimulation further shortened total AT down to 60 ms, the site of latest activation now being found in the LRA. Due to multidirectional atrial activation, triple-site pacing could further reduce AT down to 40 ms. Interestingly, addition of the LRA pacing site markedly advanced excitation of the medial HLA compared with bialtrial pacing. Thus, the site of latest activation moved to the LAA. Introducing a fourth pacing site in the HLA only served to advance activation of the LAA, thus reducing AT to 32 ms. However, the activation pattern remained otherwise unchanged. Due to almost simultaneous activation of both atria, septal stimulation resulted in an epicardial AT as short as 36 ms, with sites of latest activation in the lateral right atrium, the lateral left atrium and the LAA.

Total epicardial activation times in relation to the site(s) of pacing. Based on the activation maps, total ATs were calculated as the difference between the latest and the earliest epicardial AT, the latter one being defined by the timing of the pacing artifact at the site(s) of pacing. While bialtrial pacing from electrodes located in the HRA and LLA significantly shortened AT compared with HRA pacing, dual-site right atrial pacing from the HRA and LRA did not, obviously because left atrial activation was not sufficiently advanced. Triple-site stimulation from the HRA, LRA and LLA induced a further shortening of AT compared with bicaltrial stimulation, reaching statistical significance only relative to dual-site right atrial but not to bialtrial pacing. Quadruple-site stimulation, however, did not produce a further reduction in AT compared with triple-site pacing (Table 1A).

Activation maps obtained from the septal subgroup revealed that single-site septal stimulation produces epicardial ATs comparable with quadruple-site pacing, due to almost simultaneous activation of both atria. Thus, in analogy with triple- and quadruple-site pacing, single-site septal stimulation was shown to significantly shorten AT compared with dual-site right atrial pacing from the HRA and LRA (Table 1B).

To evaluate the degree of multidirectionality in atrial activation, the percentage of electrodes with changes in the direction of activation relative to HRA pacing was analyzed for all pacing modes. As detailed in Table 1, multidirectionality can be maximized with triple- and quadruple-site stimulation, whereas a fourth site does not seem to further increase this parameter. Obviously due to an almost complete reversal of right atrial activation, pacing from the interatrial septum results in a relatively high percentage of electrodes with changes in the direction of activation, comparable with bialtrial pacing from the HRA and LLA (Table 1B).
Effects of multisite and septal pacing on functional conduction blocks. In three dogs unidirectional functional conduction blocks occurred in individual maps. The blocks were exclusively located in the right atrium, preferably in the intercaval region. They were encountered either during single-site HRA pacing or during bifocal pacing from the HRA + LRA and HRA + LLA (Table 2). Based on a mean interelectrode distance of 4 mm, the length of respective lines of block amounted to 18 ± 11 mm, the length of respective lines of block amounted to 18 ± 11 mm (range 8–32). During triple- and quadruple-site, as well as during septal stimulation, however, no evidence of conduction disturbance was found in any case. Figure 2 illustrates a characteristic finding (dog #11): during HRA pacing, a line of block was found extending in a posterolateral direction from the SVC to the atrophicventricular ring. During bifocal pacing from the HRA and LRA, the former arc of block was no longer apparent due to rapid bidirectional activation of the right atrium with collision of the wavefronts in the former area of block. However, a new line of block had been established along the intercaval axis just medial to the LRA pacing site. During triple-site pacing, this block was no longer manifest because LLA pacing led to rapid bidirectional activation of the LRA with premature activation of the area beyond the former line of block.

Local atrial refractoriness in relation to the site(s) of pacing and to directional changes in activation. Multisite pacing did not affect local ERPs or their dispersion, as detailed in Table 1A. Even when specifically evaluating sites where the direction of activation changed by ≥90° versus HRA pacing (CDA) or where ≥2 wavefronts were colliding (COL), local refractoriness remained entirely unaffected (132 ± 14 vs. 132 ± 13 ms, control vs. CDA; 136 ± 14 vs. 137 ± 12 ms, control vs. COL; p = not significant, respectively). Thus, directional changes in refractoriness are obviously not of relevance in normal canine atria. However, due to shortening of local ATs, local recovery intervals, that is, the sum of local refractory periods and local ATs, were reduced significantly with biaatrial pacing compared with single-site and triple-site stimulation compared with dual-site right atrial pacing, respectively (Table 1A).

DISCUSSION

To the best of our knowledge, epicardial activation and refractory patterns during multisite pacing have not been previously published. Epicardial multielectrode mapping, as applied in this study, provides a means to visualize changes in the spread of activation, to repeatedly measure local refractory periods at predefined electrode sites and to determine local recovery intervals. Due to a marked advancement of left atrial activation, biaatrial pacing from the HRA and LLA was found to significantly reduce total AT compared with HRA pacing alone, while dual-site right atrial stimulation from the HRA and LRA did not. Interestingly, single-site stimulation from the interatrial septum produced epicardial ATs comparable with quadruple-site pacing, obviously resulting from almost simultaneous activation of both atria. Activation patterns obtained during simultaneous stimulation from three and four epicardial pacing sites revealed that total atrial AT can be minimized by triple-site stimulation, while quadruple-site pacing does not produce a further shortening. Obviously due to multidirectional atrial excitation, functional conduction blocks apparent in several dogs during HRA pacing were shown to disappear during multisite pacing due to premature activation of the area beyond the block. The degree of multidirectionality of atrial activation, expressed by the number of electrodes with changes in the direction of activation relative to HRA pacing, was found to be maximized by triple-site pacing, while four sites provided no further benefit. Contrary to the marked effects on global atrial activation, there was no evidence of directional changes in refractoriness during multisite pacing. Hence, the spatial dispersion of refractoriness also remained unchanged. However, due to shortening of local ATs, local recovery intervals were significantly reduced. The resulting homogenization of atrial repolarization might prevent the occurrence of functional conduction block and, thus, contribute to the protective effect claimed for multisite stimulation.

Comparison with previous studies. Prospective crossover studies performed in patients with recurrent drug-refractory atrial fibrillation have shown that dual-site right atrial pacing increases arrhythmia-free intervals as well as the proportion of patients free of arrhythmia recurrences (6,7). Furthermore, bifocal atrial pacing modes were found to suppress the inducibility of atrial tachyarrhythmias (8,9). However, the electrophysiological mechanisms underlying these preventive effects remained largely speculative.

In patients with atrial fibrillation or flutter, both dual-site right atrial and biaatrial pacing can significantly reduce the p-wave duration compared with HRA stimulation alone (8,15). Although supposedly reflecting a shortening of total atrial AT, the abbreviation of p-wave duration was not
correlated with the suppression of atrial tachyarrhythmia inducibility (8). As suggested by previous experimental studies in dogs with atypical atrial flutter (16), regional conduction delay may exist even in the presence of a relatively short p wave duration. Thus, surface electrocardiogram characteristics do obviously not allow reliable conclusions regarding total atrial AT and activation pattern.

A large body of experimental data substantiates the importance of regional right atrial conduction delay for initiation of atrial tachyarrhythmias (9,10,13,15,17–22). In patients with recurrent atrial fibrillation, biatrial pacing can abolish right atrial conduction delay due to advancement of low right atrial activation, resulting in a markedly lower inducibility rate of atrial fibrillation (9). Furthermore, conduction delay towards the left atrium, as apparent during S2 stimulation from the HRA, can be prevented by both dual-site right atrial and biatrial pacing (15). In addition to that, our data indicate that functional conduction blocks found in the right atrium during S1 HRA stimulation at a relatively short cycle length can be prevented by multisite pacing due to premature excitation of the area beyond the line of block. A previous study using the same mapping technique in dogs with single loop atrial flutter showed that the central obstacle of respective reentrant circuits had a minimum length of 25 mm, proving that at least half of the blocks encountered in this study reached a length potentially sufficient to maintain macroreentrant circuits (10). The microreentrant circuits encountered in dogs with experimental atrial fibrillation, however, may be as short as a few millimeters (23). Thus, alleviation of regional conduction delay and prevention of conduction block due to multidirectional atrial activation might represent the major mechanisms underlying the beneficial effects attributed to multisite stimulation. As triple-site stimulation was shown to minimize total atrial AT and to maximize the multidirectionalality of excitation, this pacing mode should be even more efficient than dual-site stimulation for prevention of atrial tachyarrhythmias although this study was not designed to provide direct evidence of this hypothesis. Single-site septal stimulation produced similar epicardial ATs but was not quite as efficient with respect to the percentage of electrodes showing a change in the direction of activation. Assuming that more organization in atrial activation translates into more marked protective effects, septal stimulation should be at least as efficient as bifocal pacing modes for prevention of atrial fibrillation. However, this hypothesis has to be confirmed by controlled clinical studies.

Numerous experimental and clinical studies have proven that an increase in the dispersion of refractoriness favors the occurrence of atrial fibrillation (24–26). Based on this observation, one might speculate that the suggested protective effects of multisite pacing are related to a decrease in the dispersion of atrial refractoriness. However, in spite of multiple measurements of ERPs with different pacing modes, local ERPs, as well as their dispersion, remained unchanged. Previous experimental data obtained in ventric-
ular myocardium suggest changes in local refractory periods (27) and action potential duration (28) dependent on the direction of activation relative to fiber orientation. Furthermore, refractoriness was found to be affected by collision of wavefronts (29). According to our results, however, directional differences in repolarization do not seem to exist in normal atrial myocardium because refractoriness remained unaffected even at sites with marked changes in the direction of activation and at collision sites. These findings are in keeping with a previous study performed in human atra that failed to demonstrate general anisotropy in right atrial free wall epicardium (30), probably based on the complexity of atrial architecture (31).

However, this study demonstrated that multisite pacing shortens local recovery intervals due to shortening of local ATs. This might homogenize atrial repolarization and, thus, exert antiarrhythmic effects. For the canine ventricles, shortening of recovery intervals has been suggested to prevent reentry (14). In analogy to these observations, we could demonstrate that functional conduction blocks occurring in the right atrium during S1 stimulation at a relatively short cycle length were no longer apparent during multisite pacing due to premature activation of areas distal to the arc of block.

Methodological considerations. The electrode array used in this study is limited by a lack of septal recordings. Thus, the epicardial ATs measured might have underestimated total atrial ATs, assuming that the interatrial septum represented the area of latest activation. However, this limitation applies to all pacing modes alike, and, thus, the relative changes in epicardial AT seen with the various pacing modes should still hold true. Furthermore, it might have been prudent to combine stimulation from the septum with the various epicardial sites because our results suggest that a combination of septal and epicardial sites might be most efficient in organizing atrial activation.

The study was designed to exclusively compare activation and refractory patterns during various pacing modes. Thus, other aspects of preventive pacing, like avoidance of short-long-short cycles or bradycardia-related arrhythmias, have not been addressed. Due to the variation in sinus rate from dog to dog and from measurement to measurement, activation and refractory patterns during HRA pacing rather than during sinus rhythm were chosen to define reference values. Activation patterns, total atrial ATs, mean atrial ERPs and dispersion of ERPs are, in fact, very similar when comparing HRA pacing with sinus rhythm (32). Still, it is possible that at the slower sinus rate and given the spontaneous changes in cycle length, refractory patterns might, at least temporarily, exhibit significant inhomogeneities, which are no longer evident during constant, relatively fast pacing. The study was performed in normal dog hearts, and, thus, our findings are only expected to apply to this particular situation. It is conceivable that a given disease might primarily change the existing activation or refractory pattern, and this, in turn, might modify the response to pacing interventions.

Clinical implications. As detailed above, our results suggest that biatrial pacing from the HRA and LLA is more efficient in organizing atrial activation than dual-site right atrial stimulation from the HRA and LRA. Furthermore, triple-site pacing from the HRA, LRA and LLA, as well as single-site septal pacing, would be expected to be more efficient than biatrial and dual-site right atrial pacing, respectively. Although any translation into antiarrhythmic efficacy is purely speculative for the moment, better organization of atrial activation could be antiarrhythmic and might account for the benefits claimed for multisite pacing. However, the model used did not allow testing of this hypothesis. Clinical crossover studies in patients with recurrent atrial fibrillation should be designed to compare biatrial pacing with single-site septal, dual-site right atrial pacing and triple-site pacing from the HRA, coronary sinus ostium and the distal coronary sinus.

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