Primary Radiofrequency Ablation of Ventricular Tachycardia Early after Myocardial Infarction: Evaluation in an Ovine Model

Running title: Hsieh et al.; Primary ablation of post-infarct VT

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Abstract:

**Background** - Ventricular tachycardia (VT) is a significant complication of myocardial infarction. Radiofrequency ablation (RFA) for post-infarct VT is reserved for drug refractory VT or VT storms. Our hypothesis is that RFA in the early post-infarct period could abolish or diminish late recurrences of VT.

**Methods and Results** - Myocardial infarct was induced by balloon occlusion of the left anterior descending artery in 35 sheep. The 25 survivors underwent programmed ventricular stimulation and electroanatomical mapping 8 days post-infarct. Animals with inducible VT (12/25) underwent immediate RFA. Further VT inductions were performed 100 and 200 days post-infarct. At day-8, 3.0±0.9 VT morphologies per animal were inducible. All were successfully ablated with 24±6 applications of RF energy. All had ablations on the left ventricular endocardium, and 67% had ablations on the right ventricular aspect of the interventricular septum. All targeted arrhythmias were successfully ablated acutely. One animal was euthanized due to hypotension from a serous pericardial effusion. The other 11 survived and remained arrhythmia free on subsequent inductions on the 100\(^{th}\) and 200\(^{th}\) days (p<0.001). The 13 animals without inducible VT remained non-inducible at the subsequent studies. A historical control arm of 9 animals with inducible VT at day-8 remained inducible at day-100.

**Conclusions** - Radiofrequency ablation on the 8\(^{th}\) day after infarction abolished inducibility of VT at late induction studies up to 200 days in an ovine model. Early identification and ablation of VT after infarction may prevent or reduce late ventricular arrhythmias, but needs to be validated in clinical studies.

**Key words:** ablation, myocardial infarction, ventricular tachycardia arrhythmia
Introduction

Ventricular arrhythmias are responsible for the majority of cases of sudden cardiac death (SCD) following myocardial infarction (MI), with the greatest risk within the first 30 days. Implantable cardioverter-defibrillators (ICDs) reduces the risk of SCD in the post-infarct population at high risk.2,3

Catheter radiofrequency (RF) ablation of ventricular arrhythmias is indicated only in patients with a distant infarct and an ICD with recurrent ventricular tachycardia (VT) or VT storms refractory to medications. In this population, catheter ablation has been shown to be effective.4 ICD implantation combined with prophylactic catheter ablation remote from the infarct (8-13 years) has been found to reduce the incidence of ICD-delivered therapy.5,6

Our hypothesis is that radiofrequency ablation of inducible VT and its substrate early after an infarct would abolish or diminish late ventricular tachyarrhythmias.

Methods

Study Design

This study was designed as an equivalence study in which the primary outcome was the mid-term noninducibility of VT. MI’s were induced in 35 male cross-bred merino sheep (weight 58±11kg). In the 25 (71%) survivors, programmed ventricular stimulation (PVS) was performed 8 days post-infarct. The animals that had inducible VT (VT_{rfa}) underwent immediate catheter-based ablation, and had subsequent PVS 100 and 200 days post-infarct. The control arm of animals without inducible VT (VT_{neg}) underwent the same PVS studies (figure 1). A transthoracic echocardiogram was acquired pre-infarct and pre-PVS. A secondary analysis of efficacy compared VT_{rfa} animals with an historical control arm of animals with VT not ablated (VT_{pos}), but followed up only to 100 days.
**Myocardial infarction**

Under general anesthesia and without class III antiarrhythmics, temporal occlusion by percutaneous angioplasty balloon (2.5-4.0x8-20mm) of the mid-homonymous artery (left anterior descending artery equivalent) for 3 hours induced an MI.7

**Electroanatomical Map**

On the 8th post-infarct day, an electroanatomic map and simultaneous noncontact and contact data were collected via the Ensite multi-electrode array (MEA) system (St Jude, St. Paul, MN) as previously described.(Hsieh CHC et al, supplementary material) Mapping was performed prior to PVS on each day.

The dynamic substrate mapping (DSM) system was used to identify substrate on the noncontact system. Pacing from multiple sites and sinus rhythm (SR) were recorded, and the local unipolar electrogram peak negative voltage was used to create a global ratiometric map. Areas of dense injury, borderline injury, and normal myocardium were defined by both contact bipolar electrograms (≤0.5mV, 0.5-1.5mV, >1.5mV respectively) collected during sinus rhythm, and noncontact DSM (≤30%, 30-50%, >50% of the local unipolar electrogram peak negative voltage).8,9

Electrograms were classified using standard criteria by 2 independent observers:-10-12

1. Normal electrograms with ≤3 sharp intrinsic deflections, amplitude ≥3mV, duration <70ms, and/or amplitude/duration >0.046

2. Fractionated potentials with >3 deflections, amplitude ≤0.5mV, duration ≥133ms, and/or amplitude/duration <0.005.

3. Isolated potentials with additional signals separated from the local electrogram by >20ms isoelectric interval.
4. Late potentials with additional signals occurring ≥100ms after the QRS.

Programmed Ventricular Stimulation and VT Ablation

On the 8th, 100th and 200th days, PVS was performed from the RV (pulse width 2msec, drive train 8 beats, and ≤4 premature extrastimuli). The protocol was repeated twice each from 2 pacing sites (RV apex and basal septum), and with 2 drive trains (400ms and 450ms). The endpoint of stimulation was the final stimulus reaching refractoriness, or initiation of a sustained ventricular arrhythmia. An animal was considered VT inducible if any induced arrhythmia was: monomorphic, cycle length ≥200ms, sustained for ≥30sec if hemodynamically stable or ≥10sec if unstable, and reproducible. All induced VTs were considered for ablation. A 10-20 second segment of the induced arrhythmia was recorded prior to termination.

Ablation technique

Entrainment and contact activation mapping were not possible as all VTs were not hemodynamically tolerated. Therefore, substrate modification was performed during SR within the region identified to be critical for sustaining VT, with ≥1 of the following criteria:14-16

1. Corresponding to early activation site determined by non-contact mapping (earliest onset of QS deflection with virtual electrograms during VT).17
2. Paced QRS morphology similar to target VT (match ≤11/12 EKG leads)18
3. Stimulus-QRS interval >40ms pacing from the site in SR
4. Anatomic continuity with other lesions

Ablation was placed using a 3.5mm, saline-irrigated tip 4-electrode deflectable ablation catheter (Navistar Thermocool, Biosense-Webster, Diamond Bar, CA). RF energy was delivered for 90-120sec in power control mode with 50W maximum power, and automatically terminated if the maximal temperature (48°C) or impedance (300ohms) was exceeded. Saline flow was maintained
at 2mL/min and increased to 30mL/min during RF delivery.

Sequential point lesions created lines both parallel and perpendicular to the infarct border. The ablations were extended ≥1cm into the infarcted region. Parallel lesions were extended into distinctly non-infarcted tissue (≥2mV). All ablations which targeted the septum had corresponding ablations from the RV to create transmural lesions. Post-ablation, repeat PVS protocol was performed to reinitiate VT. If another VT was induced, further ablations were performed. The location of the new VT was determined by the same technique described above. The endpoint of the procedure was defined as noninducibility of any VT using the PVS protocol.

**Data analysis**

Data were analysed using Matlab v2010a (Mathworks, Natick, MA). Isochronal maps were created with local activations, defined as the maximum negative deflection of the virtual electrogram.

Statistical analysis was performed using SPSS v16 (SPSS Inc., Chicago, IL, USA). Two-tailed tests with 5% significance level were used throughout. Continuous variables were summarised as mean ± standard deviation. Association between categorical variables was tested using Fisher’s exact test. Repeated measures analysis of variance (ANOVA) was used to test for interaction between the effects of VT inducibility and time on substrate area and to test for changes over time separately within each group.

**Animal Care**

The care of the animals and study protocol was approved by the Sydney West Area Health Service Animal Ethics Committee, and complied with the ethical standards of the National Health and Medical Research Council, Australia.

**End Points**
The primary endpoint of the study was the long-term non-inducibility of VT. Acute success was defined as non-inducibility of any VT ≥ 200ms at the end of the ablative procedure. Long-term success was defined as non-inducibility at 2 subsequent PVSs on days 100 and 200. A sample size of 12 per group (VT_{rfa} and VT_{neg}) has > 90% power to establish equivalence between VT_{rfa} and VT_{neg} groups to within δ = 12.5% (2-sided α 5%) if the rate of noninducibility of VT at day-200 is 99% in the VT_{neg} group. The secondary analysis was an efficacy comparison between VT_{rfa} animals and a historical control arm of 9 animals with inducible VT at day-8 followed till day-100 under identical conditions with the same research group. A sample size of 9 animals in each arm has 80% power to detect a statistically significant difference between an expected non-inducibility rate at day-100 of 99% in VT_{rfa}, and a rate of ≤ 40% in the historical control arm (5% significance level with 2-sided test).

**Results**

MI was induced in 35 healthy male sheep. Twenty-five (71%) animals survived and underwent subsequent experiments. Infarcts produced anterior and septal wall akinesis on echocardiography. The mean left ventricular ejection fraction was 36±6%, 37±8% and 36±7% on the 8th, 100th, and 200th days respectively without a statistical difference between VT_{rfa} and VT_{neg} animals.

**VT Characteristics**

At the day-8 electrophysiological study, 12/25 survivors (48%) had inducible sustained VT. A total of 37 VTs were induced, with 3.0±0.9 distinct morphologies of VT per animal, cycle length 251±27ms, and requiring 3.5±0.7 extrastimuli for induction. There was a predominance of left bundle branch pattern (23/37). Successful termination of the induced VT by anti-tachycardia
pacing (ATP) occurred in 29 arrhythmias (78%). The remaining 8 required DC cardioversion due to either unsuccessful reversion with ATP, or rapid hemodynamic compromise (supplementary table a).

The earliest noncontact unipolar activation was 23±9ms earlier than the earliest surface EKG deflection. The most common region with the earliest activation was the apicoseptum (17/37). Substrate mapping by DSM located the earliest presystolic activation site as 2.0±3.0mm internal to the boundary between dense and borderline injury (DSM 30th percentile).

**VT Substrate**

There were 516±181, 568±161, and 429±121 contact points collected on days 8, 100, and 200 respectively. Prior to application of RF energy at day-8, there was no statistical difference in the area of dense and borderline injury by contact or noncontact measurements in VT_{rfa} or VT_{neg} animals (supplementary table b). There was a larger area of dense injury by contact measurements at day-100 in ablated VT_{rfa} animals compared to VT_{neg} animals (10.2±6.2 vs 7.9±5.0, p=0.04), but this statistical difference was not detectable day-200. There was no change in the area of dense or borderline injury in either group between day-100 and day-200.

The contact electrogram characteristics were more marked, with increased split, late and fractionated potentials at all time points in the VT_{rfa} animals (figure 2).

**VT Ablation**

A total of 37 VTs were targeted for catheter ablation. All ablations were performed from the LV endocardial surface with 67% (8/12) requiring ablations on the RV side of the interventricular septum to create a transmural lesion for arrhythmias arising from this location.7

Each animal required 24±6 applications of RF energy and a total time of RF application of 49±23min. The power delivered was 47 (range 46-48)W with a temperature of 40 (range 38-
42°C. Ablation extended the total procedure time from 5.0±2.3hrs to 8.4±1.6hrs (p=0.001) and fluoroscopy time from 25.7±17.7min vs 38.9±26.8min (p=0.162). There was no statistically significant difference in procedure or fluoroscopy times on other experimental days.

A representative animal with 3 inducible VTs is shown in figure 3. VT-1: RBBB, northwest axis morphology and cycle length 245ms. The exit point, based on earliest virtual electrogram activation 37ms prior to onset of QRS on the surface EKG was the mid-anteroseptum. VT-2: LBBB, LAD axis morphology and cycle length 205ms. The exit point was the apex, 15ms earlier than the surface EKG. VT-3: RBBB, LAD axis and cycle length 290ms. The earliest presystolic activation site was the apical anteroseptum. Each of these 3 VTs were targeted in turn for ablation, with ablation lines drawn both perpendicular and parallel to the scar border. The ablation line targeting VT-3 joined the former 2 ablation lines.

**Procedural Success**

Acute success, as defined as freedom from inducible sustained VT at the end of the day-8 ablation, was 100% (12/12 animals).

The 30-day mortality rate was 1/12 (8%). This animal had a hemodynamically significant pericardial effusion secondary to the MI found on day-8 prior to experimentation. Hemodynamics did not improve after PVS and the animal was euthanized due to ethical concern regarding its condition. An immediate autopsy of the animal confirmed a serous effusion, with no perforation seen. All other animals survived and completed the 100th and 200th day procedures. Two animals required diuretics for 2 days post RF ablation, but there was no long-term heart failure. No significant morbidity or mortality in the VTneg group (13/13 survived 200 days) was seen.

PVS and complex mapping was repeated on the 100th and 200th days. Monomorphic VT
was not re-inducible on either day in any of the ablated animals (12/12 VT_{rfa} animals day-8 prior to ablation, cf 11/11 VT_{rfa} animals day-100 and day-200, \( p<0.001 \)). No inducible arrhythmia was seen in the VT_{neg} control arm on subsequent studies (13/13).

The historical VT_{pos} arm of 9 animals with inducible VT at day-8 remained inducible at day-100, and was compared to the VT_{rfa} group, which was rendered non-inducible at day-100 with intervention at day-8 (9/9 vs 11/12, \( p=1.0 \)). Areas of deep and borderline injury did not differ significantly between VT_{pos} and VT_{rfa} groups at day-8 prior to application of radiofrequency energy, or at day-100. There was not a statistically significant difference in split potentials between the 2 groups. However, there was a significant reduction in late and fractionated potentials with ablations (supplementary table c).

**Discussion**

**Main Findings**

This longitudinal study demonstrates that noncontact-electroanatomical mapping-guided RF ablation of VT induced at day-8 post-infarct abolished inducible VT or SCD up to 200 days without major adverse events. Conversely, early non-inducibility of VT post-infarct resulted in freedom from inducible VT or SCD up to 200 days.

**Early Post-infarct PVS**

The role of PVS in risk stratification in the remote infarct setting has previously demonstrated benefit.\(^2,19\) Inducible VT at 9-21 days post-infarct was associated with an increased risk of SCD or spontaneous VA, and non-inducibility conversely was associated with a lower mortality risk.\(^20-22\) Our recent work in an ovine model has demonstrated inducibility and non-inducibility of VT, the earliest presystolic activation site, and the underlying voltage substrate remain stable from 8 to 100 days post-infarct.(Hsieh CHC et al, supplementary material)
Early Post-infarct RFA

In this study, acute ablation success of post-infarct VT in the early period (day-8) demonstrated non-inducibility at 2 subsequent studies spanning a further 192 days.

To the knowledge of the authors, there are no studies of ablation of VT in this subacute period post-infarct, though there have been a number of studies introducing the idea of earlier ablations. The SMASH-VT study randomized patients with a prior MI with unstable VT, VF or syncope with inducible VT and an ICD to ICD therapy alone or ICD combined with substrate-based prophylactic catheter ablation. The incidence of ICD therapy decreased from 33% to 12% (p=0.007) over 2 years with catheter ablation. The VTACH trial randomized post-infarct patients with their first episode of stable VT to ICD therapy alone or ICD and RFA. In an intention to treat analysis, patients in the ablation arm had a longer time to first ICD therapy (18.6 vs 5.9 months) and greater freedom from VT/VF at 2 years (47% vs 29%). These trials demonstrated a significant benefit of earlier ablative therapy. However, they enrolled patients years remote from their infarcts.

It is difficult to compare the success rate of this study and the above-mentioned clinical studies given the different end points. Acute success in catheter ablation of VT in remote MI is 73-86%. Long-term recurrence rates are reported as 16-66%. Our acute success rate of RF ablation in the early post-infarct period was 100%, which is unexpectedly high, possibly related to the ablations being performed in the subacute period, prior to significant LV remodelling. Evolving substrate and fibrosis over time may contribute to potentially multiple reentrant circuits and make ablation more difficult. The mid-term success, measured by re-inducibility over 200 days, is impressive and may have important clinical implications. This cannot be directly compared to clinical studies with ICD recordings of spontaneous events. Further corroboration
with clinical trials are indicated.

Our technique of using combined substrate and noncontact activation mapping proved to be effective in the early post-infarct period, with faster and hemodynamically unstable VT. These arrhythmias in the remote infarct setting, have been treated with RF ablation targeting substrate. The authors felt that targeting substrate only, when scar tissue has not yet been fully established, may not be as reliable in this early post-infarct period. Noncontact mapping and ablation has been previously validated in the setting of chronic post-infarct VT ablation. Pratola et al achieved an acute success rate defined as VT noninducibility of 95%. Our study demonstrates similar acute success rates and evidence of longer-term noninducibility with the noncontact system. However, the relative merits of the two approaches can only be established by further direct comparison.

**VT substrate**

Noncontact mapping was utilized due to the rapid rate (251±27ms cycle length) and poor hemodynamic tolerability of the early post-infarct induced VT. This is consistent with clinical studies of VTs induced 1 week post-infarct (220ms), and disparate from chronic post-infarct VT (428ms).

Similar to our previous animal (Hsieh CHC et al, supplementary material) and reported clinical studies, the earliest presystolic VT activation site was found within the infarct borderzone (DSM<50%), usually in close proximity to the boundary between borderline and dense injury (DSM 30th percentile). This borderzone activation site was confirmed on contact mapping by Verma et al.

Our study demonstrated a no statistically significant difference between areas of dense and borderline injury between day-8 and day-100 between the VT_{tra} and historical control VT_{pos}.
groups. However, this study was not powered to see a difference in these comparisons made post-hoc.

Our study found a significant increase in the quantity of late and fractionated potentials in VTrfa animals compared to VTneg animals at all time points, and in split potentials at days 8 and 100. However, compared to the VTpos group, VTrfa animals had a statistically significant reduction in late and fractionated potentials, secondary to the day-8 ablations. Our findings are consistent with Haqqani et al, who found that in ischaemic cardiomyopathy, spontaneous VT was associated with more split, late and fractionated potentials compared to patients without spontaneous events.10 Haqqani et al noted higher proportion of fractionated, split and late potentials compared to the present study, but this is likely related to variations in the clinical population with different infarct territories, revascularisation and in the number of previous infarcts. Haqqani et al also found larger areas of lower voltage in the population with spontaneous VT.

**RF ablation vs ICD**

Current prophylaxis for post-infarct SCD is ICD implantation. The benefit of ICDs however, is marred by several problems. ICD therapy is not successful in preventing SCD in 3-7%, and is associated with a decline in psychosocial quality of life.25 Multiple ICD shocks, whether appropriate or inappropriate, are associated with a 3.4-5.7-fold increase in relative risk for death.3,26 The current view is that ICD shocks are a marker for increased mortality, but may not be mechanistically related to death.27 However, ICD shocks are associated with adverse cellular and mechanical responses temporarily and permanently.27

Collectively, these results suggest that avoidance of ICDs and shock delivery would improve patient outcomes. Our study suggests that prophylactic ablative therapy delivered in the
subacute period may prevent or reduce the need for defibrillators. This needs further clinical corroboration.

**Adverse Events**

Subacute ablation of post-infarct VT needs to have a low complication rate to be a viable option. In a meta-analysis of chronic ischemic VT ablation, the adverse event rate was 6.3%. This included death, stroke or transient ischemic attacks, perforation, and third-degree atrio-ventricular block. In our animal study there were no major procedural complications. Overall LV function and the incidence of heart failure were not impacted by the ablations, likely due to the ablations primarily targeting areas of dense and borderline injury. Again, this needs confirmation in further studies.

**Study Limitations**

This study used an animal model, and had a moderate but not prolonged follow-up period of 200 days. Clinical post-infarct VT may appear for the first time years after the infarct. However, if VT is not inducible using a vigorous induction protocol such as in this study, clinical studies suggest a low chance of late VT.

Due to the hemodynamic instability of the induced VTs in this study, we were unable to perform detailed contact activation or entrainment mapping. However, this reflects reality, where only ~30% of patients with post-infarction VT can tolerate their arrhythmia for contact activation mapping.

**Conclusion**

Early ablation of inducible VT 8 days post-MI resulted in a high acute and chronic success rate and seemed to be safe in this animal model. This novel approach of radiofrequency ablation needs to be validated in clinical studies.
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**Conflict of Interest Disclosures:** None.

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Figure Legends

**Figure 1:** Flowchart of experimental protocol

**Figure 2:** Panel A demonstrates scar-related electrograms in a VT$_{neg}$ animal in the top row and in a VT$_{rfa}$ animal in the bottom row. From left to right the pictures are for days 8, 100 and 200. Images are orientated as labelled. S: septum. LAD: left anterior descending artery. Color scale for DSM-based voltage substrate mapping. Electrograms are annotated as: fractionated potentials (blue), split potentials (white), late potentials (yellow). Fractionated and split potentials found in borderzone, and late potentials usually found in lower voltage areas. Panel B demonstrates the higher percentage of split, late and fractionated potentials at all time points in VT$_{rfa}$ animals. Analysis by repeated measures demonstrated a significant effect of both time and ablation status in split ($p$=0.013), late ($p$<0.001), and fractionated ($p$=0.006) potentials.

**Figure 3:** Three separate activation patterns of VT induced in this example, with subsequent radiofrequency ablations. Color scale of activation time to left (msec). Ap: apex, Ao: aortic root, AL: anterolateral wall, S: septal wall. Left homonymous artery and first diagonal branch marked as a red line. Solid white line DSM 30% demarcation for dense injury, dotted white line DSM
50% demarcation for borderline injury. For each diagram, a representative ECG (lead I) and 4 virtual electrograms with corresponding green numbers on the diagram to the bottom right. Yellow dots demonstrating placement of ablations. The first ablation set (left diagram) targeted the mid-septal earliest endocardial activation site, with ablations performed both perpendicular and parallel to the activation near the borderline and dense injury areas. The second ablation set (middle diagram) targeted an apical earliest endocardial activation site. The broader “front” required a longer line of ablation. The third ablation set (right diagram) targeted a VT originating in the apicolateral area. The line of ablation was joined to the first ablation set.
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