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

Calvin H.C. Hsieh, MBBS(Hons), BSc(Med), FRACP; Ee-May Chia, MBBS, BSc(Med), MPH, FRACP; Kaimin Huang, BSc; Juntang Lu, Dip(Vet); Michael Barry, BE; Jim Pouliopoulos, BSc, PhD; David L. Ross, MBBS, FRACP; Stuart P. Thomas, MBBS, FRACP, PhD; Pramesh Kovoor, MBBS, FRACP, PhD

Background—Ventricular tachycardia (VT) is a significant complication of myocardial infarction. Radiofrequency ablation for postinfarct VT is reserved for drug refractory VT or VT storms. Our hypothesis is that radiofrequency ablation in the early postinfarct 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 postinfarct. Animals with inducible VT (12 out of 25 animals) underwent immediate radiofrequency ablation. Further VT inductions were performed 100 and 200 days postinfarct. At day 8, 3.0±0.9 VT morphologies per animal were inducible. All were successfully ablated with 24±6 applications of radiofrequency 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 because of hypotension from a serious pericardial effusion. The other 11 survived and remained arrhythmia free on subsequent inductions on the 100th and 200th days (P<0.001). The 13 animals without inducible VT remained noninducible 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 eighth day after infarction abolished inducibility of VT at late induction studies ≤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. (Circ Arrhythm Electrophysiol. 2013;6:1215-1221.)

Key Words: catheter ablation □ myocardial infarction

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

Clinical Perspective on p 1221

Catheter radiofrequency ablation (RFA) 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. 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.

Our hypothesis is that RFA 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 midterm noninducibility of VT. MIs were induced in 35 male cross-bred merino sheep (weight, 58±11 kg). In the 25 (71%) survivors, programmed ventricular stimulation (PVS) was performed 8 days postinfarct. Animals with inducible VT (VTrfa) underwent immediate catheter-based ablation and had subsequent PVS 100 and 200 days postinfarct. The control arm of animals without inducible VT (VTneg) underwent the same PVS studies (Figure 1). A transthoracic echocardiogram was acquired preinfarct and pre-PVS. A secondary analysis of efficacy compared VTrfa animals with a 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 (2.5–4.0×8–20 mm) of the midm runners artery (left anterior descending artery equivalent) for 3 hours induced an MI.
Electroanatomical Map
On the eighth postinfarct day, an electroanatomic map and simultaneous noncontact and contact data were collected via the Ensite multielectrode array system (St Jude, St. Paul, MN) as previously described.8 Mapping was performed before 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 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 (≤0.5, 0.5–1.5, and >1.5 mV, respectively) collected during sinus rhythm and noncontact DSM (≤30%, 30%–50%, and >50% of the local unipolar electrogram peak negative voltage).9,10 Electrograms were classified using standard criteria by 2 independent observers11–13:

1. Normal electrograms with ≤3 sharp intrinsic deflections, with amplitude ≥3 mV and duration <70 ms, or amplitude/duration >0.046.
2. Fractionated potentials with >3 deflections, with amplitude ≤0.5 mV and duration ≥133 ms, or amplitude/duration ≤0.005.
3. Isolated potentials with additional signals separated from the local electrogram by >20 ms isoelectric interval.
4. Late potentials with additional signals occurring ≥100 ms after the QRS.

PVS and VT Ablation
On the eighth, 100th, and 200th days, PVS was performed from the right ventricular (pulse width 2 ms, drive train 8 beats, and ≤4 premature extrastimuli). The protocol was repeated twice each from 2 pacing sites (right ventricular apex and basal septum), and with 2 drive trains (400 and 450 ms). The end point 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 ≥200 ms, sustained for ≥30 s if hemodynamically stable or ≥10 s if unstable, and reproducible.14 All induced VTs were considered for ablation. A 10- to 20-s segment of the induced arrhythmia was recorded before termination.

Ablation Technique
Entrainment and contact activation mapping were not possible as all VTs were not hemodynamically tolerated. Therefore, substrate modification was performed during sinus rhythm within the region identified to be critical for sustaining VT, with ≥1 of the following criteria15–17:

1. Corresponding to early activation site determined by noncontact mapping (earliest onset of QS deflection with virtual electrograms during VT).18
2. Paced QRS morphology similar to target VT (match ≤11/12 ECG leads).19
3. Stimulus-QRS interval >40 ms pacing from the site in sinus rhythm.
4. Anatomic continuity with other lesions.

Ablation was placed using a 3.5 mm, saline-irrigated tip 4-electrode deflectable ablation catheter (Navistar Thermocool; Biosense-Webster, Diamond Bar, CA). Radiofrequency energy was delivered for 90 to 120 s in power control mode with 50 W maximum power, and automatically terminated if the maximal temperature (48°C) or impedance (300 Ω) was exceeded. Saline flow was maintained at 2 mL/min and increased to 30 mL/min during radiofrequency delivery. Sequential point lesions created lines both parallel and perpendicular to the infarct border. The ablations were extended ≥1 cm into the infarcted region. Parallel lesions were extended into distinctly noninfarcted tissue (≥2 mV).20 All ablations that targeted the septum had corresponding ablations from the right ventricular to create transmural lesions.7 Postablation, 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

Figure 1. Flowchart of experimental protocol. VT indicates ventricular tachycardia.
technique described above. The end point of the procedure was defined as noninducibility of any VT using the PVS protocol.

Data Analysis
Data were analyzed using Matlab version 2010a (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 version 16 (SPSS Inc, Chicago, IL). Two-tailed tests with 5% significance level were used throughout. Continuous variables were summarized as mean±SD. Association between categorical variables was tested using Fisher exact test. Repeated measures 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 were 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 end point of the study was the long-term noninducibility of VT. Acute success was defined as noninducibility of any VT≥200 ms at the end of the ablative procedure. Long-term success was defined as noninducibility at 2 subsequent PVSs on days 100 and 200.

A sample size of 12 per group (VT_dia and VT_meg) has >90% power to establish equivalence between VT_dia and VT_meg 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_meg group. The secondary analysis was an efficacy comparison between VT_dia and VT_meg animals and a historical control arm of 9 animals with inducible VT at day 8 followed until 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 noninducibility rate at day 100 of 99% in VT_meg 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 eighth, 100th, and 200th days, respectively, without a statistical difference between VT_dia and VT_meg animals.

VT Characteristics
At the day 8 electrophysiological study, 12 out of 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±27 ms, and requiring 3.5±0.7 extrastimuli for induction. There was a predominance of left bundle branch pattern (23 out of 37 animals). Successful termination of the induced VT by antitachycardia pacing occurred in 29 arrhythmias (78%). The remaining 8 required DC cardioversion because of either unsuccessful reversion with antitachycardia pacing or rapid hemodynamic compromise (Table I in the online-only Data Supplement).

The earliest noncontact unipolar activation was 23±9 ms earlier than the earliest surface ECG deflection. The most common region with the earliest activation was the apico-septum (17 out of 37 animals). Substrate mapping by DSM located the earliest presystolic activation site as 2.0±3.0 mm 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. Before application of radiofrequency energy at day 8, there was no statistical difference in the area of dense and borderline injury by contact or noncontact measurements in VT_dia or VT_meg animals (Table II in the online-only Data Supplement). There was a larger area of dense injury by contact measurements at day 100 in ablated VT_dia animals compared with VT_meg animals (10.2±6.2 versus 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 days 100 and 200.

The contact electrogram characteristics were more marked, with increased split, late, and fractionated potentials at all time points in the VT_dia animals (Figure 2).

VT Ablation
A total of 37 VTs were targeted for catheter ablation. All ablations were performed from the left ventricular endocardial surface with 67% (8 out of 12 animals) requiring ablations on the right ventricular side of the interventricular septum to create a transmural lesion for arrhythmias arising from this location.7 Each animal required 24±6 applications of radiofrequency energy and a total time of radiofrequency application of 49±23 minutes. The power delivered was 47W (range, 46W–48W) with a temperature of 40°C (range, 38°C–42°C). Ablation extended the total procedure time from 5.0±2.3 to 8.4±1.6 hours (P=0.001) and fluoroscopy time from 25.7±17.7 versus 38.9±26.8 minutes (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: right bundle branch block, northwest axis morphology, and cycle length 245 ms. The exit point, based on the earliest virtual electrogram activation 37 ms before onset of QRS on the surface EKG, was the midanteroseptum. VT−2: left bundle branch block, left anterior descending axis morphology, and cycle length 205 ms. The exit point was the apex, 15 ms earlier than the surface EKG. VT−3: right bundle branch block, left anterior descending axis morphology, and cycle length 290 ms. 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 out of 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 before experimentation. Hemodynamics did not improve after PVS, and the animal was euthanized.
because of ethical concern about its condition. An immediate autopsy of the animal confirmed a serious effusion, with no perforation seen. All other animals survived and completed the 100th and 200th day procedures. Two animals required diuretics for 2 days postradiofrequency ablation, but there was no long-term heart failure. No significant morbidity or mortality in the VT<sub>neg</sub> group (13 out of 13 survived 200 days) was seen.

PVS and complex mapping was repeated on the 100th and 200th days. Monomorphic VT was not reinducible on either day in any of the ablated animals (12 out of 12 VT<sub>rfa</sub> animals).

Figure 2. A, Scar-related electrograms in a VT<sub>neg</sub> animal in the top row and in a VT<sub>rfa</sub> animal in the bottom row. Left to right, Days 8, 100, and 200. Images are orientated as labeled. Color scale for dynamic substrate mapping–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. B, The higher percentage of split, late, and fractionated potentials at all time points in VT<sub>neg</sub> 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. LAD indicates left anterior descending artery; S, septum; and VT, ventricular tachycardia.

Figure 3. Three separate activation patterns of ventricular tachycardia (VT) induced in this example, with subsequent radiofrequency ablations. Color scale of activation time to left (ms). Left homonymous artery and first diagonal branch marked as a red line. Solid white line dynamic substrate mapping (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) targeted the midseptal 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) targeted an apical earliest endocardial activation site. The broader front required a longer line of ablation. The third ablation set (right) targeted a VT originating in the apicolateral area. The line of ablation was joined to the first ablation set. AL indicates anterolateral wall; Ao, aortic root; Ap, apex; and S, septal wall.
day 8 before ablation compared with 11 out of 11 VTpos animals day 100 and day 200;  $P<0.001$). No inducible arrhythmia was seen in the VTneg control arm on subsequent studies (13 out of 13 animals).

The historical VTpos arm of 9 animals with inducible VT at day 8 remained inducible at day 100 and was compared with the VTria group, which was rendered noninducible at day 100 with intervention at day 8 (9 out of 9 versus 11 out of 12 animals;  $P=1.0$). Areas of deep and borderzone injury did not differ significantly between VTpos and VTria groups at day 8 before 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 ablation (Table III in the online-only Data Supplement).

### Discussion

#### Main Findings

This longitudinal study demonstrates that noncontact-electro-anatomical mapping-guided radiofrequency ablation of VT induced at day-8 postinfarct abolished inducible VT or SCD ≤200 days without major adverse events. Conversely, early noninducibility of VT postinfarct resulted in freedom from inducible VT or SCD ≤200 days.

#### Early Postinfarct PVS

The role of PVS in risk stratification in the remote infarct setting has previously demonstrated benefit.2–8 Inducible VT at 9 to 21 days postinfarct was associated with an increased risk of SCD or spontaneous VA, and noninducibility conversely was associated with a lower mortality risk.21–23 Our recent work in an ovine model has demonstrated inducibility and noninducibility of VT, the earliest presystolic activation site, and the underlying voltage substrate remain stable from 8 to 100 days postinfarct.8

#### Early Postinfarct RFA

In this study, acute ablation success of postinfarct VT in the early period (day 8) demonstrated noninducibility 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 postinfarct, although there have been several studies introducing the idea of earlier ablations. The SMASH-VT study randomized patients with a previous MI with unstable VT, VF, or syncope with inducible VT and an ICD–ICD therapy alone or ICD combined with substrate-based prophylactic catheter ablation. The incidence of ICD therapy decreased from 33% to 12% ($P=0.007$) >2 years with catheter ablation. The Ventricular Tachycardia Before Defibrillator Implantation in Patients with Coronary Heart Disease (VTACH) trial randomized postinfarct 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 versus 5.9 months) and greater freedom from VT/VF at 2 years (47% versus 29%).6 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% to 86%.4,17 Long-term recurrence rates are reported as 16% to 66%.16,24 Our acute success rate of radiofrequency ablation in the early postinfarct period was 100%, which is unexpectedly high, possibly related to the ablations being performed in the subacute period, before significant left ventricular remodeling. Evolving substrate and fibrosis over time may contribute to potentially multiple reentrant circuits and make ablation more difficult. The midterm success, measured by inducibility >200 days, is impressive and may have important clinical implications. This cannot be directly compared with clinical studies with ICD recordings of spontaneous events. Further corroboration with clinical trials is indicated.

Our technique of using combined substrate and noncontact activation mapping proved to be effective in the early postinfarct period, with faster and hemodynamically unstable VT. These arrhythmias in the remote infarct setting have been treated with radiofrequency ablation targeting substrate.15 We thought that targeting substrate only, when scar tissue has not yet been fully established, may not be as reliable in this early postinfarct period. Noncontact mapping and ablation has been previously validated in the setting of chronic postinfarct VT ablation.15,25 Pratola et al19 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 2 approaches can only be established by further direct comparison.

#### VT Substrate

Noncontact mapping was used because of the rapid rate (251±27 ms cycle length) and poor hemodynamic tolerability of the early postinfarct induced VT. This is consistent with clinical studies of VTs induced 1 week postinfarct (220 ms),23 and disparate from chronic postinfarct VT (428 ms).4

Similar to our previous animal and reported clinical studies,19 the earliest presystolic VT activation site was found within the infarct borderzone (DSM<50%), usually in close proximity to the boundary between borderzone and dense injury (DSM 30th percentile). This borderzone activation site was confirmed on contact mapping by Verma et al.15

Our study demonstrated a no statistically significant difference between areas of dense and borderzone injury between day 8 and day 100 between the VTpos and historical control VT 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 VTpos animals compared with VTneg animals at all time points, and in split potentials at days 8 and 100. However, compared with the VTpos group, VTpos 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,11 who found that in ischemic cardiomyopathy, spontaneous VT was associated with more split, late, and fractionated potentials compared with patients without spontaneous events. Haqqani et al11 noted higher proportion of fractionated, split, and late
potentials compared with the present study; however, this is likely related to variations in the clinical population with different infarct territories, revascularization, and in several previous infarcts. Haqqani et al also found larger areas of lower voltage in the population with spontaneous VT.

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

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
Subcutaneous ablation of postinfarct 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 atrioventricular block. In our animal study, there were no major procedural complications. Overall left ventricular function and the incidence of heart failure were not impacted by the ablations likely because of the ablations primarily targeting areas of dense and border-line 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 postinfarct VT may seem 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.

Because of 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 postinfarction VT can tolerate their arrhythmia for contact activation mapping.

Conclusions
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 RFA needs to be validated in clinical studies.

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Disclosures
None.

References


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**CLINICAL PERSPECTIVE**

Ventricular tachycardia (VT) is a potentially lethal complication of myocardial infarction. In an ovine model, we have observed that VT that is inducible early after myocardial infarction remains inducible at late follow-up, suggesting a possible role for early identification by programmed stimulation for potential treatment. This article tackles the question of whether early intervention with radiofrequency ablation can abolish inducible VT early and prevent late inducible VT in this model. Myocardial infarcts were induced in 35 animals, 12 of the 25 survivors had inducible VT on the eighth postinfarct day and underwent radiofrequency ablation, rendering all noninducible at the end of the procedure. At repeat study, 100 and 200 days postinfarction, no VT was inducible. The findings in this animal model suggest that an early VT ablation approach for patients with inducible VT early after myocardial infarction warrants consideration for further study.
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