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Author: Wijnmaalen, Adrianus Pieter
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Chapter 3
Reversed polarity of bipolar electrograms to predict a successful ablation site in focal idiopathic right ventricular outflow tract arrhythmias

Carine F.B. van Huls van Taxis, Adrianus P. Wijnmaalen, Dennis W. den Uijl, Marcin Gawrysiak, Hein Putter, Martin J. Schalij, K. Zeppenfeld

Abstract

Background: Radiofrequency catheter ablation (RFCA) for idiopathic right ventricular outflow tract (RVOT) arrhythmias is typically guided by local activation time (LAT) mapping and unipolar electrogram morphology (QS-configuration). However, LAT mapping is limited by the large variation among patients and the area demonstrating a QS-configuration of the unipolar electrogram may be larger than the focal source. Reversed polarity has been proposed as criterion to guide RFCA.

Objective: The aim of this study was to investigate the value of reversed polarity of adjacent bipolar electrograms to predict a successful ablation site in idiopathic RVOT arrhythmias.

Methods: Twenty-five consecutive patients (12 male [48%], 43±15 years) undergoing RFCA for RVOT arrhythmia were studied. Electrograms of ablation sites and of points within a 15mm radius to the successful site were evaluated for LAT, unipolar electrogram morphology and the presence of reversed polarity of adjacent bipolar electrograms. Electrogram characteristics of successful ablation sites were compared to non-successful ablation sites. The spatial distribution of each electrogram characteristic was studied.

Results: Successful ablation sites more often demonstrated reversed polarity and had an earlier LAT than non-successful sites. A wide spatial distribution was observed for unipolar electrograms with a QS-configuration around the successful ablation site. Mapping based on LAT and reversed polarity had a higher predictive value for a successful ablation site than mapping based on LAT and QS-configuration.

Conclusion: The presence of reversed polarity has a high predictive value for successful ablation sites in focal idiopathic RVOT arrhythmias and is likely to reduce the number of RFCA applications.
Introduction

Ventricular arrhythmias (VA) in the absence of structural heart disease are a common entity. Patients presenting with idiopathic VA account for 10% of patients referred for evaluation and treatment of VA and more than 70-80% of idiopathic VA originate from the right ventricular outflow tract (RVOT). Although idiopathic VAs are generally considered benign, they can cause severe symptoms and may be associated with a VA induced cardiomyopathy. Current guidelines indicate anti-arrhythmic drugs as first choice therapy for symptomatic patients; however drugs are often ineffective or hampered by side effects. Radiofrequency catheter ablation (RFCA) is a reasonable alternative and acutely highly effective with procedural success rates of more than 80%. Although considered safe, serious complications may occur and the application of a limited number of radiofrequency lesions particular is preferred.

To guide RFCA, conventional strategies are based on bipolar local activation time (LAT) mapping and the presence of a QS-configuration of the unipolar electrogram to predict a successful ablation site. However, the use of LAT is limited by its large variation among patients and the area demonstrating a unipolar QS-configuration may be larger than the focal source. A more specific electrogram characteristic to predict a successful ablation site in RVOT arrhythmias is therefore desirable.

The feasibility of guiding ablation by reversed polarity of adjacent bipolar electrograms has been demonstrated in pulmonary vein isolation based on the hypothesis that the excitation wavefront propagates radially from the breakthrough site of the left atrium to the pulmonary vein. A similar reversal of the initial deflection of adjacent bipolar electrograms, indicative for wavefront propagation in opposite directions, has been demonstrated in patients with accessory pathways and focal atrial tachycardias. This phenomenon however, has not been well documented in focal RVOT arrhythmias.

The aim of this study was to investigate the value of reversed polarity mapping to identify an arrhythmogenic focal source and to predict a successful ablation site in focal RVOT arrhythmias.

Methods

Patient population

The patient population consisted of 25 consecutive patients undergoing RFCA of idiopathic focal VA originating from the RVOT. To rule out structural heart disease, a comprehensive clinical evaluation was performed including medical history, 12-lead electrocardiogram (ECG) and two-dimensional transthoracic echocardiography in all patients. If deemed necessary to exclude structural heart disease, exercise testing, coronary angiography, cardiac
multi-detector computed tomography, magnetic resonance imaging and/or nuclear imaging were performed. Prior to RFCA, a 12-lead ECG recording of the VA and a 24-hour Holter registration were acquired in all patients. Ventricular arrhythmias consisting of more than three consecutive monomorphic beats were classified as ventricular tachycardia (VT) and VA ≤3 consecutive monomorphic beats were classified as premature ventricular contraction (PVC).

After RFCA, all patients were monitored for 24 hours to detect early VA recurrence. All patients were evaluated on a regular basis at the outpatient clinic 3 months after discharge. Each visit included a clinical history, 12-lead ECG and 24-hour Holter registration.

**Electrophysiological examination and catheter ablation**

After informed consent was obtained electrophysiological evaluation was performed comprising electrical programmed stimulation (EPS) and right ventricular electroanatomical activation mapping to identify the site of origin within the RVOT. During mapping and ablation, conscious sedation was avoided whenever possible. Anti-arrhythmic drugs were discontinued for at least 5 half-lives. None of the patients was using amiodarone prior to the procedure. Heparin was administered to maintain an activated clotting time of 250-300s. Catheters were placed through a right femoral vein approach. A quadripolar catheter was inserted in the right ventricle and used for EPS. In the presence of a spontaneous clinical VA, activation mapping was performed using the surface VA QRS as a temporal reference. If no spontaneous VA occurred EPS was performed before and after intravenous isoprotenerol (2-8 µg/min) infusion, if necessary. The EPS protocol consisted of 3 drive-cycle lengths (600, 500 and 400 ms) with up to 3 ventricular extra stimuli and incremental burst pacing from 2 different right ventricular sites.

A 3.5mm irrigated-tip quadripolar mapping catheter (2-5-2mm inter-electrode spacing, Navistart ThermoCool, Biosense Webster Inc, Diamond Bar, CA, USA) was used to create an electroanatomical activation map. Electroanatomical mapping was performed using a 3-D non-fluoroscopic mapping system (CARTO XP™, Biosense Webster Inc, Diamond Bar, CA, USA).

Bipolar electrograms recorded from the distal (M1-M2) and proximal (M3-M4) electrode pair of the mapping catheter (filtered at 30-400Hz), the unipolar electrogram recorded from the distal electrode (M1; filtered at 1-240Hz, Wilson central terminal) and the 12-lead surface ECG were displayed simultaneously and stored on an electrophysiological recording system (Prucka Cardiolab, GE Healthcare, Piscataway, NJ, USA) and on the 3-D mapping system for off line analysis. Bipolar electrograms recorded from the mid electrode pair (M2-M3) were only displayed and stored on the electrophysiological recording system.

To guarantee accurate electroanatomical activation mapping and to avoid annotation of catheter induced PVCs, the VA QRS-morphology of each acquired mapping point was compared to a 12-lead QRS template of the clinical arrhythmia.
Target sites for RFCA were selected based on 1) LAT, 2) the presence of a unipolar QS-configuration and 3) the presence of reversed polarity. Local activation time was measured from the bipolar electrogram recorded from the distal electrode pair of the mapping catheter and was defined as the interval between the initial sharp peak of the electrogram and the onset of the VA QRS. Unipolar electrograms were recorded from the distal electrode of the mapping catheter. The presence of reversed polarity was evaluated from the bipolar electrograms recorded from the distal (M1-M2) and mid (M2-M3) electrode pairs of the mapping catheter and was defined as a rapid simultaneous deflection in opposite direction of the initial part of the bipolar electrograms occurring before the onset of the VA QRS. To record reversed polarity the mapping catheter was positioned parallel or in a shallow angle to the endocardial surface (Figure 1).

Radiofrequency energy was applied at 20-30W with a maximum temperature of 40°C and with external irrigation at 20ml/min to achieve an impedance-fall of 10ohm. If the VA was abolished within 30s, the energy application was continued for 60s. If the VA was not abolished within 30s, the energy application was terminated, the site was tagged as non-successful ablation site on the map and mapping was continued. A successful ablation site was defined as the location where RFCA abolished the VA and was tagged on the map. The procedural endpoint was reached when the targeted VA did not occur spontaneously after a waiting period of 30min after the last application and could not be induced by EPS before and after isoprotenerol infusion.

**Electrogram analysis**

Electrogram characteristics at successful ablation sites, non-successful ablation sites and at mapping sites within the close vicinity of the successful ablation site (area points) were analyzed. Area points were defined as mapping points acquired within a radius of 15mm from the successful ablation site. The distance between area points and non-successful ablation sites to the VA termination site was measured using the software provided by the CARTO XP system. Area points were further categorized according to the distance to the successful ablation site (1-5mm; 6-10mm; 11-15mm) to study the spatial distribution of the different electrogram characteristics with regard to the successful ablation site. For each analyzed mapping point (1) LAT, (2) unipolar electrogram morphology and (3) the presence of reversed polarity were evaluated. Local activation time, a unipolar QS-configuration and the presence of reversed polarity were compared for successful and non-successful ablation sites.

To further determine the accuracy of LAT, unipolar QS-configuration and the presence of reversed polarity to predict a successful ablation site, electrogram characteristics of successful sites were compared to the characteristics of area points. The cut-off value for LAT to predict a successful ablation site was determined based on the value with the highest combined sensitivity and specificity.
Figure 1.
Panel A. Schematic of an arrhythmogenic focal source within the RVOT (red) with radial wavefront propagation and the position of the quadripolar mapping catheter. The distal (M1-M2) and mid (M2-M3) electrode pairs are simultaneously activated showing a rapid simultaneous deflection in opposite direction of the initial part of the bipolar electrograms defined as reversed polarity.
Panel B. Local bipolar electrograms recorded from the distal (M1-M2), mid (M2-M3) and proximal (M3-M4) electrode pairs of the ablation catheter and the 12-lead surface ECG of idiopathic RVOT arrhythmias (sweep-speed 200mm/sec) in two patients. A single radiofrequency application at the recording site abolished the arrhythmia.
To study the impact of reversed polarity on the accuracy to predict successful ablation sites, two different electrophysiological mapping strategies were compared: (1) a conventional approach which was guided by LAT and unipolar QS-configuration and (2) a newly proposed approach guided by LAT and reversed polarity. Both approaches used LAT as a first selection criterion to delineate the area around the focal source within the RVOT. Next, within this area a unipolar QS-configuration or reversed polarity was used to identify the site of origin.

All electrograms were analyzed off-line by two independent observers blinded to the location of the mapping point and to the result of the ablation procedure. In case of discrepancy between the two observers, agreement was reached by consensus.

**Statistical analysis**

Statistical analysis was performed using SPSS, version 16.0 (SPSS Inc, Chicago, IL, USA). A p-value of <0.05 was considered statistically significant. Normality of distribution was tested using the Kolmogorov-Smirnoff test. Continuous variables are expressed as mean±SD and were compared using the unpaired student’s t-test. Categorical variables are expressed as number (%) and were analyzed using the chi-square test. In order to correct for correlations due to multiple measurements within the same patient, robust standard errors were calculated using Sandwich estimators. Adjustment for multiple testing was performed using the Bonferroni correction. To determine the optimal cut-off value for LAT to predict a successful ablation site, a receiver operating characteristic curve was constructed. The cut-off value was based on the LAT value with the highest combined sensitivity and specificity. Finally, to test the clinical impact of electrophysiological mapping based on LAT and reversed polarity on the accuracy to identify a successful RFCA site, the net reclassification improvement compared to conventional mapping was calculated.

**Results**

Twenty-five consecutive patients (12 male, 43±15 years) with a total of 26 registered VA (22 PVC (85%)) were included in the study. All patients had been symptomatic for 38±40 months and were refractory to therapy with 1.3±1.3 anti-arrhythmic drugs. The VA burden on 24-hour Holter monitoring was 22±17%. All patients had normal left and right ventricular function (mean left ventricular ejection fraction 58±5%) on echocardiography. To rule out structural heart disease additional diagnostic testing was performed and was normal in all patients. Twenty patients underwent exercise testing, coronary angiography was performed in 10 patients, cardiac multi-detector computed tomography in 1 patient, magnetic resonance imaging in 11 patients and nuclear imaging in 3 patients.
**Electrophysiology study and radiofrequency catheter ablation**

During electrophysiological study, the clinical VA occurred spontaneously in 22/25 (88%) patients. In 3 patients isoprotenerol infusion was required to induce the clinical VA, additional burst pacing was required to initiate the clinical VA in 1 patient. One patient presented with 2 spontaneous VA morphologies (both were targeted).

Electroanatomical activation mapping of the RVOT was performed prior to ablation in all patients (40±29 mapping points per VA). All VA were successfully abolished with a mean of 2.3±1.8 RF applications. Procedural time was 76±24min (including a 30min waiting period after the last RF application) and a fluoroscopy time of 13±8min. Procedural success was achieved in all patients. No procedure related complications occurred and all patients were discharged without in hospital VA recurrence.

![Graph](image)

**Figure 2.** Frequency of local activation time (LAT) at successful ablation sites (black bars) versus non-successful ablation sites (grey bars). The dashed lines indicate the normal distribution of the LAT in the two groups. Please note the important overlap of LAT between successful and non-successful ablation sites.

After 8±7 months of follow-up all patients were free of symptoms without the use of antiarrhythmic drugs. Twenty patients had a VA burden of <1% on 24-hour Holter monitoring. In 2 patients the VA burden was 2 en 6%, respectively; however the VA QRS-morphology differed from the VA QRS-morphology targeted during the index procedure. In 3 asymptomatic patients, who had disabling symptoms before ablation, 24-hour Holter monitoring was not available.

None of the 4 patients with VT prior to ablation had VT recurrence.
Successful versus non-successful ablation sites

Electrogram characteristics from 26 successful and 33 non-successful ablation sites were compared. Local activation time was significantly earlier at successful ablation sites as compared to non-successful ablation sites (-28±7ms versus -22±8ms, p=0.002). However, there was a considerable overlap in LAT between both groups (Figure 2). Reversed polarity of adjacent bipolar electrograms was observed at 21 of 26 successful ablation sites (85%). In contrast, reversed polarity was absent at all non-successful ablation sites (p<0.001). The presence of a unipolar QS-configuration was similar between successful and non-successful ablation sites (22 (85%) versus 19 (83%), p=0.850).

Spatial distribution of electrogram characteristics

Local activation time, unipolar QS-configuration and the presence of reversed polarity were compared between 26 successful ablation sites and 139 area points within three different categories (Table 1). Local activation time was significantly earlier at successful ablation sites as compared to area points. The best cut-off value to discriminate between a successful ablation site and an area point was a LAT of -23ms. In addition, area points beyond a 5mm radius from the successful ablation site demonstrated less often a unipolar QS-configuration when compared to the successful ablation sites. However, no differences in unipolar electrogram morphology were found between successful ablation sites and area points within a 5mm radius. Moreover, the prevalence of a unipolar QS-configuration at distances between 6-10mm and 11-15mm remained high (63% and 53%, respectively) (Figure 3). Importantly, successful ablation sites showed significantly more often reversed polarity than area points across all categories. The sensitivity to discriminate between a successful ablation site and an area point was slightly higher for LAT (88%) as compared to a unipolar QS (85%) and the presence of reversed polarity (81%), however the specificity to identify a successful site was

<table>
<thead>
<tr>
<th>N</th>
<th>Successful ablation site</th>
<th>Area point 1–5mm</th>
<th>Area point 6–10mm</th>
<th>Area point 11–15mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>43</td>
<td>51</td>
<td>45</td>
</tr>
<tr>
<td>LAT (ms)</td>
<td>-28±7</td>
<td>-21±8*</td>
<td>-18±8*</td>
<td>-18±8*</td>
</tr>
<tr>
<td>Unipolar QS-configuration, n (%)</td>
<td>22 (85)</td>
<td>37 (79)</td>
<td>32 (63) †</td>
<td>24 (53) ‡</td>
</tr>
<tr>
<td>Reversed polarity, n (%)</td>
<td>21 (81)</td>
<td>2 (5)*</td>
<td>3 (6)*</td>
<td>5 (11)*</td>
</tr>
</tbody>
</table>

LAT= Local activation time; * p<0.001 compared to successful ablation site; † p<0.05 compared to successful ablation site; ‡ p<0.02 compared to successful ablation site
Comparison of two mapping strategies to predict a successful ablation site

To study the clinical impact of reversed polarity on the accuracy of electrophysiological mapping of idiopathic RVOT arrhythmias, a comparison was made between a conventional mapping strategy and a newly proposed mapping strategy including reversed polarity. For both strategies, LAT>-23ms was applied as the first criterion. If LAT was >-23ms, this mapping site could be excluded as a successful ablation site with a 97% likelihood. However, if LAT at a certain location was ≤-23ms, the accuracy to positively predict a successful ablation site was only 36%. After excluding mapping sites with LAT>-23ms the conventional mapping strategy used the presence of a unipolar QS-configuration as the second criterion to identify a successful ablation site whereas the new mapping strategy used the presence of reversed polarity. The presence of a unipolar QS-configuration identified the successful

Figure 3. Electroanatomical activation map of a right ventricular outflow tract arrhythmia (posterior view). Local activation time (LAT) is color coded with isochronal steps of 5 ms according to the color bar. The white dotted line delineates the area around the successful ablation site (red tag) that demonstrated a unipolar QS-configuration. Black-with-green icons indicate areas demonstrating unipolar QS-configuration and white-with-red icons correspond to the area demonstrating a unipolar rS configuration. (for figure in color see page: 254)
Table 2. Electrogram characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAT ≤-23ms</td>
<td>88</td>
<td>71</td>
<td>0.97</td>
<td>0.36</td>
</tr>
<tr>
<td>Unipolar QS-configuration</td>
<td>85</td>
<td>35</td>
<td>0.92</td>
<td>0.20</td>
</tr>
<tr>
<td>Reversed polarity</td>
<td>81</td>
<td>93</td>
<td>0.96</td>
<td>0.68</td>
</tr>
</tbody>
</table>

LAT = Local activation time; NPV = negative predictive value; PPV = positive predictive value

Ablation site with 40% accuracy. In contrast, application of reversed polarity as the second criterion led to the identification of the successful ablation site with 86% accuracy (Figure 4). Moreover, mapping based on reversed polarity resulted in a net reclassification improvement of 0.189 (p=0.028). This index of reclassification illustrated that mapping based on LAT and reversed polarity resulted in a significant ‘gain of certainty’ to identify a successful RFCA site compared to conventional mapping based on LAT and unipolar QS-configuration.

![Figure 4](image)

**Figure 4.** The predictive value of a new mapping strategy guided by local activation time (LAT) and reversed polarity was compared to a conventional mapping strategy guided by LAT and unipolar electrogram morphology. Both approaches use LAT as the primary selection criterion. The new approach uses reversed polarity as the second selection criterion whereas the conventional approach uses the unipolar electrogram morphology (i.e. presence of unipolar QS-configuration). NPV = negative predictive value; PPV = positive predictive value.
Discussion

Key findings of the present study are: (1) the presence of reversed polarity was associated with a high likelihood for a successful RF application; and (2) mapping of idiopathic RVOT arrhythmia based on LAT and reversed polarity resulted in a higher predictive value for a successful ablation, compared to a conventional mapping strategy based on LAT and unipolar electrogram morphology.

Conventional mapping strategies

Several electrophysiological strategies have been described to guide RFCA of focal RVOT arrhythmias. Typically, mapping procedures are guided by unipolar and bipolar electrograms. Unipolar electrograms provide information about the direction of the wavefront: an initial positive deflection of the unipolar electrogram indicates propagation towards the mapping catheter and has a high negative predictive value for a successful ablation site. As the wavefront reaches the electrode and propagates away, the deflection sweeps negative. When the electrode is located at the focal source the wavefront propagates away producing a monophasic QS complex. However, unipolar electrograms provide information about a large area and contain important far-filed signals. In contrast, in bipolar electrograms the far field signal is subtracted out thereby providing information about the local electrical activity, but do not contain information about the direction of the wavefront. Currently, most RFCA procedures for focal arrhythmias are guided by LAT defined by the initial peak of the bipolar electrogram and the rapid negative deflection of the unipolar electrogram, the unipolar electrogram morphology and pace-mapping. Although these criteria have demonstrated their practical value, each technique is associated with its own inherited limitations. The spatial resolution of a good pace-map has been found to be 1.8±0.6cm² and inferior to the spatial resolution of activation mapping. Based on this observation pace-mapping was not systematically investigated in our study.

In the current study, LAT was significant earlier at successful ablation sites (-28±7ms) as compared to ablation sites that did not abolish the VA (22±8ms), which is in line with prior studies reporting LAT at effective sites between -24±7 ms and -29±7ms. However, we could demonstrate a significant overlap in LAT between successful and non-successful ablation sites. Although the best cut-off value for LAT (-23ms) to discriminate between a successful site and a site in a proximity of less than 15mm provided a high negative predictive value, only a minority of successful sites could be identified correctly. This finding suggests that a cut-off value for LAT can be used to delineate the area of interest, but is not accurate enough to identify a site where RF energy should be applied. Furthermore, the current study confirms and extends prior observations that the area around a site of origin of a focal RVOT VA that exhibits a unipolar QS-configuration is considerably broad. The wide spatial
distribution of a unipolar QS is in line with the low additional value to predict a successful ablation site found in this study.

**Reversed polarity**

Reversed polarity of bipolar electrograms to guide ablation of focal RVOT arrhythmia was first suggested in a case report by Fisher et al using a custom-built orthogonal electrode array. However, this method to target focal RVOT arrhythmias has not been applied in a large cohort of patients and using a standard quadripolar mapping catheter.

The use of reversed polarity to predict a successful ablation site is based on the hypothesis that rapid radial propagation from a focal source results in simultaneous deflection in opposite direction of the initial part of the bipolar electrograms. Provided that the bipoles are positioned orthogonally to the activation wave front with the focal source ideally located between the bipoles. Due to the cylindrical anatomy of the RVOT it is possible to align a standard quadripolar mapping catheter orthogonally to the myocardial surface.

Indicating wavefront propagation in opposite direction, reversed polarity provides additional information to LAT. A focal source can be assumed if early local activation preceding the VA QRS is present and activation is observed in opposite directions. Combining these two electrogram characteristics is therefore likely to provide a reliable endpoint for catheter mapping. Accordingly, our suggested approach to map focal RVOT arrhythmias by combining LAT with reversed polarity resulted in a high negative predictive value but importantly also in a high positive predictive value to identify a successful ablation site. In contrast, conventional mapping based on LAT and a unipolar QS-configuration had comparable negative predictive but poor positive predictive value.

**Procedural aspects**

Patients suffering from idiopathic focal RVOT arrhythmias are commonly young and healthy. Therefore important goals when targeting focal RVOT arrhythmias are reduction of radiation exposure and number of RFCA applications needed to terminate the VA. Prior studies reported on mean fluoroscopy time up to 54 minutes targeting RVOT arrhythmias whereas in the current study mean fluoroscopy time was only 13±8min. Moreover, the mean number of RFCA applications needed to terminate the VA ranged from 3 to 8 in previous studies but could be reduced to only 2.3±1.8 RFCA applications in the current study. These results indicate that implementation of reversed polarity is likely to reduce both radiation dose and number of RFCA applications.

**Limitations**

The present study comprised a relatively small number of patients. Therefore the results should be confirmed in a larger population. Furthermore, for statistical purposes LAT was dichotomized according to the cut-off value provided by the ROC-curve analysis, although
this may not fully reflect clinical practice. In addition, during ablation target sites for RFCA were selected based on the combination of early LAT, the presence of a unipolar QS-configuration and the presence of reversed polarity. However, the decision to apply RF energy was made by the operator in a non-randomized fashion. The analyses of LAT, the presence of a unipolar QS-configuration and the presence of reversed polarity have been performed retrospectively. Ideally the newly proposed strategy, combining early LAT and reversed polarity presence, should have been validated prospectively. Finally, based on theoretical considerations the ablation catheter should be pulled back slightly when reversed polarity is recorded to ensure that the catheter tip is in the position of the second electrode. However, this was not systematically evaluated in the present study but seems to be unlikely to further reduce the number of RF applications needed.

**Clinical implication**
The presence of reversed polarity is easily to obtain and has a high predictive value to identify a successful ablation site in idiopathic focal RVOT arrhythmias. Combining LAT and reversed polarity can predict a successful ablation site with higher accuracy than conventional mapping based on LAT and unipolar QS-configuration. Its clinical application is likely to reduce the number of RFCA applications and radiation exposure to both patient and operator.

**Conclusion**
The presence of reversed polarity has a high predictive value for a successful ablation site in focal idiopathic RVOT arrhythmias. Combining local activation time and reversed polarity improves the accuracy of identifying the site of origin compared to conventional mapping strategies.
Chapter 3 Reversed Polarity in Idiopathic VT

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