Drug-Refractory Ventricular Tachycardias Following Myocarditis:
Endocardial and Epicardial Radiofrequency Catheter Ablation

Running title: Dello Russo et al.; Ventricular tachycardia in myocarditis

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Abstract:

**Background** - Ventricular tachycardia (VT) is a significant therapeutic challenge in patients with myocarditis. This study aimed to assess the efficacy and safety of radiofrequency catheter ablation (RFCA) of VT in pts with myocarditis.

**Methods and Results** - We enrolled 20 patients (15 males, age 42 [28-52] years) with a history of biopsy-proven viral myocarditis and drug-refractory VT; 5 patients presented with electrical storm. The median left ventricular ejection fraction was 55 (45-60)%. All patients underwent endocardial RFCA with an irrigated catheter, using contact electroanatomical mapping. Recurrence of sustained VT after endocardial RFCA was treated with additional epicardial RFCA. Endocardial RFCA was acutely successful in 14 patients (70%), while in the remaining 6 (30%) clinical VT was successfully ablated by epicardial RFCA. In one patient, hemodynamic instability required an intraaortic balloon pump to complete RFCA. No major complication occurred during or after RFCAs. Over a median follow-up time of 28 (11-48) months, 18 patients (90%) remained free of sustained VT; two patients (10%, both with baseline LVEF ≤ 35%) died of acute heart failure unrelated to ventricular arrhythmias.

**Conclusions** - In patients with myocarditis, RFCA of drug-refractory VT is feasible, safe and effective. Epicardial RFCA should be considered as an important therapeutic option to increase success rate.

**Key words:** myocarditis, ventricular tachycardia, catheter ablation
Introduction

Myocarditis is simply defined as an inflammatory condition mainly located in the heart muscle,\(^1\) although considerable uncertainties still persist as to its aetiological, pathological and clinical sub-classifications.\(^4,5\) In addition to the possibility of an aspecific flu-like prodrome, possible presentations include different degrees of heart failure (ranging from cardiogenic shock to subtly progressive chronic heart failure), chest pain, conduction anomalies, brady- and tachyarrhythmias (including sudden cardiac death). The clinical course is also variable,\(^6-9\) as a spontaneous recovery may occur after the acute phase in up to 50% of patients, while chronic myocarditis and dilated cardiomyopathy sustained by viral persistence and/or autoimmune self-perpetration represent a common evolution of the disease.

Myocarditis may cause arrhythmias both in its acute phase, due to inflammatory infiltration and myocyte necrosis, and in its chronic phase, due to immune reaction, fibrosis, and resulting electrical remodeling. Therapy is essentially supportive for arrhythmias in the acute phase of disease, which can last several weeks but may regress spontaneously. Even in chronic myocarditis, therapy is largely confined to antiarrhythmic drugs, with limited efficacy, and to implantable cardioverter-defibrillator (ICD) for higher-risk cases, such as those with hemodynamically unstable ventricular tachycardia (VT) and aborted sudden cardiac death.\(^2,3,10\) Radiofrequency catheter ablation (RFCA) has been demonstrated to be effective in reducing VT occurrence in patients with Chagas cardiomyopathy.\(^11\) In non-Chagasic myocarditis, isolated reports suggest that RFCA of VT may be effective,\(^12-14\) but its safety and long-term efficacy in this setting is unclear. This study evaluates safety and effectiveness of RFCA in a series of consecutive patients with persisting drug-refractory VTs following a biopsy diagnosis of myocarditis.
Methods

Patient population

We enrolled 20 consecutive patients (15 males) with biopsy-proven myocarditis and drug-refractory VTs who had been referred for RFCA between January 2008 and December 2010. In all patients the diagnosis of viral myocarditis was based on Dallas and immunohistochemical criteria.15

The study was approved by the institutional review board, and all patients gave their written informed consent. Non-invasive investigations before RFCA included chest X-rays, 12-lead ECG and color-Doppler echocardiography. Invasive characterization of the myocardial substrate was also performed before VT ablation and included coronary, left ventricular (LV) and right ventricular (RV) angiography, three-dimensional electro-anatomic mapping (EAM) and endomyocardial biopsy guided by EAM whenever low-voltage zones were observed, or otherwise performed at the interventricular septum.16-18

Mapping and endocardial ablation procedure

Via transfemoral puncture, a quadripolar catheter was placed at the RV apex and the RV outflow tract; a ventricular stimulation study was performed with up to three extra-stimuli to induce VT. Three-dimensional EAM was aided by CARTOSOUND™ intracardiac echocardiography (Biosense Webster, Diamond Bar, CA, USA).19, 20 In all patients a 3.5 mm open irrigated ablation catheter (Biosense Webster) was used for ventricular mapping. We decided whether to map the RV or LV by presuming the most likely origin of the arrhythmia based on surface ECG criteria. During LV endocardial mapping, performed through a retrograde aortic or trans-septal approach, heparin was administered intravenously to maintain a target activated clotting time of 300 s. Detailed substrate mapping of the chambers of interest was obtained. In accordance with
previous studies, the reference value for normal endocardium bipolar signal amplitude was set at 1.5 mV.\textsuperscript{18, 21} In patients with hemodynamically tolerated VT, activation mapping, entrainment mapping and pace-mapping maneuvers were performed. If VTs were not inducible or were hemodynamically unstable, pace mapping was performed and areas of scar were circumscribed with radiofrequency (RF) pulses, delivered with a maximum power of 40 W and at a maximum temperature of 43°C.

After ablation, all patients were monitored in the electrophysiology laboratory for up to an hour; also, VT reinduction was attempted with up to three ventricular extra-stimuli with and without isoprenaline infusion.

**Epicardial ablation procedure**

In patients in whom endocardial ablation failed (including three who had undergone previous ablation at another Institution), epicardial RFCA was performed, with the same instrumentation described above, with the addition of epicardial mapping via the sub-xiphoid approach.\textsuperscript{22}

Intracardiac echocardiography (ICE) was used to assess the presence of possible pericardial effusion and to locate critical structures, such as the coronary arteries. After completing EAM, the above-mentioned criteria were used to select sites for RF pulses, which were delivered with a maximum power of 45 W and at a maximum temperature of 41°C. Ablation was performed remote from the left coronary arteries based on selective coronary angiography. In regions close to the phrenic nerve, high-output pacing (20 mA) was performed via the ablation catheter, and these locations were marked on the EAM. Post-ablation monitoring and reinduction attempts were performed as described above.

**Clinical follow-up and outcomes**
After discharge, each patient was re-evaluated and underwent 24-hour ECG Holter monitoring at 1, 3, 6 months after ablation, and thereafter every six months. In ICD carriers, device memory was used to detect VT episodes.

**Statistical analysis**

Continuous variables are reported as median with first and third quartiles (Q1-Q3), while categorical variables are reported as frequencies and percentages. Between-group (e.g., patients with recurrent VT vs. those who remained free from VT at follow-up) comparisons were performed with the Wilcoxon rank sum test. Within group comparisons of pre- and post-ablation values of continuous variables (e.g., left ventricular ejection fraction) were performed with the Wilcoxon signed-rank test. All tests were 2-sided, and a value of \( P < 0.05 \) was considered statistically significant. Statistical analyses were performed using the STATA 10.0 (Stata Corporation, College Station, Texas, USA) statistical package.

**Results**

**Patient characteristics**

Table 1 shows the clinical characteristics of the 20 enrolled patients (median age 42 [28-52] years, 15 males). Pre-ablation echocardiography showed a median LV ejection fraction (LVEF) of 55% (45%-60%). (Table 1)

EAM-guided biopsy was performed a median of 5 (3-5) months before ablation and showed in all patients active myocarditis according to Dallas criteria, with immunohistochemical evidence of activated T lymphocytes. No evidence of sarcoid granulomas or giant cells was observed in any myocardial specimen. On the basis of persistent ventricular arrhythmias and histological findings, all patients received a diagnosis of chronic active myocarditis at the time of biopsy.
The patients had been suffering from documented ventricular arrhythmias for a median of 8 (6-24) months (range: 1-36 months) and all had proven refractory to antiarrhythmic therapy with 2.1±1.4 drugs, including amiodarone in 9 patients (45%). Three patients (15%) had been previously implanted with an ICD. Five (25%) presented with electrical storm, including all three ICD carriers. Three patients (15%) came to our attention following an unsuccessful previous RFCA at another institution.

After ablation, one patient (5%) was implanted with an ICD before discharge because, in addition to having LVEF 35%, she also showed alternating bundle branch block and symptomatic paroxysmal 2nd-degree type II atrioventricular block.

Electrophysiologic features and short-term success of RFCA

Table 2 summarizes electrophysiological findings in enrolled patients. (Table 2)

Clinical VT could be induced on programmed stimulation from the endocardium in 19/20 patients (95%) and from the LV epicardium only in the remaining one (5%). The induced VTs had a median cycle length of 300 (270-350) ms, were all monomorphic, and originated from the LV in 12/20 (60%) patients and from the RV in the remaining 8/20 (40%); VTs were associated with a low-voltage in 12/20 patients (60%), while the remaining 8/20 (40%) there were no low-voltage areas on electroanatomical mapping.

In 3/20 patients (15%), VTs were invariably associated with haemodynamic instability and stabilization required inotropic support (in two patients) or intra-aortic balloon pump counter-pulsation (in one patient). The remaining 17/20 (85%) had tolerated VTs and underwent complete activation and entrainment mapping.

Endocardial RFCA was acutely successful in 14/17 (82%) patients undergoing their first ablation at our Institution; the remaining 3/17 (18%) cases included two patients in whom endocardial
RFCA proved ineffective and one in whom no arrhythmia could be induced by endocardial RV and LV stimulation. Figure 1 shows a case of effective endocardial RFCA using electroanatomic mapping aided by intracardiac echocardiography. (Figure 1)

In the 6/20 patients (30%) in whom endocardial RFCA was ineffective or infeasible, epicardial ablation was performed 10 days (range: 2-27) after the previous endocardial procedure; in these patients VT was found to originate from the RV in one patient, from the LV in the remaining five. Epicardial RFCA was performed from the coronary sinus in one patient and by a sub-xiphoid approach in the other five, in all cases with acute success. Figures 2-4 illustrate the case of a patient with failed endocardial RFCA and subsequent successful epicardial ablation. (Figure 2-4)

No major complication occurred during the procedures or the remaining hospital stay. At discharge, antiarrhythmic drug therapy was continued in 7/20 patients (35%).

**Long-term outcome**

After a median follow-up of 28 (11-48) months, 3/20 patients (15%) remained on antiarrhythmic drugs: 1 patient (5%) because of frequent polymorphic premature ventricular beats and 2 (10%) because clinical sustained VT recurred. Figure 5 shows long-term freedom from recurrent VT by the Kaplan-Meier survival analysis. (Figure 5)

One year after RFCA, there was a statistically significant increase in median LVEF (56% [45%-60%] vs. 60% [57%-63%], p < 0.001). In one case, after two years without VT episodes, the ICD was removed at the patient’s request.

Two patients (10%) died during follow-up. The one patient with LVEF 33% in whom intraaortic balloon contropulsation had been necessary during RFCA ultimately died of acute heart failure two months after discharge; ICD interrogation excluded ventricular tachyarrhythmias as the
precipitating factor. The other patient had LVEF 35% and had originally presented with electrical storm; three months after discharge, he developed bacterial endocarditis requiring cardiac surgery and ultimately died of post-operative complications.

Discussion

Main findings

This case series of consecutive patients with biopsy-proven myocarditis is the first study to evaluate prospectively the safety and efficacy of RFCA in this clinical setting. Our results demonstrate that RFCA of drug-refractory VTs persisting over months following a diagnosis of myocarditis is feasible without major complications and is associated with a high acute success rate. At long-term follow-up, up to 90% of patients remained VT-free, while there was a small increase (about 5%) in LVEF over time. The relative stability of ventricular function over time corroborates the notion that patients were treated in a phase of consolidated disease; this might suggest that the disappearance of ventricular arrhythmias might be mainly credited to a successful RFCA. Moreover, during follow-up, 2/10 patients (10%) with reduced LVEF died, which is consistent with current epidemiological data on myocarditis.1, 8, 9

Ventricular arrhythmias in myocarditis

Patients with myocarditis frequently display a wide spectrum of conduction disturbances, atrial and ventricular tachyarrhythmias.23-25 When arrhythmias persist beyond the acute phase, the arrhythmogenic substrate consists of replacement fibrosis and chronic inflammation, which may be related to self-maintaining autoimmune mechanisms, or to viral persistence when a virus is the cause. A recent study with FDG-PET in patients with sustained monomorphic ventricular tachycardia and sarcoidosis or tuberculosis, demonstrated that myocardial inflammation may
cause life-threatening ventricular arrhythmias and abnormal electroanatomic mapping findings even in the absence of scar at cardiac magnetic resonance and in the presence of normal ventricular dimensions and function.26

Moreover, it has been demonstrated that continuing myocardial damage can persist even in the absence of overt inflammation, for example through the release of viral proteases capable of cleaving cytoskeletal dystrophin.27,28

The 2006 ESC/ACC/AHA guidelines on ventricular arrhythmias and sudden cardiac death 10 recommend drug therapy for life-threatening ventricular arrhythmias in myocarditis. In the acute phase, treatment is usually largely supportive. This can then be associated with possible ICD implantation if arrhythmias persist after the acute phase despite pharmacotherapy. RFCA is not mentioned at all in this context and is not contemplated in more specific guidelines on myocarditis.2, 3 This absence reflects the lack of specific evidence on RFCA of VT in myocarditis, as most of the published evidence consists of case reports.12-14, 29

A significantly larger body of published evidence is available on RFCA of VTs in patients with Chagas disease, a dilated cardiomyopathy due to infestation by the protozoan Trypanosoma cruzi.11

In these patients, RFCA (both endocardial and epicardial) has been demonstrated to reduce VT recurrences,30-32 which might in turn help reduce shocks in ICD carriers.

Similarly, effective RFCA has been reported in patients with cardiac sarcoidosis,33,34 whose inflammatory granulomatous lesions often produce structural and clinical features resembling ARVC, representing an important cause of ventricular arrhythmias and sudden cardiac death.

**Procedural considerations**
We feel the choice of resorting to an irrigated ablation catheter is justified by the need for deeper RF lesions, in consideration of the high likelihood of intramural and/or subepicardial disease involvement.

Of the utmost interest is the finding that an epicardial RFCA was needed to suppress VT in 6/20 patients (30%), in five because endocardial lesions were ineffective and in one because they were not attempted as VT could only be induced by LV epicardial stimulation. This supports the concept that VTs may involve intramural or epicardial reentry circuits, as in fact, pathology and MRI studies indicate that in myocarditis the inflammatory process frequently starts from the epicardium. Accordingly, De Cobelli and colleagues found that in patients with chronic myocarditis presenting with either heart failure or ventricular arrhythmias and with MRI evidence of late enhancement, the latter was intra-mural in 62.5% of cases and subepicardial in the remaining 37.5%.35 In our study, epicardial RFCA too was shown to be feasible, safe and effective.

The use of intracardiac echocardiography is a standard approach in VT ablation for all operators involved in this study. It proved useful not just in its ability to monitor for pericardial effusion, but also to locate structures of critical importance (such as the coronary arteries) and to confirm the adherence of EAM to ventricular anatomy. We feel this could also help to better visualize subtle morphological anomalies, such as microaneurysms, which were indeed present in one of our patients, or motion anomalies which might suggest presence of scar.

Study limitations

We recognize that the natural history of VTs in myocarditis has not been adequately documented, therefore RFCA success and disease regression act as reciprocal confounders when evaluating long-term freedom from VT. Even when biopsy documents immunologically active
chronic inflammation, this may not necessarily be the pathological substrate sustaining VT persistence indefinitely, as inflammation may become quiescent and still arrhythmias may be caused by “spent” residual myocardial damage. A distinction between ongoing inflammation and residual injury cannot be made on clinical grounds alone, and no precise evidence basis is available on whether the two possibilities carry different prognostic implications that might justify repeat invasive and/or costly investigations. In addition, we recognize that in view of the high incidence of intramural and subepicardial disease, in selected cases an epicardial approach to RFCA may be reasonable from the start, rather than defaulting to a second-line option as we did, and that ECG and/or MRI findings\(^{35}\) might help guide this choice.

**Conclusions**

Radiofrequency catheter ablation of VTs in patients with chronic active myocarditis is safe, feasible and effective in eliminating VTs. Epicardial ablation should be considered as an important option to increase the success rate in these patients.

**Acknowledgments:** The authors thank Eng. Daniela Gravina and Lorenza Pirola (Biosense Webster, Italy) for their expert technical support.

**Conflict of Interest Disclosures:** C.T. has served as a member of the advisory board of Biosense Webster and has been a consultant for, and received lecture fees from, St Jude Medical. A.N. has received compensation for belonging to the speakers’ bureau for St Jude Medical, Boston Scientific, Medtronic, and Biosense Webster and has received a research grant from St Jude Medical. A.N. is also a consultant for Biosense Webster. L.D.B. is a consultant for Hansen Medical and Biosense Webster. The other authors declare no significant relationships with industry.
References:


Table 1. Baseline clinical features of enrolled patients

<table>
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<tr>
<th>Feature</th>
<th>Patients (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>42 (28-52)</td>
</tr>
<tr>
<td>Males</td>
<td>15/20 (75%)</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>55 (45-60)</td>
</tr>
<tr>
<td>LV ejection fraction ≤40%</td>
<td>4/20 (20%)</td>
</tr>
<tr>
<td>Previous ICD implantation</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Previous VT ablation</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>VT episodes in previous 6 months</td>
<td>11 (2-18)</td>
</tr>
<tr>
<td>Spontaneous VT cycle (ms)</td>
<td>335 (307-360)</td>
</tr>
</tbody>
</table>

Values express as number of patients (%) or as median (Q1-Q3).
LV = left ventricle; ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia
Table 2. Electrophysiological and procedural features of enrolled patients

<table>
<thead>
<tr>
<th>Patients (n = 20)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced VT cycle (ms)</td>
<td>300 (270-350)</td>
</tr>
<tr>
<td>Non-tolerated VT induced</td>
<td>3/20 (15%)</td>
</tr>
<tr>
<td>Number of VTs induced per patient</td>
<td>1 (1-1)</td>
</tr>
<tr>
<td>VT origin from the RV</td>
<td>8/20 (40%)</td>
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<tr>
<td>RV outflow tract</td>
<td>6/8 (75%)</td>
</tr>
<tr>
<td>RV free wall</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>VT origin from the LV</td>
<td>12/20 (60%)</td>
</tr>
<tr>
<td>LV outflow tract</td>
<td>4/12 (33%)</td>
</tr>
<tr>
<td>LV inferior wall</td>
<td>3/12 (25%)</td>
</tr>
<tr>
<td>LV antero-lateral wall</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>Ablation effectiveness</td>
<td></td>
</tr>
<tr>
<td>On first attempt (endocardial)</td>
<td>14/20 (70%)</td>
</tr>
<tr>
<td>On second attempt (epicardial)</td>
<td>6/20 (30%)</td>
</tr>
<tr>
<td>Procedural features</td>
<td></td>
</tr>
<tr>
<td>Fluoroscopy time (minutes)</td>
<td>51 (43-91)</td>
</tr>
<tr>
<td>Total procedural time (hours)</td>
<td>4.5 (3.2-5.3)</td>
</tr>
<tr>
<td>Number of RF pulses</td>
<td>45 (18-66)</td>
</tr>
<tr>
<td>Maximum power (watts)</td>
<td>41 (38-42)</td>
</tr>
<tr>
<td>Median RF time (minutes)</td>
<td>25 (7-44)</td>
</tr>
</tbody>
</table>

Values express as number of patients (%) or as median (Q1-Q3).

VT = ventricular tachycardia; RV = right ventricle; LV = left ventricle; RF = radiofrequency

Figure Legends:

Figure 1: Endocardial left ventricular ablation. Endocardial voltage map of the LV in right (panel A) and left (panel B) anterior oblique views, with intersecting CARTOSOUND™ intracardiac echocardiography fans. Panel C shows the same echo fan as panel B. Intracardiac echocardiography allows to identify aneurysmatic dilatations (white line and arrow) not observed on transthoracic echocardiogram. Panel D shows a run of non-sustained VT in the same patient.

Figure 2: Endocardial and epicardial left ventricular ablation. Panel A: Endocardial activation map of the LV in left anterior oblique (LAO) view. The earliest activation is at the distal portion...
of the coronary sinus (arrow), suggesting an epicardial origin of the arrhythmia. Panel B: Endocardial voltage map (LAO view) showing normal bipolar potentials in almost all of the LV; a localized low-voltage area is evident at the basis of antero-lateral wall. Panel C: Epicardial voltage map (left lateral view) of the LV showing a large low-voltage area involving the lateral wall.

**Figure 3:** Endocardial and epicardial entrainment pacing. Entrainment pacing performed from the mapping/ablation catheter. In panel A pacing was performed at the best activation site in the endocardial map; the entrainment was concealed with a post-pacing interval equal to the VT cycle and with a long interval between the stimulus and the local ventricular potential. In panel B, pacing was performed at the best activation site in the epicardial map; in this case too the entrainment was concealed with a post-pacing interval equal to the VT cycle, but the stimulus and the local ventricular potential occur quite concurrently, suggesting that the mapping catheter is positioned at the exit of the hypothetical critical isthmus.

**Figure 4:** Epicardial access and tachycardia termination. Panel A: Fluoroscopic right anterior oblique (RAO) view, showing the ablation catheter (arrow) in the pericardial space at the level of the earliest ventricular activation during VT. Panel B: Radiofrequency energy applied at the site of earliest activation terminated VT during ablation.

**Figure 5:** Arrhythmia-free survival. Kaplan-Meier survival analysis showing long-term freedom from recurrent VT.
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Circ Arrhythm Electrophysiol. published online January 31, 2012;
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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