Outcomes of Catheter Ablation of Ventricular Tachycardia in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy

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Background—Prior studies evaluating the efficacy of catheter ablation of ventricular tachycardia (VT) among patients with arrhythmogenic right ventricular dysplasia/cardio-myopathy (ARVD/C) have reported varied outcomes. More recently, studies have suggested that an epicardial ablation is necessary for improved outcomes after catheter ablation of VT. The overall objective of the present study was to assess the efficacy of radiofrequency catheter ablation (RFA) of VT in ARVD/C, with particular focus on newer ablation strategies, including epicardial catheter ablation.

Methods and Results—The study population included 87 patients with ARVD/C who underwent a total of 175 RFA procedures between 1992 and 2011 at 80 different electrophysiology centers. Recurrence of VT following RFA and effect of RFA on the burden of VT were assessed. The mean age of the cohort was 38±13 years. Over a mean follow-up of 88.3±66 months, the overall freedom from VT of the 175 procedures was 47%, 21%, and 15%, at 1, 5, and 10 years, respectively. The cumulative freedom from VT following epicardial RFA was 64% and 45% at 1 and 5 years, respectively, which was significantly longer than endocardial RFA (P=0.021). Survival free of VT among procedures with 3D electroanatomic mapping was significantly longer compared to those without (P=0.016). Burden of VT was reduced irrespective of the ablation strategy (P<0.001).

Conclusions—Although VT recurrences are common, RFA results in a significant reduction in the burden of VT in patients with ARVD/C. Further, although the use of 3D electroanatomic mapping systems and epicardial ablation strategies are associated with longer survival free of VT, recurrence rates remain considerable. (Circ Arrhythm Electrophysiol. 2012;5:499-505.)

Key Words: arrhythmogenic right ventricular dysplasia • catheter ablation • tachycardia ventricular
mapping systems and epicardial VT ablation, (2) to evaluate the complications associated with VT ablation in patients with ARVD/C, and (3) to determine the impact of catheter ablation on the burden of VT.

Methods

Study Population
The study population included 87 patients enrolled in the Johns Hopkins ARVD Registry who were classified as having definite ARVD/C according to 2010 revised task force criteria and who had undergone ≥1 attempts at RFA for treatment of VT. The result of RFA in 24 of these patients was included in an earlier investigation. A total of 175 RFA procedures were performed in this cohort between 1992 and 2011 at 80 different electrophysiology (EP) centers throughout the United States and Canada. The majority (55%) of the total RFA procedures were performed in 33 academic centers that were affiliated with a medical school. Among the procedures performed at academic centers, 44% were performed at the Brigham and Women’s Hospital, Johns Hopkins Hospital, and the Hospital of the University of Pennsylvania.

Of the entire cohort, 23 patients with ARVD/C underwent 26 epicardial catheter ablation procedures, which were performed in 8 referral centers specialized in catheter ablation of VT. Nineteen of the 23 patients had at least 1 previously failed endocardial ablation procedure. In these cases, the decision to proceed with an epicardial ablation procedure was based on the findings from the prior electrophysiology study in which endocardial mapping suggested an epicardial VT circuit and endocardial ablation was unsuccessful. The decision to perform an epicardial ablation as the first procedure among 4 patients was guided both by recent publications in this field and the discretion of the electrophysiologist. Ten procedures were solely epicardial, with the remainder being endocardial and epicardial procedures.

All patients included in this registry provided written informed consent. The study was approved by the Johns Hopkins School of Medicine Institutional Review Board.

Data Collection
Detailed clinical information regarding noninvasive and invasive testing was available for each patient. Electrophysiology procedure reports for all RFA procedures were obtained. Details of electroanatomic mapping, type of ablation catheter, and the particular ablation strategy and acute outcomes of the RFA procedure were recorded.

Electrophysiology Study, Mapping, and Ablation Techniques
Electrophysiology testing and RFA procedures, including conventional mapping and ablation techniques and substrate-based ablation targeting isolated late potentials, have been previously described. Clinical VTs were defined by comparison of a 12-lead ECG of spontaneous and induced VT and when not available, by comparison of induced and spontaneous VT cycle lengths and stored ICD electrograms. Conventional endocardial mapping and ablation techniques included pace mapping, activation mapping, and entrainment mapping. Electroanatomic mapping, including activation and voltage mapping, facilitated ablation during many of the procedures. Epicardial mapping and ablation was performed in a subset of patients by accessing the pericardium through a percutaneous subxiphoid puncture, as previously described.

Catheters used for mapping and ablation included the standard 4-mm-tipped deflectable ablation catheter or the 3.5-mm externally irrigated-tip catheter (Thermocool; Biosense Webster). Acute procedural success was defined as total if all VTs remained noninducible during programmed stimulation, partial if clinical VT was noninducible but other VT morphologies remained inducible, and failure if clinical VT remained inducible at the end of the ablation.

Follow-up
All patients were followed routinely by their treating electrophysiologist and contacted at yearly intervals. In patients with ICDs, the interrogation reports were reviewed by an experienced electrophysiologist (H.C.). Recurrence of VT and appropriateness of ICD therapy were determined based on review of the stored electrograms. In patients without ICDs, VT recurrence was based on documented sustained VT on event monitoring or clinical presentation with sustained VT. Any VT recurrence during follow-up, whether symptomatic, treated, or untreated, was considered as a failure. Arrhythmia burden was determined in a subset of patients in whom complete ICD interrogation information was available for detailed review and analysis for 1 year before and after the ablation. In rare cases in which there were multiple procedures within 1 year, the rate of sustained VT per month was extrapolated from a shorter time period.

Definitions
Sustained VT was defined as tachycardia originating in the ventricle with a rate of >100 beats/min and similar QRS morphology from beat to beat lasting ≥30 s or that requires an intervention for termination. VT recurrence was defined as appropriate ICD intervention or spontaneous, sustained VT based on the analysis of a 12-lead ECG, event monitor, or 24-hour Holter monitor subsequent to the ablation procedure. VT burden was defined as the rate of appropriate ICD intervention per month and compared between the 1-year interval before and after catheter ablation.

Survival Data and Statistical Analysis
Continuous variables are expressed as mean±SD and categorical variables as frequency (percent). Follow-up time was determined from the time of the procedure until the occurrence of a VT event, loss to follow-up, heart transplant, or death. Kaplan-Meier survival analysis was used to determine the cumulative VT recurrence and ICD shock-free survival in the study population.

The patients who had ≥1 procedure were reentered into the survival analysis after their initial recurrence and were followed up until they experienced an event or were censored again. To include the subsequent procedures in the survival analysis, a staggered entry approach was used. This process was repeated for each time that a new RFA procedure was performed on the same patient. Repeated procedures performed on the same patient were assumed to be independent. Comparisons in the cumulative event-free survival were made using the log-rank test. The burden of VT before and after an ablation procedure was compared using the Wilcoxon signed rank test.

All data analyses for research aims were performed using SAS version 9.2 (SAS Institute) software. P<0.05 was considered significant.

Results

Patient Characteristics
The patient population comprised 87 patients who underwent RFA for VT. The baseline characteristics of the study population are listed in the Table. The mean age at the first procedure was 38±13 years, and 45 (52%) patients were men. The majority (95%) of patients had an ICD, except for 5 (5%) patients who did not have an ICD at the end of follow-up. All patients met the revised diagnostic criteria for definite ARVD/C.

Of the 87 patients, 18 required a single procedure, with the remainder requiring an average of 2.3 procedures (range, 2–5 procedures). Thirty-eight percent of patients had failed on at least 1 class 1 or 3 antiarrhythmic medication before their first ablation procedure, whereas 59% had failed on at least 1 antiarrhythmic drug before their last ablation procedure. Fifty-six percent of patients remained on an antiarrhythmic medication after their most recent ablation procedure.
Among patients who had undergone an epicardial catheter ablation, 63% were on antiarrhythmic drug therapy before catheter ablation, whereas 41% remained on antiarrhythmic drug therapy during the follow-up period. Sotalol was the most frequently used antiarrhythmic medication followed by amiodarone.

Electrophysiology Study, Mapping, and Ablation
Three-dimensional electroanatomic mapping was used to facilitate ablation in 114 (69%) of 166 total procedures in which information on the use of a mapping system was available. Radiofrequency energy was delivered through an irrigated-tip catheter during 50 (29%) procedures and through a standard 4-mm-tipped deflectable ablation catheter in the remaining procedures. The clinical VT was successfully ablated in 82% of the procedures. Total acute success was observed in 47%, partial success in 38%, and procedural failure in 15% of 160 procedures (this information was unavailable for 12 procedures). Forty-six (53%) of 87 patients underwent repeat procedures.

Impact of Catheter Ablation on VT Recurrence
The mean follow-up duration was 88.3±66.1 months (median, 72.1 months). VT recurrence-free survival for the 175 procedures in 87 patients is shown in Figure 1. Freedom from VT after a single endocardial RFA was 45% (95% CI, 36.6–52.6), 29% (95% CI, 21.6–36.6), and 19% (95% CI, 12.7–26.7) compared to 64% (95% CI, 44.1–82.8), 45% (95% CI, 23.9–72.3), and 45% (95% CI, 23.7–71.0) after a single epicardial RFA at 1, 2, and 5 years, respectively (P=0.021). The cumulative VT-free survival after a single endocardial ablation procedure was 75% at 2.4 months, 50% at 8.4 months, and 25% at 33.6 months. The cumulative VT-free survival after a single epicardial RFA was 75% at 9.6 months and 50% at 16.8 months. Additionally, there were 10 epicardial procedures and 8 endocardial procedures matched by age, 3D mapping technique, repetition of procedure, and center performing RFA among 18 patients who underwent catheter ablation after 2005. VT-free survival was significantly longer after epicardial RFA than after endocardial RFA among this matched cohort (P=0.003) (data not shown). VT-free survival was significantly longer among patients in whom a 3D electroanatomic mapping system was used to

Table. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Overall Population (N=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at time of first procedure, y</td>
<td>38±13</td>
</tr>
<tr>
<td>Male sex</td>
<td>45 (52)</td>
</tr>
<tr>
<td>ICD implantation</td>
<td></td>
</tr>
<tr>
<td>Before first procedure</td>
<td>38 (44)</td>
</tr>
<tr>
<td>At follow-up*</td>
<td>44 (51)</td>
</tr>
<tr>
<td>No ICD</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Drugs, baseline/follow-up*</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>8 (9/18 (21)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>15 (18/22 (26)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>0 (0/2 (2)</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>1 (1)/0 (0)</td>
</tr>
<tr>
<td>Procainamide</td>
<td>1 (1)/1 (1)</td>
</tr>
<tr>
<td>Quinidine</td>
<td>0 (0)/1 (1)</td>
</tr>
<tr>
<td>Mexiletine</td>
<td>4 (4)/4 (4)</td>
</tr>
<tr>
<td>Flecainide</td>
<td>3 (4)/1 (1)</td>
</tr>
<tr>
<td>Propafenone</td>
<td>2 (2)/1 (1)</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD or n (%). ICD indicates implantable cardioverter-defibrillator.

*Follow-up represents the interval after last catheter ablation procedure.
†Baseline represents the interval before first catheter ablation procedure.
facilitate the ablation procedure (Figure 3). Freedom from VT following a single ablation procedure facilitated by 3D electroanatomic mapping was 50% (95% CI, 40.5–58.9), 34% (95% CI, 25.5–44.4), and 24% (95% CI, 15.4–34.7) compared to 36% (95% CI, 23.3–49.3), 16% (95% CI, 7.2–27.1), and 8% (95% CI, 2.2–16.9) following a single ablation procedure not facilitated by 3D electroanatomic mapping at 1, 2, and 5 years, respectively (P=0.016). Survival analysis showed no significant differences in freedom from VT based on acute procedural success (total success, partial success, or failure of ablation procedure), repetition of ablation procedure, type of ablation catheter (standard versus irrigated), and the facility where the ablation was performed (academic versus community hospital) (all P>0.05) (data not shown).

Impact of Catheter Ablation on VT Burden
Forty-three patients had detailed data on the frequency of VT 1 year before and 1 year after the RFA procedure. Figure 4 illustrates VT burden 1 year before and after all RFA procedures. The mean frequency of VT was significantly lower after VT ablation (0.2±0.4 VT episodes/month; median, 0.08 VT episodes/month [2±5 episodes/year]) compared with the VT frequency before ablation (0.4±0.5 VT episodes/month; median, 0.16 VT episodes/month [5±6 episodes/year]; P<0.001) (Figure 4A). Among epicardial catheter ablation procedures, the mean VT burden was reduced from 0.42±0.4 episodes/month (median, 0.2 episodes/month) before RFA to 0.05±0.1 episodes/month (median, 0.0 episodes/month) after RFA (P<0.001) (Figure 4B).

Complications
There were 2 major complications in this cohort, and both were associated with epicardial mapping and ablation. One patient developed incessant VT with associated hypotension during the procedure refractory to pharmacological and mechanical support, resulting in emergent thoracotomy. He later died of postoperative pulmonary complications. The other major complication was delayed myocardial infarction 10 days after an epicardial mapping and ablation procedure. The patient had an occlusion of the distal posterior descending branch of the right coronary artery, which did not undergo intervention.

Discussion
This comprehensive study reports the outcomes among 87 patients with definite ARVD/C undergoing catheter ablation of VT at 80 different centers in the United States and Canada. To our knowledge, this study represents the largest cohort of patients with ARVD/C to date who have undergone catheter ablation of VT and most closely reflects the outcomes achieved in widespread clinical practice. There are several main findings of the study. First, the overall results reveal a high rate of VT recurrence after catheter ablation among patients with ARVD/C. Second, although the increasing use of electroanatomic mapping systems and epicardial ablation strategies are associated with longer freedom from VT, recurrences remain common. Finally, catheter ablation results in a significant reduction in the burden of VT among patients with ARVD/C, regardless of ablation strategy.
Efficacy of Catheter Ablation of VT in ARVD/C

Prior Reports

The novel approach of treating VT in patients with ARVD/C with catheter ablation using direct current fulguration was first described by Fontaine and colleagues during the late 1980s.\textsuperscript{15-21} Subsequently, catheter ablation of VT using radiofrequency energy was described in 6 patients with ARVD/C in 1992.\textsuperscript{22} Since then, there have been numerous studies investigating RFA outcomes in VT in patients with ARVD/C. These studies have reported variable rates of short- and long-term success after catheter ablation of VT.\textsuperscript{6-9,11,19-21,23-31} Our group and others have reported poor long-term outcomes following conventional RFA in ARVD/C.\textsuperscript{29} Interpretation of these results is complicated by varying mapping and ablation strategies, differing definitions of procedural success, variable follow-up, single-center studies, and operator experience.

However, over the past several years, the strategy and technology involved in mapping and ablation of VT in patients with ARVD/C has evolved.\textsuperscript{32} The limitations of conventional mapping, such as noninducibility or hemodynamic instability, were overcome by using a substrate-based mapping strategy facilitated by the use of electroanatomic mapping systems. Marchlinski et al\textsuperscript{28} defined the perivalvular substrate using electroanatomic mapping and reported good outcomes with a substrate-based ablative strategy in 19 patients with ARVD/C. Using this technique, Verma et al\textsuperscript{30} reported good short-term success, but VT recurrences became increasingly common during long-term follow-up.

The pathological substrate in ARVD/C often is diffuse and involves the epicardium.\textsuperscript{3} The variable results achieved with catheter ablation may be related to inadequate characterization of the substrate. The importance of the epicardial approach was first recognized by Fontaine et al,\textsuperscript{24} who attempted epicardial ablation in a few cases with failed endocardial ablation. More recently, Garcia et al\textsuperscript{31} showed that the scar in ARVD/C is predominantly epicardial, and isolated late potentials were much more frequently encountered in the epicardium in ARVD/C. In their cohort, a simultaneous endocardial/epicardial substrate-based ablation strategy was associated with low recurrence rates of VT during long-term follow-up. Schmidt and colleagues\textsuperscript{32} corroborated these findings by showing that the presence of an epicardial substrate in ARVD/C was high (83\%), and 90\% of the successful procedures, defined as abolishing the clinical VT, required an epicardial approach. They reported recurrence of sustained VT in 38\% patients with ARVD/C during follow-up. Additionally, a recent prospective, multicenter study showed that an endocardial/epicardial ablation strategy was associated with higher long-term freedom from VT compared with endocardial ablation in patients with ARVD/C.\textsuperscript{10}

Impact of RFA on VT Recurrence

The study results are representative of catheter ablation outcomes achieved in broad clinical practice and reveal that freedom from VT was only 15\% among all procedures at 10-year follow-up, with the majority of events occurring within the first year after catheter ablation. The majority of patients in the present cohort required several catheter ablation procedures and continued to remain on antiarrhythmic drug therapy during long-term follow-up. Despite the considerable rate of VT recurrence among the overall cohort, the use of electroanatomic mapping and epicardial-based ablation strategies are associated with longer survival free of VT recurrence.

The benefits of an epicardial catheter ablation need to be carefully weighed against the risks associated with percutaneous subxiphoid pericardial access, mapping, and ablation. In the present cohort, all the complications associated with catheter ablation occurred in patients undergoing epicardial catheter ablation. Among all epicardial procedures, there was a 7.7\% incidence of major complications. This is consistent with the findings of Sacher and colleagues,\textsuperscript{33} who reported the risk of an acute or delayed complication to be 7\%. Given these findings, epicardial catheter ablation generally should be considered after an endocardial ablation procedure fails. As with other complex procedures, the best results are likely to be achieved at centers with a particular interest in VT ablation.

Interestingly, successful ablation of the clinical VT in patients with ARVD/C does not translate into improved long-term survival free of VT. This finding emphasizes the importance of an ablation strategy targeting not only the critical circuit responsible for the clinical VT, but also all regions of slow conduction because of the existence of multiple reentrant pathways. Additionally, unlike other arrhythmias, such as atrial fibrillation, repetition of the procedure did not result in improved long-term survival free of VT. This may possibly be related to a progressive disease process or inadequate substrate modification. Further, there was no significant discrepancy in outcomes between procedures performed in community and academic hospitals, suggesting homogeneity in the level of expertise among centers. However, these data do not reflect individual centers, and it is possible that outcomes may vary among centers that specialize in catheter ablation of VT.

Impact of RFA on VT Burden

To date, only 1 single-center study has evaluated the burden of VT after RFA in a very small population of patients with ARVD/C.\textsuperscript{26} In the present study, among all catheter ablation procedures, the mean burden of VT was significantly reduced after RFA when comparing appropriate ICD interventions in the year before and after catheter ablation. Similarly, among epicardial ablation procedures, there was a significant decrease in the mean VT burden. Therefore, although VT recurrences are common after catheter ablation, the burden of VT is significantly decreased regardless of the ablation strategy, which in itself is sufficient justification for treatment of recurrent VT with catheter ablation.

Clinical Implications

Recurrence of VT after catheter ablation is not uncommon in ARVD/C and emphasizes the fact that catheter ablation cannot be considered as curative in the long term and should not be viewed as an alternative to placement of an ICD. On the other hand, catheter ablation of VT in patients with ARVD/C does reduce VT burden, and because of this, it should be viewed as an important treatment option for the subset of patients who experience frequent recurrences of VT despite ≥1 antiarrhythmic medications. Catheter ablation of VT is also an important treatment option in patients who
experience intolerable side effects to antiarrhythmic medications or who prefer not to take antiarrhythmic medications. Although epicardial catheter ablation is more effective than endocardial procedures, it should generally be considered after a prior failed endocardial ablation procedure given the higher complication rates associated with pericardial access, mapping, and ablation. This recommendation is tempered by a particular institution’s experience and outcomes. In certain highly experienced centers, an initial combined endocardial/epicardial approach would also be appropriate.

Limitations
The study has several limitations. First, because the data were obtained as a part of a large registry, it is likely that there might be significant variability in the level of experience and expertise in catheter ablation of VT among the centers that perform these procedures. Although this is a limitation of the data, it also represents a strength because the results are likely to be applicable to the large body of electrophysiologists interested in catheter ablation of VT. In this regard, it is notable that the data showed no difference in outcomes between tertiary referral versus community centers. Second, many patients were referred to our hospital for further evaluation and management ARVD/C, which may have resulted in selection bias. This issue can only be resolved by a prospective, randomized study. Third, ICD programming changes following RFA were not systematically tracked when assessing VT recurrences and burden. However, we included both ATP therapy and ICD shock in the analysis. Fourth, correlation of the use of antiarrhythmic drugs based on physician preference and arrhythmia occurrence during follow-up. Fifth, staggered entry survival analysis may have been inadequate to discern the differences between subgroups and to account for the relatedness of repeat procedures within the same patient. However, we found no difference in survival free of VT between first or repeat procedures. Finally, the follow-up on patients who underwent epicardial ablation procedures was shorter because the majority of these procedures were performed in the past 5 years. However, the majority of VT recurrences among all the procedures occurred within the first year.

Conclusions
Although the use of advanced mapping systems and epicardial substrate-based ablation strategies are associated with improved catheter ablation outcomes in ARVD/C, VT recurrence rates remain considerable. However, catheter ablation of VT in patients with ARVD/C results in a significant reduction in the frequency of VT episodes, regardless of the ablation strategy. Epicardial ablation procedures were associated with a 7.7% risk of major complications.

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Disclosures
Dr Calkins is a consultant for Biosense Webster and Medtronic Inc. The other authors report no conflicts. The Johns Hopkins University Conflict of Interest Committee manages all commercial arrangements.

References
Studies evaluating the efficacy of catheter ablation of ventricular tachycardia (VT) among patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) have reported varied outcomes using an endocardial-based ablation strategy. More recent studies have suggested that epicardial ablation is necessary for improved outcomes after catheter ablation of VT. This comprehensive study reports the outcomes among 87 patients with definite ARVD/C who underwent a total of 175 radiofrequency catheter ablation procedures (RFA) for VT at 80 different centers in the United States and Canada. Twenty-three ARVD/C patients underwent 26 epicardial catheter ablation procedures. During a mean follow-up of 88.3 ± 45 months, the overall freedom from VT among patients was 47%, 21%, and 15% at 1, 5, and 10 years, respectively. Cumulative freedom from VT following a single epicardial RFA was 45%, 29%, and 19% compared with 64%, 45%, and 45% following a single epicardial RFA at 1, 2, and 5 years, respectively ($P<0.021$). The use of 3-dimensional electroanatomical mapping was associated with longer survival free of VT ($P=0.016$). Further, catheter ablation resulted in a significant reduction in VT burden, regardless of ablation strategy ($P<0.001$). Last, there was a 7.7% incidence of major complications among epicardial ablation procedures. In summary, although the use of advanced mapping systems and epicardial substrate-based ablation strategies are associated with improved catheter ablation outcomes in ARVD/C, VT recurrence rates remain considerable. Although VT recurrences are common, RFA results in a significant reduction in the burden of VT in ARVD/C patients. The benefits of an epicardial ablation approach need to be carefully weighed against the risks associated with the procedure.
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