Quantitative Evaluation of a Directly Depolarized Area Induced by High-Output Pacing on the Cardiac Muscle

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Quantitative information is needed on the directly depolarized area (DDA) induced by high-output energy during a precise mapping procedure to detect the origin of a tachycardia. In the present study, a DDA caused by high-output energy was quantitatively evaluated in the exposed canine heart. In 8 dogs, the right atrial and ventricular surfaces were exposed through a right thoracotomy and pacing with various outputs was delivered from the epicardial surface. A comb-shaped 16 polar electrode array and/or a 224 polar mat electrode array were used for recording the epicardial electrograms. The local activation time was measured at each electrode site, and the relationship of the distance between the electrode location from the pacing site and the local activation time was plotted and fitted to a primary regression line. The intercept of the regression line on the horizontal axis was defined as the radius of the 'DDA' and this was evaluated at each pacing output. The radius of the DDA was 0.6 ± 0.1 mm with a 2 V and 3.8 ± 0.2 mm with a 10 V output when it was evaluated in a direction perpendicular to the fiber orientation of the pectinate muscle, 0.8 ± 0.1 mm with a 2 V and 4.1 ± 0.3 mm with a 10 V output in a direction parallel to the pectinate muscle fiber orientation, and 0.9 ± 0.3 mm with a 2 V and 3.6 ± 0.5 mm with a 10 V output in the right ventricle. The DDA extended according to the increase in stimulation outputs at all sites, and there was no significant difference in the pacing site or the direction of the stimulation propagation. The DDA caused by high-output energy is a purely physical phenomenon that depends only on stimulation output and tissue resistance. The diameter of the DDA exceeded 4 mm (ie, the size of a standard tip electrode for catheter ablation) when pacing was delivered with an output greater than 6 V. (*Jpn Circ J* 2000; 64: 876–882)

Key Words: Directly depolarized area; Electrophysiological study; High-output pacing; Stimulation output

Cardiac pacing through an electrode catheter is one of the basic methods used in the mapping procedure in electrophysiological studies (EPS). In cases of structural heart disease, high-output energy may be required for local capture when pacing is performed in degenerated tissues (eg, fibrosis), but such pacing may result in simultaneous capture of a relatively large area. When devising a precise mapping procedure for the tachycardia reentrant circuit, it is important to obtain quantitative information on the directly depolarized area (DDA); that is, how large an area will be stimulated simultaneously by the high-output energy.

In the present study, the DDA was quantitatively evaluated by delivering high-output energy on the surface of the exposed canine heart.

Methods

Subjects and Surgical Procedure

In 8 adult beagle dogs weighing 9.5–14.5 kg, the right atrial and ventricular surfaces were exposed via a right thoracotomy^{1,2} under pentobarbital anesthesia (30 mg/kg bodyweight, iv) and mechanical ventilation (Model SN-480-

5, Shinano Manufacturing, Tokyo, Japan) with room air. The body temperature of each dog was kept within the physiological range with a heating pad, and a heating lamp was also used to warm the exposed cardiac surface. All studies were performed in accordance with the guidelines specified by the Institutional Animal Care and Use Committee of the Kitasato University School of Medicine.

To avoid superimposition of the ventricular signal on the small atrial signal, radiofrequency ablation of the His bundle was performed through an ablation catheter inserted from the right femoral vein.^{3,4} A pair of electrodes was sutured on the epicardial surface of the right ventricular apex and used for VVI pacing at a rate of 130–150 beats/min.

High-Output Pacing and Measurement of the DDA

Recording With a Comb-Shaped 16 Polar Electrode Array

In all 8 dogs, a comb-shaped 16 polar electrode array was used for pacing and recording. The interpolar distance was 1.2 mm and the diameter of each pole was 0.4 mm. The most proximal pair of electrodes was used for stimulation and the other pairs were used for recording (Fig 1A). On the surface of the right atrium, the comb-shaped electrode array was positioned at the central part of the pectinate muscle (PM) perpendicular or parallel to the direction of the PM fiber orientation. On the right ventricular surface, the electrode array was positioned at the central part of the right ventricular free wall parallel to the left anterior descending coronary artery (Fig 1B). A saline solution was continuously dripped on the cardiac surface to mimic the pacing conditions within blood flow. After confirming that the diastolic

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Fig 1. (Panel A) Schema of the comb-shaped hand-held 16 polar electrode array with an inter-electrode distance of 1.2 mm. The most proximal pair of electrodes was used for stimulation and the others for recording. (Panel B) The comb-shaped electrode array was placed at the center of the pectinate muscle (PM) lesion in the right atrium perpendicular to the muscle fiber orientation ①, at the same area but parallel to the PM fibers ②, and at the center of the right ventricle ③.

pacing threshold was around 1 V, pacing with a fixed cycle length of 250 ms and at a pulse width of 2 ms was delivered with a gradually higher pacing output; that is, 2, 4, 6, 8 and 10 V (BC-03, Fukuda-Denshi Co, Tokyo, Japan). Local electrograms from each pair of electrodes were recorded (Omniace 8100, NEC Inc, Tokyo, Japan) at a paper speed of 200 mm/s. The local activation time was measured as the time interval between the stimulation artifact and the first steep negative deflection in each recorded electrogram (Fig 2A). At each position of the electrode array, the relationship between the electrode distance (ie, the spatial distance between the centers of the pairs of pacing and recording electrodes, Fig 1A), and the local activation time was plotted. By fitting the data from each pacing output to the primary regression line, the intercept of the regression line with the horizontal axis was defined as the radius of the DDA (Fig 2B).

Recording With a 224 Polar Electrode Array In 5 selected dogs, a 224 polar mat electrode array was used for simultaneous multi-site recording on the surfaces of the right atrium and ventricle (Fig 3B). The electrode array had 14×16 electrodes with an inter-electrode distance of 4.0 mm (Fig 3A). For the pacing, a pair of platinum plunge electrodes was inserted at the center of the PM in the right atrium or the center of the right ventricular surface underneath the mat electrode array placed on the cardiac surface. After confirming that the diastolic pacing threshold was around 1 V, pacing with a fixed cycle length of 250 ms and at a pulse width of 2 ms was delivered with a gradually higher pacing output in a similar manner to the previous protocol. The unipolar signals recorded through each electrode on the electrode array were stored in a computer hard-drive (CardiolabTM, Purka Engineering, Inc, USA) and retrieved as bipolar electrograms between each pair of successive electrodes on the array. The local activation time of each recording site was determined as the steepest negative deflection of the recorded electrograms on the computer

screen. An isochronous map of the activation sequence during pacing was drawn using the stimulation artifact as the time reference.

High-Output Pacing Around an Ablated Area on the Right Ventricle

To evaluate the DDA around degenerated tissue, high-output pacing was delivered around an ablated area on the right ventricle in 5 selected dogs. From the epicardial side of the exposed right ventricle, radiofrequency ablation was performed to make a linearly ablated lesion of 5×30 mm². To avoid an impedance rise during ablation, saline solution (37°C) was continuously dripped around the electrode tip of the ablation catheter. The width of the ablated lesion was measured after the ablation procedure, and the depth (transmurality) of the ablated lesion was confirmed microscopically after sacrificing each animal.

Pacing Inside the Ablated Area and Recording With a Comb-Shaped 16 Polar Electrode Array The most proximal pair of electrodes for pacing (poles 1 and 2) was placed at the center of the ablated lesion (Fig 4). Although pacing with low-output energy could not capture the ventricular tissue with the ablation procedure, pacing with a fixed cycle length of 250 ms and at a pulse width of 2 ms was delivered with a gradually increasing pacing output until the pacing captured the surrounding intact ventricular muscle by the pacing stimulus. When the pacing captured the surrounding ventricle, the radius of the DDA with that pacing output was considered to exceed the distance between the pacing site and the edge of the ablated area.

Pacing at the Edge of the Ablated Area and Recording With a 224 Polar Electrode Array A pair of platinum plunge electrodes was inserted at the intact ventricular muscle close to the center of the ablated lesion and a 224 polar mat electrode array was used to cover that area. After confirming that the pacing diastolic threshold was around 1 V, pacing with 250 ms cycle length and a gradually increas-

Fig 2. Relationship between the local activation time and the electrode distance from the pacing site. (Panel A) Local electrograms from each pair of electrodes during 6 V pacing in a direction perpendicular to the fiber orientation of the right atrium. The local activation time was measured as the time interval between the stimulation artifact and the first steep negative deflection in each recorded electrogram. (Panel B) An example of the data plot for each stimulation output. The vertical axis indicates the local activation time and the horizontal axis marks the electrode distance from the pacing site. The data from each pacing output were fitted to a primary regression line and the intercept of the regression line with the horizontal axis was defined as the radius of the DDA. The arrow indicates the radius of the DDA at a pacing output of 10 V.

Fig 3. (Panel A) Schematic of the 224 polar mat electrode array. The inter-electrode distance was 4.0 mm. (Panel B) Stimulation was delivered at the center of the pectinate muscle lesion of the right atrium (1) and the center of the right ventricle (2). The 224 polar electrode array was placed on the right atrial or ventricular surface to cover the area surrounding the pacing sites.

ing pacing output was repeated. An isochronous map of the activation sequence during the pacing was drawn using the stimulation artifact as the time reference in a similar manner to the previous protocol.

Statistical Analysis

Data are expressed as mean $\pm$ SD. Basic comparative statistics were performed with the one-way ANOVA test or paired t-test. A p value <0.05 was considered significant.

Results

High-Output Pacing and Evaluation of the DDA

Recording With a Comb-Shaped 16 Polar Electrode Array Fig 2 is an example of the evaluation of the DDA in one dog. The local activation time measured at each pair of electrodes of the comb-shaped electrode array was plotted. When high-output pacing was performed, the local electrogram was fused with the stimulation artifact, particularly at the recording site close to the pacing site, and these recordings were eliminated from the measurement. The distance of each recording site from the pacing site is shown in the horizontal axis. The data for each pacing output are shown by the different symbols fitted to the primary regression line and the intercept of the regression line with the horizontal axis was defined as the radius of the DDA for each pacing output. Although the radius of the DDA increased according to the increase in pacing output, the slope of the primary regression line with each pacing output was almost the same, indicating that the conduction velocity outside the DDA was constant regardless of the size of the DDA or pacing output.

Radius of the DDA

All data on the radius of the DDA estimated from recordings through the comb-shaped 16 polar electrode arrays are summarized in Table 1. The radius of the DDA increased according to the increase in stimulation output, regardless of the recording site or direction of activation conduction (Fig 5). With the 2 V pacing, the diameter (ie, the 2-fold radius) of the DDA was almost equal to the distance from the bipolar pacing electrodes (ie, 1.2 mm) in this electrode array. Note that the diameter of the DDA exceeded 4 mm

Fig 4. Pacing inside the ablated lesion. The most proximal pair of electrodes of the hand-held comb-shaped electrode array was placed at the center of the linearly ablated lesion in a 5×30 mm site. Pacing with a gradually increasing high output was delivered from the electrodes placed inside the ablated lesion and electrograms were recorded via the other pairs of electrodes.

(ie, the size of a standard tip electrode for catheter ablation) and extended up to 7–8 mm with 10 V pacing. There was no significant difference in the size of the DDA for the pacing site or the direction of activation conduction.

Fig 6 is an example of the series of isochronous maps of the activation sequence during pacing with various pacing outputs at the PM pacing site in the right atrium. The higher the stimulation output, the larger the DDA extended. Although the central area expanded depending on the increase in the stimulation output, the density of the isochrone's lines was unchanged, indicating that the conduction velocity outside the DDA was the same regardless of the stimulation output.

Stimulation Around the Ablated Lesion

The width of the linearly ablated lesion in the 5 dogs was 5.0 ± 0.3 mm. When the pacing was delivered inside the ablated lesion in the right ventricle, the lowest stimulation output to capture the surrounding intact ventricular tissue was 6.3 ± 1.2 V (range, 5.0–8.0 V). The distance between the pacing site and the intact ventricular tissue in this protocol (ie, ≈ 2.5 mm) was a good match with the expected radius of the DDA from the previous study protocol (ie, 2.2 ± 0.5 mm for 6 V pacing in the right ventricle; Table 1).

Fig 7 is an example of the pacing at the intact ventricular site close to the edge of the ablated lesion. With 6 V pacing, the opposite ventricle to the pacing site was activated by a wave front coming around both ends of the linearly ablated

Fig 5. Radius of the directly depolarized area (DDA) estimated in 8 dogs with various stimulation outputs. The DDA expanded according to the increase in stimulation output. There was no significant difference between the pacing sites and the direction of activation conduction. PM, pectinate muscle; RV, right ventricle.

Table 1 Estimated Radius of the Directly Depolarized Area With Various Pacing Outputs

Output (V)	Right atrium perpen- dicular to PM (mm)	Right atrium parallel to PM (mm)	Right ventricle (mm)	p value
2	0.6±0.1	0.8±0.1	0.9±0.3	NS
4	1.3±0.1	2.0±0.2	1.4±0.3	NS
6	2.2±0.3	2.7±0.3	2.2±0.5	NS
8	3.1±0.2	3.2±0.3	2.7±0.4	NS
10	3.8±0.2	4.1±0.3	3.6±0.5	NS

PM, pectinate muscle.

Fig 6. Isochronal map of activation propagation during pacing with various stimulation outputs on the right atrial surface. Each color in the map indicates the same local activation time at each recording site using the stimulation artifact as the time reference. Note that the central dark red area (ie, the directly depolarized area (DDA)) expanded depending on the increase in the stimulation output. However, the density of the isochrone's lines (ie, the width of each color band) was unchanged, indicating that the conduction velocity outside the DDA was the same regardless of the stimulation output.

lesion because the activation could not propagate through the anatomical barrier. However, during 8 V pacing, very early activation appeared at the opposite ventricle to the pacing site, indicating that the radius of the DDA exceeded the width of the ablated lesion (ie, 5.0 ± 0.3 mm) in this case.

In the 5 dogs studied in this protocol, direct capture of the opposite ventricle to the pacing site required 8 V. The distance from the jumping capture to the other ventricle (ie, ≈ 5 mm in this protocol) was slightly larger, but close to the expected radius of the DDA from the first study protocol (ie, 3.6 ± 0.5 mm for 10 V pacing in the right ventricle; Table 1).

Fig 7. Isochronal map of activation propagation during right ventricular pacing at a site close to the ablated lesion with 6 V (upper panel) and 8 V output (lower panel). Each color indicates the local activation time at each recording site using the stimulation artifact as the time reference. During 6 V pacing, the ventricle opposite to the pacing site was activated by a wave front coming round both ends of the ablated lesion. However, during 8 V pacing, early activation appeared at the ventricle opposite to the pacing site.

Discussion

In EPS, high-output energy is required for local capture when pacing is performed in degenerated cardiac muscle and it is well known that pacing with high-output energy may result in simultaneous capture of a relatively large area. Using a practical mapping procedure, the electrophysiological findings related to pacing are considered to result from the capture of the cardiac muscle just beneath the electrode tip of the pacing catheter. However, when relatively high-output energy is used for pacing, myocardium distant from the pacing site may be captured and the findings during pacing may not represent the electrophysiological property of the pacing site. If the DDA resulting from high-output energy is small enough, it may not be a problem in the ablation procedure, but there are not any reports evaluating the relationship between pacing output and the size of the DDA.

Evaluation of the DDA

There is not an electrophysiological definition for the DDA caused by high-output energy pacing. Technically, the DDA should be evaluated as the area that shows the earliest simultaneous activation responding to the electrical stimulation, but with high-output energy pacing it is practically impossible to distinguish local electrograms from the stim-

ulation artifact. An optical mapping system with voltage-sensitive dye can evaluate this more precisely,⁶⁻⁹ but the physiological change in voltage caused by the pacing itself cannot be excluded completely. In the present study, the relationship between the local activation time and the electrode distance from the pacing site was fitted to a primary regression line, and the intercept of this line with the horizontal axis was defined as the radius of the DDA. The result was that the radius of the DDA expanded depending on the pacing output, and with a 10 V output reached 3.8 ± 0.2 mm when evaluated on the right atrial surface and 3.6 ± 0.5 mm on the right ventricle. The diameter of the DDA exceeded 4 mm (ie, the size of a standard tip electrode for catheter ablation) when pacing was delivered with an output higher than 6 V, which indicates that the electrophysiological findings obtained during pacing with a 6 V or higher energy output may not reflect the electrophysiological properties of the pacing site just underneath the electrode tip.

To confirm the reliability of this evaluation of the DDA, we additionally performed a study of pacing around an ablated area of cardiac muscle. When pacing was delivered inside the ablated lesion, the lowest stimulation output for capturing surrounding intact cardiac muscle at a distance of 2.5 mm was 6.3 ± 1.2 V, and this was a good match with the radius of the DDA estimated in the previous study protocol. Moreover, when the pacing was delivered at the edge of the ablated lesion, pacing with an 8 V output directly captured the intact cardiac muscle on the opposite side, which was 5.0 ± 0.3 mm from the pacing site. These results indicate that the method for evaluating the radius of the DDA in this study was a good match with the electrophysiological findings in clinical EPS.

In the present study, the local activation time was analyzed with bipolar recording. Rationally, the local activation time should be determined by the steepest negative deflection in the unipolar recording, but that evaluation was practically impossible because of the influence of the large stimulation artifact caused by the high-output pacing. However, the DDA estimated by the bipolar recording matched well with the findings from the stimulation around the ablated area.

Factors That Influence the DDA

Activation propagation in the cardiac muscle is influenced by the direction of the fiber orientation, which is known as anisotropic conduction.¹⁰⁻¹⁴ In the present study, the radius of the DDA was evaluated at different pacing sites and in different directions to the muscle fiber orientation. The results showed that there was no significant difference in the radius of the DDA for the pacing site or the direction of the muscle fiber orientation, which indicates that the DDA caused by high-output energy is a purely physical phenomenon that depends only on stimulation output and tissue resistance.

There are many factors that may influence the DDA other than stimulation output, such as the tissue resistance, the electric current, the duration of the stimulus, the shape of the electrode, etc. We could not evaluate the local electric current and voltage change inside and around the DDA, but we aimed to evaluate the DDA in a standard procedure used in a clinical EPS. However, those other factors might be important and should be analyzed individually.

Clinical Implications

With the practical mapping procedures used in EPS, pacing must often be performed in degenerated cardiac

muscle, especially at the origin or the slow conduction zone of the ventricular tachycardia reentrant circuit in cases of structural heart disease!⁵⁻¹⁷ In those cases, output energy higher than 5 V is often required for local capture. When the findings during pacing are adequate, the position of the electrode catheter is considered as the appropriate site for ablation and radiofrequency energy may be delivered. By considering the DDA caused by high-output energy, the electrophysiological findings during pacing can reflect the electrophysiological properties of the tissue within the radius of the DDA. Therefore, pacing with an unnecessarily high output energy should be avoided in order to achieve precise mapping. The present study is important because it is the first systematic evaluation of the relationship between pacing output and the size of the DDA. From the present study, pacing with an energy of 6 V or higher should be avoided because the diameter of the DDA exceeds the size of the standard electrode tip for ablation.

Study Limitations

This study had several important limitations. First, pacing was performed from the epicardial side of the exposed heart, and the pacing conditions were possibly different from those at the endocardial side. Also, saline solution (37°C) was continuously dripped on the cardiac surface to mimic the pacing conditions within blood flow. In addition, the study was performed in normal cardiac muscle. Although pacing in an acutely ablated lesion simulated pacing in degenerated cardiac muscle, the conditions may be different from those in actual structural heart disease. Finally, the electrode distance used in this study (ie, 1.2 mm) limited the spatial resolution for the evaluation of the size of the DDA.

Conclusions

The size of the DDA was quantitatively evaluated on the epicardial surface of the exposed canine heart. The DDA expanded according to the increase of the pacing output. The pacing site or the direction of the muscle fiber orientation did not influence the size of the DDA. The diameter of the DDA exceeded 4 mm (ie, the size of a standard tip electrode for catheter ablation) when the pacing output was higher than 6 V.

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