

## REVIEW

### Insights into Catheter Ablation of Ventricular Tachycardias in Arrhythmogenic Right Ventricular Cardiomyopathy / Dysplasia

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#### Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), mostly affecting young/middle-aged individuals, poses a significant risk of malignant ventricular arrhythmias (VAs) and subsequent sudden cardiac death (SCD). Antiarrhythmic agents (AAA) provide insufficient arrhythmia suppression and prevention and can be proarrhythmic. Thus, the implantable cardioverter-defibrillator (ICD) is considered the first-line treatment, especially in patients with secondary prevention indication. Nevertheless, catheter ablation is an additional therapy to the ICD which has proved its efficacy in primary and secondary prevention of fatal arrhythmias and sudden cardiac death. The superiority of the combined endo- and epicardial VT ablation in this population is clear since ARVC/D substrate has been shown to be mostly epicardial. Due to progressive nature of ARVC/D, ablation seems to be a useful tool for the patients who experience recurrent VT episodes or electrical storms.

**Key Words:** sudden cardiac death; arrhythmogenic right ventricular cardiomyopathy/dysplasia; ventricular tachycardia/fibrillation; implantable cardioverter defibrillator; catheter ablation/mapping

#### Abbreviations

AAA = antiarrhythmic agents; ARVC/D = arrhythmogenic right ventricular cardiomyopathy / dysplasia; EAM = electroanatomical mapping; EPS = electrophysiology study; ICD = implantable cardioverter defibrillator; LV = left ventricle(-ular); RFA = radiofrequency catheter ablation; RV = right ventricle(-ular); SCD = sudden cardiac death; VAs = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular tachycardia

#### Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) poses a significant risk of malignant ventricular arrhythmias (VAs) and subsequent sudden cardiac death (SCD).<sup>1</sup> On top of the fact that young/middle-aged individuals are mostly affected, imperative issues emerge regarding primary and secondary prevention of catastrophic ventricular arrhythmogenesis.<sup>1</sup> Antiarrhythmic agents (AAA) provide insufficient arrhythmia suppression and prevention and can be

proarrhythmic.<sup>2</sup> In this context, implantable cardioverters-defibrillators (ICDs) are considered the first-line treatment, especially in patients with an indication for secondary prevention of SCD.<sup>3</sup> However, a substantial amount of discrepancy remains as to which patients without documented VAs are optimal candidates for ICD implantation, based on arrhythmic risk stratification schemes. Prospective studies in patients with implanted ICDs according to the arrhythmic risk factors let somebody see that only a minority of them receive appropriate ICD intervention, while significant proportions present with inappropriate ICD interventions and/or device-related complications.<sup>4</sup>

In all cases, what ICDs are incapable of is prevention of arrhythmias occurrence and, of more importance, modification or elimination of the arrhythmogenic substrate. Radiofrequency catheter ablation (RFA) effectively modifies and/or eliminates abnormal arrhythmogenic substrate. In post-infarction patients with mainly subendocardial scars and slow conduction areas, RFA is an established therapy for malignant ventricular arrhythmias.<sup>5</sup> Regarding ARVC/D, though, the abnormal substrate appears not to be confined to the subendocardium. In fact, recent research work has demonstrated the presence of scarring, creating re-entry circuits due to slow conduction and unidirectional block promoting thus arrhythmogenesis in the epicardium.<sup>6</sup> State-of-the-art ablation procedures include epicardial electroanatomical mapping (EAM) and ablation, not only after failure of endocardial ablation, but even as first-line approach.<sup>7</sup> The combined use of endocardial and epicardial ablation has given more than encouraging results in patients presenting with VAs and has raised significantly rates of arrhythmia-free survival.<sup>7,8</sup>

#### Electroanatomic and Electrophysiologic Substrate

ARVC/D is a genetically determined cardiomyopathy which typically affects the right ventricle (RV); involvement of the left ventricle (LV) is now commonly recognized, especially in the late stages of the disease, while recent data suggests that it may in fact precede the onset of significant RV dysfunction.<sup>9-12</sup> It primarily results from defective desmosomal proteins with the subsequent myocardial degeneration and death causing replacement of right and/or ventricular myocardium by fibrofatty tissue.<sup>9,13,14</sup> Along with RV enlargement and dysfunction, RV aneurysms are typical of ARVC/D and are detected in the so-called "triangle of dysplasia", i.e., RV outflow tract, apex, and outflow tract.<sup>15</sup> Sites of left ventricle (LV) involvement, demonstrated by late enhancement cardiac magnetic resonance (LECMR), include more often the inferolateral wall, inferior wall-septal junction, inferior wall and septum.<sup>12</sup> Through functional myocardial tissue

degeneration and replacement, the two principal prerequisites for reentry are met. The intercellular coupling is deranged leading to slower impulse conduction and, secondly, areas of anatomic and/or functional unidirectional block are created.

High-density electroanatomic mapping (EAM) has been used to characterize the electrical correlates of arrhythmogenic substrate in ARVC/D. Bipolar RV endocardium signals are considered normal if they display up to 3 deflections from baseline, with amplitude of more than 1.5 mV, while dense scar is demonstrated by amplitudes less than 0.5 mV.<sup>16,17</sup> Regarding the epicardium, an amplitude in the bipolar setting of more than 1.0 mV is considered normal, which corresponds to 95% of the signals recorded at a distance at least 1 cm from the defined large vessel coronary vasculature<sup>18</sup>. In patients with minimal or moderate endocardial disease involvement, the extent of epicardial scar can also be reliably evidenced with application of endocardial unipolar mapping, using a cutoff of <5.5 mV for normal endocardial unipolar voltage.<sup>19</sup> The areas of endocardial electroanatomic scar, as defined by studies conducted to seek endocardial ventricular tachycardia (VT) ablation efficacy, extend from the tricuspid or pulmonary valve to the RV free wall, while the RV apex seems to be excluded.<sup>20,21</sup> High-density EAM in the epicardium has revealed that low-voltage epicardial areas correspond well to endocardial anatomical ones but extend further over the surface of the RV.<sup>7,22</sup> In ARVC/D the RV epicardium activation is delayed and independent of the underlying endocardium activation. In particular, compartmentalization of the epicardium from the endocardium and VT circuits defined only to the epicardium are created, explaining the low rates of success and high rates of VT recurrence when an endocardial-only ablative strategy is applied.<sup>6</sup> Of importance, the existence of scarring and low voltage areas does not dogmatically predict arrhythmic events. As Santangeli et al<sup>23</sup> report, in primary prevention patients prospectively followed after ICD implantation, fragmented and late activation potentials recorded within the scar and not RV electroanatomic scar itself, were linked with subsequent malignant arrhythmogenesis.

**Risk Stratification and Management**

The majority of affected individuals develop symptoms during the second to fourth decade of life. The latter, especially during the early “concealed” stage of the disease, where gross changes in the cardiac muscle architecture are difficult or impossible to define, include mainly malignant ventricular arrhythmias, syncope and in some cases SCD.<sup>10</sup> Survivors of cardiac arrest present mainly with sustained ventricular tachycardia (VT) or

ventricular fibrillation (VF), receive an ICD in the context of secondary prevention and have rates of VT/VF incidence of up to 70% during follow up.<sup>24,25</sup>

The subgroup of patients without documented VAs is typically stratified according to arrhythmic risk factors. Such factors include induction of VT during an electrophysiology study (EPS), detection of non-sustained VT on noninvasive monitoring, male gender, severe RV dilation, extensive RV involvement, young age at presentation (less than 5 years), LV involvement, prior cardiac arrest, unexplained syncope and genotypes of ARVD/C associated with a high risk for SCD.<sup>3</sup> The John Hopkins registry reported 48% appropriate ICD interventions during follow-up. Inducibility at EPS, non-sustained VT and high burden of ventricular ectopy were independent strong predictors of appropriate ICD therapy.<sup>26</sup> On the other hand, Corrado et al report a lower, albeit significant, percentage of 24%. They define syncope as an important predictor of life-saving ICD intervention, while programmed ventricular stimulation seems to have a low predictive accuracy for appropriate ICD intervention.<sup>4</sup>

**Catheter Ablation**

A significant proportion of appropriate ICD therapies is delivered due to episodes of electrical storm.<sup>27,28</sup> The aforementioned data sufficiently highlight the urge for therapies that move one step forward in the field of arrhythmogenic substrate modification/elimination rather than malignant VAs termination. General recommendations regarding catheter ablation indications in patients with structural heart disease are summarized in Table 1.<sup>29</sup>

**Table1.** Indications for catheter ablation of ventricular tachycardia associated with structural heart disease<sup>29</sup>

|   |                                                                                                                                                   |
|---|---------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | Recurrent symptomatic sustained monomorphic VT (SMVT), including VT terminated by an ICD despite AAA or when AAA are not tolerated or not desired |
| 2 | Control of incessant SMVT or VT storm that is not due to a transient reversible cause                                                             |
| 3 | Recurrent sustained polymorphic VT and VF refractory to AAA when there is suspected trigger that can be targeted for ablation                     |

AAA = antiarrhythmic agents; ICD = implantable cardioverter defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia

In patients with ischemic cardiomyopathy (ICM), RFA has been shown to be more efficacious compared to individuals with non-ischemic cardiomyopathies. In the field of ARVC/D the results from the studies carried out in patients with VTs are controversial. Although there are no

large clinical trials in this population, the results are not encouraging regarding RFA. As in ICM, two end-points have been proposed indicating acute success, either non-inducibility of the clinical VT or of any inducible VTs. The first clinical studies during late 90's enrolled only a few patients and the procedures were carried out conventionally, typically with pace- and entrainment mapping techniques, without using EAM systems. One of them was conducted by Harrada et al, who enrolled 7 patients using entrainment endocardial mapping to identify the reentrant circuit. They demonstrated that RFA was most successful at narrow isthmuses of the re-entry circuits, proving that in this population re-entry predominates as VT generating mechanism.<sup>30</sup> Although nowadays RFA is the commonly used technique, in the early 1990s direct current (DC) fulguration was also widely used. According to Fontaine et al, who compared the efficacy of these two techniques in patients with ARVC/D, the effectiveness/efficacy of RFA alone was about 40%, while DC fulguration was successful after RFA failure. In these 50 patients, the success rate during the follow up was 81% for DC ablation and 93% for combined DC and RFA.<sup>31</sup>

Moreover, in the past years a non-contact mapping technique with a balloon catheter was introduced in the clinical practice of VT ablation. This technique using the far-field unipolar electrograms obtained from the endocardium allows the creation of an activation map, although sometimes it is not possible to detect the low

voltage electrograms. In patients with ARVC/D, results seem to be promising, since in a group of 32 subjects acute success was achieved in 84.4% of them and at the end of follow up 81.3% were free of VT.<sup>32</sup>

Table 2 summarizes the results from the most important published clinical trials for VT ablation in patients with ARVC/D. Due to different ablation techniques, endpoints used and the overall post ablation management of the patients, regarding the use of AAA, ICDs and follow up duration, there is an obvious variability among these results. Most of the studies published after 2000 included patients with implanted ICDs, either before inclusion or during the study, since its effectiveness is undeniable. A large observational study showed that about half of the patients with ARVC/D had at least one episode of ventricular tachyarrhythmia that required ICD therapy over a mean follow-up period of 3.3 years, and 24% experienced potentially fatal arrhythmias as ventricular fibrillation or flutter, suggesting thus the beneficial effect of the ICDs.<sup>33</sup> Ablation in these patients seems to reduce the number of VA episodes especially when it is performed both endocardially and epicardially. Recently published data showed that, in a population of 49 patients, 52.2% were free of VAs or ICD therapy during a 3-year follow up after endocardial ablation compared to 84.6% after combined endo- and epi-cardial ablation (P=0.029). Moreover, patients with frequent premature ventricular contractions after ablation were more likely to have VA recurrence or ICD therapy (P<0.001).<sup>7</sup>

**Table 2. Clinical Outcomes of Ventricular Tachycardia Ablation in Patients with ARVC/D.**

| Study                           | Patients characteristics                                 | No of procedures /episodes     | Ablation approach                      | Acute success rate                                                | Complications                               | Recurrence rates                                | Additional comments                                                         |
|---------------------------------|----------------------------------------------------------|--------------------------------|----------------------------------------|-------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------|
| Harada et al <sup>30</sup>      | 7 pts, FU 19 ± 7 months                                  | 8VTs                           | Entrainment endocardial mapping & RF   | 17% of exit sites, 67% of proximal sites & 8% of outer loop sites |                                             | 1 pt (chemical ablation RCA)                    | RFA is most successful at narrow isthmuses of the reentry circuits          |
| Fontaine G et al <sup>31</sup>  | 50 pts, 48 ± 15 yrs old during 16 yrs, mean FU 5.8 yrs   |                                | Endocardial mapping, DC (27 pts) & RFA | Clinical success after 3 sessions RFA+DC: ~90%                    | Death rate 3% per year, 3 pts had tamponade |                                                 | RFA plus DC ablation effective after failed RFA in the same session         |
| Marchlinski et al <sup>37</sup> | 21 pts mapping /19 pts abl, all had ICD, FU 27±22 months | 66 VTs                         | 21 pts endo (RV, 18 pts LV)            | 14/19 (74%) acute success                                         | none                                        | 17/19 pts no VT, 2 pts (≤1 episode/3 months FU) | >1 Ablation required in 13 pts                                              |
| Verma et al <sup>38</sup>       | 22 pts, aged 41±15 y, 18 pts ICD, median FU 37 months    | 3±2 VT/pt                      | Endocardial with CARTO                 | 18/22 pts                                                         | 1 pt had cardiac tamponade                  | 8 pts, but with slower VTs                      | Scar areas: TA, proximal RVOT, anterior/inferior-apical walls               |
| Satomi et al <sup>20</sup>      | 17 pts, 26 ± 15 months                                   | 13 stable VTs, 13 unstable VTs | Endocardial with CARTO                 | 13/17 pts were free of symptoms, 2pts received ICD                | No                                          | 2 pts had VT recurrence                         | Diastolic or fragmented potentials were recorded along TA or RVOT           |
| Dalal et al <sup>40</sup>       | 24 pts, 36±9 yrs, 19 pts ICD, FU 32±36 months            | 48 RFA                         | 10 with 3D mapping/ 38 conventional    | 22/48 successful procedures                                       | 1 procedure related death                   | 8 ±10 months recurrence time after abl., 40/48  | no difference in VT recurrence-free survival between patients with complete |

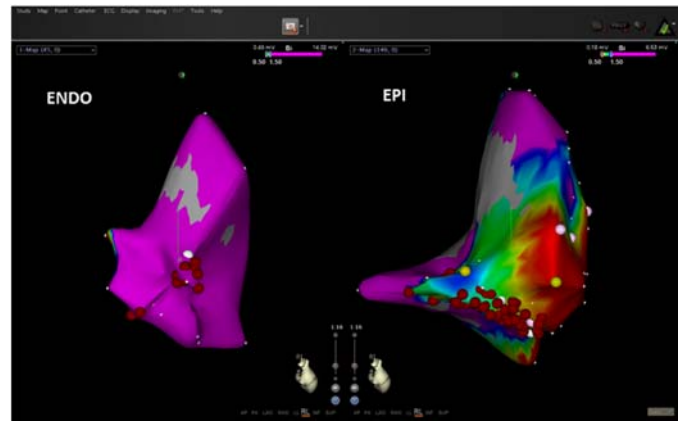
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|---------------------------------|--------------------------------------------------------------------------------------------------------|--------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------------------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 |                                                                                                        |                                                        |                                           |                                                                                                                 |                                    | procedures (85%), 4 pts el. storm                                                                                 | or partial procedural success and failure                                                                                                                              |
| Yao et al <sup>32</sup>         | 32 pts, 37±13 yrs, 2 pts had ICD, 28.6 ±16 months FU                                                   | 67 induced VTs, CL: 210±32 ms                          | Non contact mapping, Ensite               | 27/32 pts                                                                                                       | None                               | 81.3% free of VTs without AAA                                                                                     | Non contact mapping is useful for fast VTs ablation                                                                                                                    |
| Reithmann et al <sup>40</sup>   | 11 pts, 53±13 y, 6 pts had ICD implanted at end of FU, 27±17 months                                    | 18 VTs,                                                | Entrainment mapping with CARTO            | 10 VTs (9 pts) successful ablated                                                                               | No complications                   | 6/11 pts had recurrence (FU every 3 months)                                                                       | isolated diastolic potentials in SR were associated with successful RFA at reentry circuit isthmus sites                                                               |
| Garcia et al <sup>35</sup>      | 13 pts, 43±15 yrs, FU 18±13 months,                                                                    | Recurrent VTs after endocardial ablation (mean 2 abl.) | Endo- & epicardial with CARTO             | 11/13 pts (85%) non inducible monomorphic VT, 12 /13 pts (92%) elimination of all VTs                           | No complications                   | 10/13 pts (77%) free of sustained VT                                                                              | ARVC/D is associated with a more extensive epicardial area of electrogram abnormalities & frequently basal RV wall thickening                                          |
| Pokushalov et al <sup>36</sup>  | 17 pediatric pts, 14 ±4 y, FU 26±15 mos, recurrent VTs failure AAD endo- prior ablation, 5 pts had ICD |                                                        | Endo- & epicardial                        | 16/17 pts (94.1%) had non inducible VT                                                                          | 4 pts had pericardial effusion     | 12 pts (70.6%) free of arrhythmia                                                                                 | Failure of endocardial RFA due to: RV periannular thickness, 45% of pts had mismatch of endo- & epi- findings, in fibrotic areas endo-cardial ablation was ineffective |
| Komura et al <sup>41</sup>      | 35 pts (ICD & RFA), 5 pts ICD+RFA, 14 pts RFA, 45.6±15.6 y, FU 54.5±48.2 mos                           |                                                        |                                           |                                                                                                                 |                                    | 19/10 pts RFA (52.6%) 14.0±20.1 mos, 18/30 pts received ICD, recurrence 6/18 pts (33%) at 5.3±4 mos               | ICD reduced recurrence of VTs compared to RFA                                                                                                                          |
| Nair et al <sup>42</sup>        | 15 pts, 44±15 y, 5 pts had ICD, FU 25±16 months                                                        | 26 inducible VTs                                       | Only endo-cardial VTs, (Ensite system)    | 23/26 VTs were successfully ablated                                                                             | No complications                   | 2 pts had recurrence of non-clinical VT                                                                           | AAA discontinued after 6 months                                                                                                                                        |
| Bai et al <sup>7</sup>          | 49 pts with ICD, FU 1224±310 d endo-, 1175±112 days endo-epicardial                                    | 2 VTs/pt (median)                                      | 23 endo-, 26 endo-/epi-cardial with CARTO | End point: non-inducible suMVT                                                                                  | No major                           | 52.2% group 1 and 84.6% in group 2 free of VA,                                                                    | endo-epicardial RFA results in discontinuation of AAA; PVCs after RFA was associated with recurrence                                                                   |
| Della Bella et al <sup>43</sup> | 13 pts, 17.3±18.2 months                                                                               |                                                        | Endo-/epicardial                          | 9(69.2%) non inducible VT                                                                                       | 1 pt minor complication            | 4 pts (3 with the same morphology)                                                                                |                                                                                                                                                                        |
| Philips et al 2012 <sup>8</sup> | 87 pts, 38±13 years, 95% had ICD, mean FU 88.3±66 months                                               | 175 procedures, average 2.3 procedures/pt              | Endo- & epicardial                        | 47% acute / 38% partial success, & procedural failure in 15% of 160 procedures, 53% of pts had repeat ablations | 2 major associated with epicardial | 19% freedom from VT after a single endocardial RFA compared to 45% after a single epicardial RFA at 5 y (P=0.021) | VT-free survival was significantly longer after epicardial RFA than after endocardial (P=0.003)                                                                        |
| Haqqani et al <sup>6</sup>      | 18 pts, 43±15 years compared to 6 pts with normal heart, 15/18 pts had ICDs                            | 28 VTs were induced, 9 were mappable                   | Endo- & epicardial with CARTO             | 20/22 VTs after epicardial ablation were non-inducible                                                          |                                    |                                                                                                                   | Epicardial RV activation pattern is often independent of endocardial activation suggesting that the fibrosis may compartmentalize the endocardium from the epicardium  |

Although the acute success rate after VT ablation seems to be satisfactory in patients using an endocardium-confined approach, late recurrence remains a principal drawback. Recent advances in EAM and catheter ablation technology have contributed to the better understanding of the VT substrate in ARVC/D. Electroanatomical mapping data were compared between patients with ARVC/D and patients without structural heart disease who both underwent endocardial and epicardial mapping (Fig. 1). The identified scar area was larger in the epicardium compared to the endocardium ( $P=0.04$ ). Additionally, ARVC/D patients had longer epicardial and endocardial activation times compared to controls. Specifically, in these patients a more than four-fold greater delay between the last recorded endocardial activation and the latest epicardial right ventricular sites was demonstrated, simultaneously with the presence of late epicardial isolated potentials. On the contrary, the control patients had the latest epicardial activation within 20 ms after the latest RV endocardial activation.<sup>6</sup> The same activation template became clear after direct surgical mapping in 4 patients with ARVC/D, which showed the earliest activation points in the epicardium.<sup>34</sup> Garcia et al performed epicardial ablation in 12 out of 13 patients with failed endocardial ablation and after a mean follow up of  $18\pm 13$  months, 77% of the patients were free of sustained VT. The authors noted that the epicardial VT origin site was in proximity to the tricuspid annulus at the acute angle of the RV and this epicardial successful ablation region was in some of the patients  $>1$  cm away from the previous failed endocardial ablation site.<sup>35</sup> More recently, Bai et al<sup>7</sup> compared the long-term results by using endocardium-confined ablation versus endo-epicardial substrate-based ablation in patients with ARVC/D, reporting a rate of freedom from any VT of 52.2% and 84.6%, respectively. The existence of more than 10 premature ventricular complexes per minute was associated with more high percentage of VT recurrence. Added to the latter, newer data confirm the superiority of epicardial ablation in this population. In 87 patients from 80 different centers, those who underwent epicardial ablation were free from VT recurrence by 64% and 45% at 1 and 5 years of follow up, respectively, which was significantly larger compared to endocardial RFA ( $P=0.021$ ).<sup>8</sup> The incidence of major complications during the pericardial procedures was about 7.7%, similar to those reported in the literature about all VT categories epicardial ablation. Epicardial ablation seems also to be efficient in pediatric patients with ARVC. Pokushalov et al<sup>36</sup> showed that in 17 pediatric patients with recurrent VTs due to failed prior endocardial ablation or AAA inefficacy, epicardial VT ablation resulted to non-inducibility of the VT in most of them (16 of 17 pts). After a follow-up period

of  $26\pm 15$  months without receiving AAA, 70.6% of them were free of arrhythmia episodes.

## Conclusion

In patients with ARVC/D, catheter ablation is an additional therapy to the ICD which has proved its efficacy in primary and secondary prevention of fatal arrhythmias and sudden cardiac death. The superiority of the combined endo- and epicardial VT ablation in this population is clear, since the ARVC/D substrate has been shown to be mostly epicardial. Due to progressive nature of ARVC/D, ablation seems to be a useful tool for the patients who experience recurrent VT episodes or electrical storms. Using the new three-dimensional (3D) EAM mapping systems we are able to modify the arrhythmogenic endocardial and/or epicardial substrate and to abolish the re-entrant circuits which are responsible for the genesis of these macroreentry or focal tachycardias. Larger well organized multicenter trials are required to investigate the long-term effect favorable or not of the ablation therapy in these patients using the current endocardial and epicardial approach.



**Figure 1.** Endocardial (ENDO) and epicardial (EPI) voltage maps with the CARTO-3 system of a patient submitted for ventricular tachycardia ablation and diagnosis of ARVD in right lateral view. A low-voltage area is present in the epicardial surface. The epicardial scar is wider than the endocardial. Normal myocardium ( $>1.5$  mV) is coded in purple, scar ( $<0.5$  mV) is coded in red. Red dots: radiofrequency applications.

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