Core Isolation of Critical Arrhythmia Elements for Treatment of Multiple Scar-Based Ventricular Tachycardias

Running title: Tzou et al.; Core Isolation to Treat Ventricular Tachycardia

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Abstract:

**Background** - Radiofrequency ablation (RFA) of multiple or unmappable ventricular tachycardias (VTs) remains a challenge with unclear endpoints. We present our experience with a new strategy isolating core elements of VT circuits.

**Methods and Results** - Patients with structural heart disease presenting for VT RFA at 2 centers were included. Strategy involved entrainment/activation mapping if VT was hemodynamically stable, and/or voltage mapping with electrogram analysis and pace mapping. Core isolation (CI) was performed incorporating putative isthmus and early exit site(s) based on standard criteria. If VT was noninducible, the dense scar (<0.5 mV) region was isolated. Successful CI was defined by exit block (20mA at 2 ms) within the “isolated” region. VT inducibility was also assessed. 44 patients were included (mean age 63, 95% male, 73% ischemic cardiomyopathy, mean LVEF 31%, 68% with multiple unstable VTs (mean 3+2)). CI area was 11+12 cm², vs. 55+40 cm² total scar area. Additional substrate modification was performed in 27(61%), and epicardial RFA was performed in 4(9%). CI was achieved in 37(84%) and led to better VT free survival (log rank p=0.013).

**Conclusions** - Core isolation is a novel strategy with a discrete and measurable endpoint beyond VT inducibility to treat patients with multiple and/or unmappable VTs. The CI region can be selected based on standard characterization of suspected VT isthmus surrogates thus limiting ablation target size. Exit block within the isolated area is achievable in most and may further improve long-term success.

**Key words:** catheter ablation, ventricular tachycardia, arrhythmia (heart rhythm disorders)
Introduction

Catheter ablation has become a mainstay for management of drug-refractory ventricular tachycardia (VT) among patients with structural heart disease.\textsuperscript{1-4} Substrate-based ablation in particular has emerged as an integral component of the procedure, especially among the majority of patients in whom there are multiple VTs and/or VTs are not able to be mapped via standard entrainment methods.\textsuperscript{1,2,5,6} This technique has subsequently helped to increase the treatable population and provide incremental gains in prevention of recurrent VTs and implantable cardioverter defibrillator (ICD) therapies.\textsuperscript{5-8}

However, long-term success rates remain suboptimal, and have likely been limited by lack of a clearly defined or reproducible ablation endpoint. Acute noninducibility of VT following ablation has been the standard endpoint,\textsuperscript{4} but it has inherent limitations. First, lack of inducibility prior to ablation confounds interpretation of noninducibility following ablation. Second, there is a known lack of reproducibility in inducing VT, especially in the setting of concomitant antiarrhythmic drug (AAD) use. Third, changes in autonomic tone and/or use of general anesthesia may affect VT inducibility. Fourth, ablation lesions may either expand as a result of disruption of microcirculation, with consequent myocyte loss, or regress secondary to healing and resolution of edema. Finally, patients may be too unstable to tolerate additional attempts at VT induction following ablation.\textsuperscript{4,7-11} Several alternative endpoints have been studied recently, including diffusely targeting regions with abnormal electrograms, and empiric isolation of the entire region of abnormal electrograms.\textsuperscript{8,12-14}

We sought to investigate a unique ablation endpoint among patients with VT in the setting of structural heart disease by 1) identifying critical or “core” VT circuit elements based on careful electrophysiological characterization and 2) ablating these areas circumferentially...
with the goal of achieving electrical isolation. “Core isolation” thus refers to circumferential ablation around all critical VT circuit elements. We present combined experiences from two tertiary referral centers using this novel technique of core isolation (CI).

**Methods**

**Study population**

Patients referred for VT ablation to the University of Pennsylvania and the University of Colorado Health Systems between January 2011-November 2013 were evaluated. In concordance with institutional guidelines of each health system, all patients provided written informed consent both for VT ablation, and for their anonymized medical information to be included in research studies. All included patients had structural heart disease and VT that was refractory to antiarrhythmic drug (AAD) therapy. All underwent detailed electroanatomic mapping and ablation of the endocardium and/or epicardium using an open-irrigated 3.5-mm-electrode-tip catheter (ThermoCool or ThermoCool SF, Biosense Webster, Diamond Bar, CA, USA) and electroanatomic mapping system (CARTO, Biosense Webster). Included patients underwent ablation with intent to achieve CI (see below). Exclusion criteria included age <18 years, lack of low-voltage regions as determined by bipolar voltage mapping (see below), inability or refusal to provide informed consent, or individual operator decision prior to starting the case not to attempt CI as the ablation strategy.

**Electrophysiology study and mapping**

Endocardial access was obtained to the left ventricle (LV) using retrograde transaortic or transseptal approach and/or to the right ventricle (RV) using transvenous approach. When necessary, transcutaneous, subxiphoid epicardial access was obtained using fluoroscopic guidance as previously described. Heparin was administered throughout all procedures.
involving left-sided intracardiac access to maintain activated clotting times of 200-350 seconds. Heparin was occasionally administered during intracardiac RV access at operator discretion.

Mapping in sinus or paced rhythm was performed at the outset as follows. Voltage mapping was done to identify areas of scar, with bipolar electrogram (EGM) amplitudes of <0.5mV defining areas of dense scar; 0.5-1.5mV corresponding with endocardial scar border zone (0.5-1.0mV for epicardial scar border zone\textsuperscript{16}); and >1.5mV to delineate normal endocardial tissue\textsuperscript{2} (>1.0mV on epicardium). Potential channels within dense scar were additionally identified by adjusting the color scale display.\textsuperscript{17, 18} Sites with fractionated EGMs, and/or late potentials (LPs) within or adjacent to areas of dense scar were also identified. Pacemapping was performed at sites within channels as noted above, in defined areas containing abnormal electrograms, and in regions in which VT exits were suspected based on 12-lead ECGs, when available. Potential isthmus or exit sites were identified by pacemapping, as previously defined: long stimulus-QRS times (\textgtreq 40 msec) and \textgtreq 1 of the following: 1) \textgtreq 10/12 morphology match to clinical or induced VTs; 2) overall paced QRS vector concordance with clinical or induced VTs (based on bundle branch morphology in V1, frontal plane axis within 30 degrees, and precordial transition occurring at the same lead); or 3) sites in which alternating QRS morphologies were observed with pacing.\textsuperscript{2, 19, 20} These areas were annotated on the substrate maps.

Ventricular programmed electrical stimulation (PES) was performed using up to two pacing drive cycle lengths (600 and 400 msec) and up to three extrastimuli from \textgtreq 1 RV and/or LV sites. The standard PES site was the RV apex, if VT was easily inducible with up to triple extrastimuli. If VT was inconsistently inducible, non-inducible, or only inducible with triple extrastimuli at the RV apex, other sites (LV and/or RV) were used at operator discretion. Therefore, all patients underwent at least single-site RV programmed stimulation with up to
triple extrastimuli. Additional ventricular pacing maneuvers (burst pacing, with or without isoproterenol or epinephrine) were performed at the operator’s discretion with the intention of VT induction. If VT was hemodynamically tolerated, activation and/or entrainment mapping using standard maneuvers were performed to identify potential isthmus sites. Ablation was delivered when such sites were identified; those with termination without ectopy were considered to be essential VT circuitry sites. VT induction was attempted pre- and post-ablation unless there safety limitations or other factors considered prohibitive based on operator discretion.

**Ablation Strategy and Core Isolation (Figure 1)**

The first step in the ablation procedure was to attempt Core isolation (CI) within the dense scar (<0.5 mV) by circumferentially surrounding the putative isthmus, and/or entrance and early exit site(s), which were identified based on pacemapping or entrainment mapping. Sites with ablation termination were uniformly incorporated within CI regions (Figures 1&2). Regions with EGM voltage <1.0 mV were also targeted if there were features consistent with isthmus, and/or entrance and early exit sites, as defined above. If VT was noninducible at the outset and 12-lead VT ECGs were unavailable, circumferential ablation around dense scar (<0.5 mV) was performed. Therefore, the CI area incorporated critical VT circuit elements confirmed by electrophysiologic data and/or dense but electrically excitable scar as specified. Individual-point radiofrequency energy delivery using an irrigated-tip ablation catheter, as above, was routinely titrated to achieve 10-15-ohm impedance drops, maximum temperature of 45 degrees, and duration of 90 seconds. Longer lesions were delivered when insufficient changes were noted in EGM or impedance, or lesion depth, as observed on intracardiac echocardiography.

Successful CI was defined by failure to capture the ventricle with pacing from inside the
lesion set (exit block) using a pacing output of 20 mA and pulse width of 2 ms from multiple (≥ 3), discrete sites that had previously demonstrated capture. In all patients capture from multiple sites was documented prior to isolation. Importantly, pacing before and after was not performed at sites of RF lesion placement. Such an approach has been previously shown to be effective for assessing “exit block” and effective PV isolation. We noted dissociation of LPs from ventricular activation (“entrance block”) (Figure 3) and isolated firing as additional evidence, although the latter were not required for defining CI. CI was assessed at multiple sites within the isolated region to confirm isolation within the lesion set and not just a segmental effect. CI efficacy was typically assessed after a circumferential lesion set was completed around the region of interest. Pacing was usually performed with a standard ablation catheter. In selected instances, simultaneous multi-electrode catheters were used.

Next, additional, reinforcing lesions were placed at each operator’s discretion within the isolated area targeting sites of fractionated electrograms and LPs noted in sinus rhythm. Although these persistent signals may have represented far-field (midmyocardial or epicardial) activation, additional ablation “reinforcing” previous lines was occasionally performed to minimize the possibility of lack of entrance block as an explanation for the persistent signals. Ventricular PES was repeated following CI, using the same or more aggressive stimulation protocol as that used for initial induction, within limits described above, and whenever patient stability allowed. If any VT was still inducible after CI, other abnormal regions within scar but potentially outside of the isolated region were targeted as needed, based on the morphology of VT(s) induced after re-confirming CI and guided by sites with LPs and favorable pacemap characteristics, as above. Efforts to achieve CI and VT nonducibility continued as long as patient safety and tolerance allowed with emphasis on assuring continuity of lesions with
targeted 12-15-ohms impedance drop and ≥90-second duration.

Finally, epicardial mapping and/or ablation were performed in limited cases due to 1) continued inducibility of VT following endocardial ablation; 2) prior failed endocardial ablation; 3) 12-lead ECG VT characteristics suggesting epicardial exit23; and/or 4) lack of abnormal endocardial substrate. When epicardial ablation was considered, coronary angiography was performed to ensure a safe distance from major coronary arteries. Ablation was not performed within 1 cm of a major coronary artery and/or sites of persistent phrenic nerve capture with high output pacing. Details of defining the CI region for ablation was similar to that performed on the endocardium except that bipolar voltage cut-offs differed as noted.16

**Follow up**

Immediately post-procedure, patients were observed in the hospital until clinically stable for discharge. Noninvasive programmed stimulation (NIPS) was performed within 7 days of ablation or prior to discharge unless contraindicated and as previously described.9 If VT recurred during follow-up, additional treatments were performed as needed, including AADs, repeat ablation, or surgery. Any VT lasting >30 seconds or leading to syncope or appropriate ICD therapy was considered a VT recurrence. Following ablation, AADs were continued at operator discretion. Typically, amiodarone was reduced to ≤ 200 mg/day. Routinely, AAD would be continued for about 3 months post procedure and then discontinued if there were no change in clinical status. Following discharge, patients were followed at 1-3 months and then every 3-6 months, or more frequently in the case of arrhythmia recurrence or other clinical events. Visits included both clinical and ICD evaluation. Outcomes evaluated included VT recurrence, complications, and change in AAD regimen. Data, including device interrogation information, were collected from the electronic medical records at the performing institution or...
by consultation with the patient’s cardiologist.

**Statistical analysis**

Contiguous areas of abnormal bipolar voltage were measured using the surface area measurement tool on CARTO3 software. Continuous data are reported as mean ± standard deviation or median, 25-75% interquartile range for non-normally distributed variables, and categorical data are reported as number (percentage). Two-sided Student t-test was used for comparison of continuous variables; the Mann-Whitney test was used for non-parametric comparative testing. Fisher’s exact test was used for comparison of proportions. Cox proportional Hazard analysis was used to evaluate significant univariate predictors for time to ventricular arrhythmia recurrence, and results are reported as hazard ratio (95% confidence interval). Multivariate analysis was note performed due to low number of events. Kaplan-Meier survival analysis was performed evaluating VT-free survival following ablation comparing those in whom CI was achieved to those in whom CI was not achieved. Log-rank test was used for comparison of survival curves. A p value of <0.05 was considered statistically significant. IBM SPSS Statistics (Version 21, New York) was used for statistical analysis.

**Results**

**Patient Characteristics (Table 1)**

A total of 566 patients with structural heart disease underwent VT ablation between January 2011 and November 2013 at the University of Pennsylvania and University of Colorado. Of these, 44 underwent attempted CI (28 at the University of Pennsylvania, and 16 at the University of Colorado) and were included in the present study. The main reason for exclusion was individual operator preference to not try the approach prior to each case, regardless of patient characteristics. All had “core” elements identified, and the CI technique was applied to each
patient once. Baseline characteristics of the cohort are as listed in Table 1. The mean age was 63 ± 14 years, the majority of patients were male, and more than half had undergone prior VT ablation. The most common pre-ablation AAD was amiodarone, (daily oral dose 150 ± 170 mg). Most had a prior history of myocardial infarction and associated ischemic cardiomyopathy. There were 3 patients with arrhythmogenic right ventricular cardiomyopathy, 2 patients with surgically repaired tetralogy of Fallot, 1 patient with cardiac sarcoidosis, 1 patient with hypertrophic cardiomyopathy, and 1 patient with mixed cardiomyopathy (cardiomyopathy out of proportion to coronary artery disease distribution) included in the series. Nearly half of them presented with VT/VF storm or incessant VT, and most presented with multiple unstable VTs. Extracorporeal membrane oxygenation circuit was placed in 1 patient, and intraaortic balloon pump was present in 2 patients due to hemodynamic instability prior to VT ablation. Otherwise, no mechanical hemodynamic support was required or added for these ablation procedures.

**Procedural data and Acute Success**

All patients underwent detailed endocardial electroanatomic mapping (522 ± 317 points). Six patients additionally underwent epicardial mapping (456 ± 499 points), 4 of whom had idiopathic cardiomyopathy and 2 of whom had ischemic cardiomyopathy; only 5 underwent epicardial ablation due to proximity of ablation targets to major coronary arteries in one of the patients with idiopathic cardiomyopathy. The latter patient was also the only patient with nonischemic VT substrate for whom CI was unable to be achieved due to para-Hisian location of targeted core and desire not to cause complete heart block. VT was unable to be mapped (hemodynamically unstable in 20 (45%) or noninducible in 10 (23%) in the majority of patients. Isoproterenol was used in 9 (20%), and epinephrine was used in 1 (2%) of the patients, for VT induction. CI was confirmed in 37 patients (84%) (Table 2). The mean CI area was smaller than the total scar
(bipolar EGM amplitude ≤ 1.5 mV) area (11±12 cm² vs. 55±40 cm²). Patients in whom CI was not achieved tended to have lower LVEF (23% vs. 32%), although this difference was not statistically significant (p=0.07) (Table 3). There were no significant baseline differences between patients in whom CI could and could not be achieved, including number of prior ablations, mapping points obtained, and disease substrate (Table 3). Among patients in whom CI was not achieved (n=7), all but one, noted above, had ischemic substrate, 5 of whom had anterior and 1 of whom had inferior scar. Two of the patients in whom CI could not be achieved additionally underwent epicardial mapping, but only one underwent additional epicardial ablation. Notably, CI could be achieved in 11 of the 12 patients (92%) with a nonischemic VT substrate.

Following CI alone, VT was still acutely inducible in 12 (27%) patients. Of these, 3 had clinical VT still inducible, as determined by morphology. The cycle lengths of these VTs were slower or unchanged from prior. Additional, substrate ablation was then performed, depending on morphology of persistently inducible VTs following CI. Following CI + additional substrate modification outside the area of CI if needed, VT remained inducible in 7 patients, 2 (5%) of whom had clinical VT still inducible and 5 (11%) of whom had only non-clinical VT inducible. There was no statistically significant association between CI and performing additional substrate modification or acute VT noninducibility (Table 3). Among the few patients who underwent additional epicardial ablation, the CI region targeted for ablation was similar in location to that on the endocardium.

NIPS was performed in 25 (57%) of the patients 3 ± 2 days following the index procedure. Reasons for not performing NIPS were discharge over weekend and subsequent follow-up with another provider remote in location from our institutions or medical
contraindication. Of those who underwent NIPS, 14 (56%) were non-inducible for any VT. Of the 11 that were inducible on NIPS, 10 (91%) were inducible only for VT that had not been previously observed or induced. The single patient with inducible clinical VT at NIPS did not undergo repeat ablation prior to discharge but did have amiodarone re-initiated. The others for whom VT was inducible at NIPS were either maintained on the same or reduced antiarrhythmic regimen (usually amiodarone). No additional ablations were performed based on the results of NIPS. There was no significant association between CI and inducibility at NIPS (Table 3).

**Intermediate-term success and predictors of recurrence**

Over a follow-up of 17.5 ± 9.0 months (range 4.2-35.6 months), 38 patients (86%) were free of recurrent sustained ventricular arrhythmias following core isolation. Of the remaining 6, 3 received single appropriate ICD shocks or ATP for which AAD doses were resumed/increased and they have not had any further recurrences. Two underwent cardiac surgery following VT recurrence: heart transplant in one, and pseudoaneurysm resection with mitral valve replacement in the other. The remaining patient with recurrent VT underwent repeat ablation at another facility 6.7 months after the index procedure. Data from that ablation are not available.

Achievement of CI provided incremental improvement in long-term freedom from VT, even in the absence of achieving acute VT noninducibility (Figure 4).

None of the patients with VT recurrence presented in VT storm. Additionally, amiodarone doses tended to be decreased (from 0, 0-300 mg to 0, 0-200 mg, p=0.18) following ablation, although the difference by non-parametric testing did not meet statistical significance.

The only characteristic that was significantly associated with long-term VT recurrence in univariate analysis was achievement of CI (HR 0.17, p=0.03, Table 4). Notably, neither additional substrate modification beyond CI (p=0.75) nor acute VT non-inducibility (p=0.12)
was significantly associated with long-term recurrence (Table 4). Kaplan-Meier survival analysis demonstrated that those in whom CI was successfully achieved had significantly better long-term VT-free survival compared to those in whom CI was not successful (log-rank p=0.013, Figure 5).

Complications

The only complications were peri-procedural and included pseudoaneurysm at the site of intraaortic balloon pump placement (n=1) that resolved without intervention and transient hypotension (n=1) that resolved without subsequent incident. There were no cases of pericardial effusion or tamponade, thromboembolic events, hemorrhage, major vascular complications, or deaths.

Discussion

Results from this observational study demonstrate that CI is feasible and appears to be an effective catheter ablation strategy with a discrete and measurable endpoint beyond VT non-inducibility to treat patients with structural heart disease and multiple and/or unmappable VTs. Importantly, the relative ablation target size may be limited by selecting the CI region based on standard characterization of suspected VT circuit surrogates. Core isolation is achievable in most, and achieving it may further improve long-term success. In our series combining recent experiences from two tertiary referral centers, 86% of patients remain free from recurrent ventricular arrhythmias or ICD shocks following CI procedure. Importantly, this VT control has been accomplished with an overall reduction in amiodarone use and with no major complications.

Given the inconsistencies between achieving acute VT non-inducibility and predicting arrhythmia-free survival long-term\(^6\text{-}11,24\), several alternative endpoints for VT ablation have been
proposed. These endpoints have included identification and elimination of conducting channels,\textsuperscript{17,25} sites indicative of diseased conduction, e.g., late potentials or local abnormal ventricular activities\textsuperscript{12,13,26-28}, sites with good pace maps or pace-map characteristics\textsuperscript{28}, as well as diffuse scar isolation or homogenization\textsuperscript{8,14}. In almost all cases, these strategies were used in conjunction with VT noninducibility as collective endpoints, many involved a substantial amount of empiric ablation, and several of the techniques were only applied to patients with ischemic heart disease.\textsuperscript{8,14,25,28}

In the present study, additional substrate modification was performed in many of the patients due to continued VT inducibility or operator preference to place reinforcing lesions in those in whom CI had already been achieved. However, doing so did not impact long-term success. Using CI as a procedural endpoint, we achieved excellent VT-free survival at least comparable to those reported in other studies in which substrate modification and standard procedural endpoints were used. In SMASH-VT, a randomized controlled trial that investigated a strategy of early substrate-based VT ablation among patients with ischemic heart disease, freedom from treated ventricular arrhythmias was 88\% at 2 years.\textsuperscript{5} Using a similar strategy among patients with ischemic VT randomized to ablation + ICD versus ICD alone in the VTACH study, Kuck and colleagues observed a VT-free rate of 47\% at 2 years.\textsuperscript{6} More recently, Di Biase and colleagues achieved a VT-free survival rate of 81\% at 2 years using a technique of extensive endo- and epicardial scar homogenization among patients with ischemic VT and no prior cardiac surgery.\textsuperscript{8} Our series provides proof of concept that CI and good ventricular arrhythmia control can be achieved among patients with both ischemic and nonischemic etiologies of structural heart disease and that CI may be a valuable adjunct to VT noninducibility as an ablation endpoint.
Also importantly, the rate of epicardial access and ablation required in this study was not higher than that previously reported for standard VT ablation approaches and was lower in comparison to other contemporary approaches. Importantly, we still were able to achieve CI in a majority of patients without epicardial ablation. One of the key factors that may have influenced this degree of success may have been the presence of intramural substrate, particularly among patients with nonischemic heart disease.30-32 Such substrate has been demonstrated to provide relative compartmentalization of diseased myocardium; this may have conferred an advantage that allowed more targeted ablation and without the need to achieve fully transmural ablation lesions in order to achieve isolation of critical VT elements.30, 32 Rather, when ablating within areas of low voltage in ischemic or nonischemic scar, the endocardial lesion just needs to penetrate to the intramyocardial scar barrier (Figure 6).

Reasons for VT recurrence using the CI approach are likely no different than for any of the previously mentioned approaches and include novel VT arising from a region remote from that targeted and/or recurrent conduction across lines of block, similar to pulmonary vein reconnection. Reasons for continued acute VT inducibility following CI are similar, but probably weighted more to the former reason, as persistent CI was confirmed if VT remained inducible. We were unable to achieve CI in a small number of patients, which could have been because there were deep tracts of critical circuitry interspersed amidst incongruous scar; this could lead to preferential conduction via alternate exits (epicardial or endocardial), thus bypassing more relatively superficial lines of ablation. Alternatively, potentially small residual gaps in existing lines despite repeated ablation application could have persisted, “sheltered” by surrounding edema from other lesions. Further study of this technique, coupled with imaging around the time of ablation, may provide more definitive answers. For the moment, however,
the data from the present study indicates that CI is a comparably achievable endpoint as VT non-
noninducibility is, and adds incremental benefit in achieving ablation success.

Limitations

This study was observational and lacked a control group, and the sample size was relatively
small, which limits interpretation of multivariable analysis. Patient selection for CI was based on
operator preference, which could have introduced selection bias. Only patients with
arrhythmogenic substrate identified by bipolar voltage mapping were included; this strategy thus
cannot be extended to those with purely intramural myocardial substrate in which bipolar voltage
may appear normal. Additionally, due to patient safety and/or length of procedure, reassessment
of durable core isolation following a waiting period was not performed. This effort could
improve outcomes and warrants additional investigation. The patients that did recur following
CI had VT with site of origin or exit from within the preexisting scar. Even in the absence of
this step, none of the patients recurred with VT storm, and there was no evidence of pro-
arrhythmia following ablation.

Additional substrate modification, occasionally including epicardial ablation, was
performed in many patients due to either continued VT inducibility or operator preference to
reinforce lesion sets. Doing so did not contribute significantly to freedom from recurrent VT.
There is inevitable overlap in regions that would be targeted using other recently reported
approaches for VT ablation, although ours may have been more limited in proportionate area of
ablation.\textsuperscript{8,12-14} NICM patients comprised <1/3 of patients in this study, which somewhat limits
generalizability and precludes detailed analysis of this group alone. However, VT substrate
etiology was not significantly associated with either achievement of CI or VT recurrence
following CI ablation.
The higher rate of inducibility with NIPS observed following ablation compared to acute inducibility post-procedurally is difficult to interpret since not all patients underwent NIPS. Only 1 patient had clinical VT inducible at NIPS, which makes recovery of conduction an unlikely general mechanism for recurrence; there may have been substrate characteristics not readily apparent at the time of ablation. Inducibility of VT, primarily nonclinical, at time of NIPS was not predictive of VT recurrence, although the relatively small number who underwent NIPS limits interpretation.

Despite these limitations, we feel the data presented are compelling, were noted at two institutions, and clearly substantiated the ability to isolate critical areas of endocardium that demonstrate surrogates of the VT circuit, providing a unique endpoint for assessing effect of the ablation. The results encourage future prospective study comparing CI with other substrate based ablation strategies, especially among an even more heterogeneous population than were included in the present study.

Conclusion

Core Isolation is an achievable, easily assessed endpoint for ablation of ventricular arrhythmias among patients with ischemic or nonischemic heart disease, especially in the face of multiple and/or unmappable VTs. It is a strategy that may improve long-term ablation outcomes beyond acute non-inducibility of VT without the need for extensive substrate based ablation.

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**Conflict of Interest Disclosures:** None
References:


Table 1: Baseline Characteristics of Patients Undergoing Core Isolation (N=44)

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<th>Characteristic</th>
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<td>Age (years)</td>
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<td>Male</td>
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<td>Type of structural heart disease</td>
<td></td>
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<tr>
<td>Ischemic cardiomyopathy</td>
<td>32 (73)</td>
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<td>Dilated/Idiopathic cardiomyopathy</td>
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<tr>
<td>Other</td>
<td>8 (18)</td>
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<tr>
<td>LVEF (%)</td>
<td>31 ± 13</td>
</tr>
<tr>
<td>Duration of cardiomyopathy (mo)</td>
<td>162, 84-231</td>
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<tr>
<td>Time since 1st VT presentation (mo)</td>
<td>26, 9-60</td>
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<tr>
<td>Presentation in VT storm</td>
<td>21 (48)</td>
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<td>Hemodynamically tolerated VT</td>
<td>14 (32)</td>
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<td>History of prior VT ablation</td>
<td>26 (59)</td>
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<tr>
<td>Number of prior VT ablations</td>
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<td>Medications prior to ablation</td>
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<tr>
<td>Beta blocker</td>
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<tr>
<td>Angiotensin Converting Enzyme Inhibitor or Angiotensin Receptor Blocker</td>
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<td>Diuretic</td>
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<td>Sotalol</td>
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<td>Mexilitene</td>
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<td>Oral amiodarone</td>
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<td>Intravenous amiodarone</td>
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<td>Lidocaine</td>
<td>6 (14)</td>
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Values are reported in mean ± SD, median, 25-75% interquartile range, or n(%)
Table 2: Procedural Data

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<td>Endocardial mapping</td>
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<tr>
<td>Area of abnormal bipolar voltage(cm²)</td>
<td>55±40</td>
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<tr>
<td>%Endocardial bipolar scar</td>
<td>23±18</td>
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<tr>
<td>Epicardial mapping</td>
<td>6(14)</td>
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<td>Epicardial ablation*</td>
<td>5(11)</td>
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<tr>
<td>Epicardial bipolar scar area(cm²)</td>
<td>65±43</td>
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<tr>
<td>%Epicardium bipolar scar</td>
<td>14±7</td>
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<tr>
<td>Ablation data</td>
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<tr>
<td>Number of RF lesions comprising isolated region</td>
<td>111±91</td>
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<tr>
<td>Area of isolated core (cm²)</td>
<td>23±11</td>
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<td>VT terminated during ablation</td>
<td>12(27)</td>
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<tr>
<td>Additional substrate modification performed</td>
<td>27(61)</td>
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<td>Fluoroscopy time (min)</td>
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<td>Procedure time (min)</td>
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</tr>
<tr>
<td>Core isolation</td>
<td>37(84)</td>
</tr>
<tr>
<td>Clinical VT inducible following ablation</td>
<td>3(7)</td>
</tr>
<tr>
<td>Any Inducible VT following ablation</td>
<td>7(18)</td>
</tr>
</tbody>
</table>

Values are reported in mean±SD, median, 25-75% interquartile range, or n(%)
*All patients who underwent epicardial ablation also had endocardial ablation
### Table 3: Clinical Variables and Association with Successful Core Isolation (CI)

<table>
<thead>
<tr>
<th>Variable</th>
<th>CI Achieved (N=37)</th>
<th>CI Not Achieved (N=7)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63±14</td>
<td>61±12</td>
<td>0.74</td>
</tr>
<tr>
<td>Males</td>
<td>35(95)</td>
<td>7(100)</td>
<td>0.99</td>
</tr>
<tr>
<td>Ejection Fraction(%)</td>
<td>32±13</td>
<td>23±9</td>
<td>0.07</td>
</tr>
<tr>
<td>Ischemic Substrate</td>
<td>26(70)</td>
<td>6(86)</td>
<td>0.65</td>
</tr>
<tr>
<td>Disease Duration(months)</td>
<td>162, 104-230</td>
<td>132, 26-225</td>
<td>0.64</td>
</tr>
<tr>
<td>Number Prior Ablations</td>
<td>1, 0-2</td>
<td>0, 0-2</td>
<td>0.49</td>
</tr>
<tr>
<td>Number VTs Targeted</td>
<td>3±2</td>
<td>4±1</td>
<td>0.12</td>
</tr>
<tr>
<td>Endocardial Scar Area(cm²)</td>
<td>51±37</td>
<td>75±53</td>
<td>0.16</td>
</tr>
<tr>
<td>Core Isolation Area(cm²)</td>
<td>12±12</td>
<td>20±22</td>
<td>0.37</td>
</tr>
<tr>
<td>Additional Substrate Modification Performed</td>
<td>20(54)</td>
<td>6(86)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any VT inducible immediately post ablation</td>
<td>6(16)</td>
<td>1(14)</td>
<td>0.83</td>
</tr>
<tr>
<td>Any VT inducible on NIPS*</td>
<td>8(38)</td>
<td>3(75)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are reported in mean±SD or median, 25-75% interquartile range, or n(%)

* 25 patients underwent NIPS procedure within 7 days following ablation, 21 of whom had CI achieved
Table 4: Univariate Predictors of Recurrent Ventricular Arrhythmias

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio (95% confidence interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>1.00(0.94-1.05)</td>
<td>0.91</td>
</tr>
<tr>
<td>Ejection Fraction(%)</td>
<td>0.97(0.90-1.04)</td>
<td>0.40</td>
</tr>
<tr>
<td>Ischemic Substrate</td>
<td>0.38(0.08-1.91)</td>
<td>0.24</td>
</tr>
<tr>
<td>Number of Prior Ablations</td>
<td>1.26(0.78-2.04)</td>
<td>0.35</td>
</tr>
<tr>
<td>Number of VTs targeted</td>
<td>1.27(0.84-1.90)</td>
<td>0.26</td>
</tr>
<tr>
<td>Endocardial Scar Area(cm^2)</td>
<td>1.01(0.99-1.03)</td>
<td>0.36</td>
</tr>
<tr>
<td>Epicardial Ablation performed</td>
<td>1.46(0.17-12.50)</td>
<td>0.73</td>
</tr>
<tr>
<td>Core Isolation Area(cm^2)</td>
<td>0.36(0.02-6.9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Core Isolation Achieved</td>
<td>0.17(0.03-0.84)</td>
<td>0.03</td>
</tr>
<tr>
<td>Additional Substrate Modification Performed</td>
<td>1.32(0.24-7.23)</td>
<td>0.75</td>
</tr>
<tr>
<td>VT Inducible Immediately Post Ablation</td>
<td>3.83(0.69-21.20)</td>
<td>0.12</td>
</tr>
<tr>
<td>VT Inducible on NIPS</td>
<td>1.60(0.57-4.50)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Figure Legends:

**Figure 1**: Flowchart detailing the general approach for Core Isolation

**Figure 2**: Depicted are strategies for CI. Endocardial electroanatomic bipolar LV voltage maps are shown, using traditional voltage cut-offs, from patients with ischemic (A and B) and nonischemic cardiomyopathy (C). Ablation lesions are shown (red dots). (A) A relatively unique case in which isthmus, exit, and entrance sites were identified for a hemodynamically tolerated, clinical VT. Only a region surrounding a critical isthmus region was isolated. (B) Exits (arrows and associated VT morphologies) for multiple, unstable VTs were determined, based on
pacemapping and very limited entrainment and activation mapping, throughout border-zone regions around a large, antero-apical infarction. The targeted core based on these findings incorporated most of the dense scar (EGM voltage ≤0.5 mV). (C) VT could not be induced at the start of the procedure, so ablation incorporated only regions of dense scar (bipolar voltage ≤0.5 mV), with limited inclusion of adjacent LP sites with favorable pacemap characteristics as described in the text. CI was achieved in each example, and VT was noninducible and has not recurred in follow-up. Examples in B and C were more representative of the majority of cases in this series.

**Figure 3:** Example of CI in a patient with VT storm and a large anterior myocardial infarction. (A) Endocardial voltage map, antero-posterior view. The VT circuit core was defined by good pacemap (PM) sites (stars depict examples), as defined in the text, and was isolated by contiguous ablation at the junction between dense scar and border zone or regions without pacing capture at baseline. (B) LP activation map performed after CI identifying a single site of endocardial breakthrough within the isolated area. A multipolar catheter (MPC) was positioned within the CI area, and the ablation catheter (ABL) at the site of endocardial breakthrough. (C) Ablation at the earliest breakthrough results in CI, with entrance block demonstrated by disappearance of near-field LPs from the MPC during ablation (arrows). (D) After CI, dissociated potentials were recorded (arrows). (E) Following isolation, pacing from the MPC shows local myocardial capture (arrows) with exit block.

**Figure 4:** Flowchart detailing long-term freedom from VT rates based on acute VT non-inducibility and/or core isolation (CI). Those in whom both VT non-inducibilty and CI were
achieved had the best VT-free survival. Notably, freedom from recurrent VT was still good among those in whom VT was still inducible but CI was achieved.

**Figure 5:** Kaplan-Meier survival curves demonstrate significantly better VT-free survival among those in whom core isolation (CI) was versus was not achieved.

**Figure 6:** Compared to normal myocardium (left), transmural activation in patients with nonischemic cardiomyopathy (NICM) and VT (right) has been demonstrated to be delayed due to frequent presence of intramural scar. Transmural ablation lesions (requiring ablation on both endocardium and epicardium) thus are often not necessary to achieve core isolation in NICM VT patients.
General Approach to Core Isolation

Voltage Map → VT Induction

Mappable VT
- Entrainment
- +/- Termination with single ablation lesion

Unmappable VT
- Pacemapping (long stimulus- QRS + pacemap match)
- Channels with LPs

Core designed to incorporate all critical VT circuitry elements identified

Ablation performed surrounding Core

Multi-site pacing within Core to assess Entrance/Exit Block (Core Isolation)

Core Isolation not achieved

Additional ablation at suspected exit/entrance sites until core isolated

Core Isolation achieved

VT induction

VT noninducible → Case end

VT inducible

Additional ablation outside of Core or on opposing epicardium (guided by morphology)
Impact of Acute VT Inducibility and Core Isolation on Long Term Success
Follow-up 17.5 Months

VT Inducible

Yes
N=9

CI Not Achieved
N=1
0% VT free survival

CI Achieved
N=8
83% VT free survival

No
N=35

CI Not Achieved
N=6
67% VT free survival

CI Achieved
N=29
90% VT free survival
Lesions must penetrate to scar boundary (not necessarily transmural)

Normal RV or LV

NICM RV or LV

Epicardial

Epicardial

Scarf

Endocardial

Endocardial

Transmural Activation
Core Isolation of Critical Arrhythmia Elements for Treatment of Multiple Scar-Based Ventricular Tachycardias

Wendy S. Tzou, David S. Frankel, Timothy Hegeman, Gregory E. Supple, Fermin C. Garcia, Pasquale Santangeli, David F. Katz, William H. Sauer and Francis E. Marchlinski

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