Published in final edited form as:

Heart Rhythm. 2009 August ; 6(8 Suppl): S91–S97. doi:10.1016/j.hrthm.2009.03.048.

Ventricular tachycardia from the healed myocardial infarction scar: validation of an animal model and utility of gene therapy

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Abstract

Life-threatening ventricular arrhythmias generally occur in the setting of structural heart disease. Current clinical options for patients at risk for these rhythm disturbances are limited. We developed a porcine model of inducible ventricular tachycardia originating in the border region of a healed myocardial infarction scar. After validating the model, we assessed gene transfer techniques, focusing on local modification of border zone tissues. We found that gene transfer of the dominant negative KCNH2-G628S mutation to the antero-septal infarct border caused localized prolongation of effective refractory period in the target region and eliminated all ventricular arrhythmia inducibility. In this work, we characterize the animal model and review the gene transfer results.

Keywords

Ventricular arrhythmias; Myocardial infarction; Animal model; Gene transfer/Gene therapy

In spite of therapeutic advances in the care of myocardial infarction (MI) and heart failure patients and improvements in the understanding and treatment of coronary risk factors, cardiac arrest remains the most frequent cause of death in developed countries. An autopsy study of cardiac arrest victims found that a majority had some indication of coronary disease, either active ischemia or prior infarction.^{1,2} The presumed mechanism of cardiac arrest in these patients is a ventricular tachyarrhythmia (VT) causing circulatory collapse and death. Study of post-infarct patients has shown that these arrhythmias generally originate in the border zone region where fibrotic scar connects to surviving myocardium.³ Mechanisms of arrhythmia generation in the subacute period, days after infarction, have been extensively studied (for review see Pinto and Boyden).⁴ Surprisingly, considering that the majority of cardiac arrest victims are months or years away from their index infarction, there has been little study of arrhythmia mechanisms in the setting of a mature, healed infarct scar. This limitation in our understanding of scar-related arrhythmia mechanisms is reflected in the paucity of options for treating these patients.

Therapeutic options for arrhythmias arising from the mature scar border include antiarrhythmic drugs, electrophysiology study to define the arrhythmia circuit followed by ablation to

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eliminate the offending tissue, and implantable cardioverter defibrillator (ICD) therapy. Drugs were first line therapy for decades until a series of placebo-controlled clinical trials showed increased mortality with antiarrhythmic drug use in patients with either heart failure, ischemic or structural heart disease.⁵⁻⁷ The general mechanism of action for antiarrhythmic drugs is blockade of ion channels to slow conduction through the heart (in the case of sodium and/or calcium channel blocking drugs) or to prolong cellular refractory properties by increasing action potential duration (in the case of potassium channel blocking drugs). A general problem with this strategy is that therapy is global, so that areas of the heart benefiting from the antiarrhythmic actions are counterbalanced by areas of the heart in which the drug mechanism is not needed and the resulting changes can be proarrhythmic rather than antiarrhythmic. The end effect is that antiarrhythmic drugs do a good job of preventing arrhythmias most of the time but also of causing arrhythmias some of the time, and overall mortality is increased.

Radiofrequency ablation can effectively eliminate arrhythmias that come from focal sources. Either by delivering a single lesion to an isolated focus or by delivering a series of lesions in a linear pattern to block cardiac electrical impulse conduction through an isthmus of tissue, appropriately targeted ablation lesions can cure arrhythmias by destroying regions of cardiac tissue that are integral to the arrhythmia mechanism. The major limitation of ablation therapy is opposite that of drug therapy. Rather than the global effects of drug therapy, ablations are highly localized, and thus cannot easily modify large regions of diseased tissue. Individual arrhythmias can be ablated, but the arrhythmogenic substrate generally remains intact after the ablation procedure. New scar-related arrhythmias commonly develop within this substrate months or even years after a successful ablation procedure.⁸

ICD clinical trials have conclusively shown the ability of this technology to save lives.⁹⁻¹² Unlike drugs or ablation, these devices do nothing to alter the arrhythmogenic substrate. They do not prevent arrhythmias, focusing instead on returning the patient to sinus rhythm after arrhythmia occurrence. As such, ICDs are effective stop-gap measures, but they are imperfect solutions. Since the potential for arrhythmia occurrence is ever present, device therapy becomes a life-long commitment. Problems with ICDs that have become evident after widespread adoption of this technology include component failures of the hardware and procedural complications during the device implantation.¹³

Limitations of current arrhythmia treatment options have motivated an ongoing search for alternatives. To address this problem, we focused on developing an animal model of ventricular tachyarrhythmias in the setting of a mature MI scar.¹⁴ We compared functional elements of our animal model to the human situation and to existing animal models, developed gene delivery methods to modify the arrhythmogenic substrate and tested gene therapy to eliminate ventricular arrhythmias in the model.

Development of an animal MI-VT model

We considered the following attributes to develop an appropriate animal model of MI/VT: animal tolerance to the procedure, consistency of infarct creation, reliability of VT induction, and patency of the infarct-related artery for later gene transfer. We focused exclusively on large animal models with anatomical similarity to humans, for eventual translation of the results into clinical practice. In order to focus on arrhythmias coming from the mature infarct scar and to avoid duplication of the extensive body of work investigating arrhythmias occurring minutes to days after coronary occlusion, we chose to consider only models where the arrhythmia was consistently present several weeks after the infarction.

Based on literature reports showing consistent infarction and formation of VT substrate with microbead infusion into the coronary arteries,¹⁵ we first evaluated this method of infarct formation, but we were disappointed with the results. Infusion of a concentrated solution of

microbeads into the left anterior descending coronary artery (LAD) in our pigs effectively caused infarction and reliably inducible VT, but the peri-procedural mortality was unacceptably high in our hands. More than half of the pigs failed to survive the infarction procedure. When we diluted the microbead solution, we improved the survival rate, but at the expense of inconsistent infarct creation and unreliable VT inducibility. We next considered the possibilities of damaging the coronary endothelium by balloon abrasion, of instilling fractionated blood clot or infusing activated thrombin into the mid-LAD, thinking that this would be similar to the human situation of blood clot formation at a site of plaque rupture. We saw no short term adverse effects to endothelial abrasion. Blood clot or thrombin infusion was inconsistent in generation of a reliable substrate for VT. Occasionally the clot would stay at the mid-LAD level and create a large scar with VT inducibility, but frequently the clot would migrate distal in the vessel causing a small infarct. Frequently, the activated thrombin would pass through the cardiac circulation altogether and caused pulmonary embolism rather than myocardial infarction. We attempted to create infarction by infusion of ethanol, but we found this method to be unreliable in large caliber vessels like the LAD. When we used enough ethanol to saturate the perfusion bed, the animals died of ethanol toxicity. When we used smaller volumes, the infarcted area was small and not arrhythmogenic.

We avoided LAD ligation methods because they did not fulfil the criteria of maintaining artery patency for later gene transfer. Finally, we settled on prolonged balloon occlusion of the LAD as the most reliable method for creation of an infarct scar that was a reliable substrate for VT. We found that balloon occlusion of 60 minutes or less did not typically cause transmural scar formation in the pig. With 2 ½ hour balloon occlusion of the LAD, we found the method that we had been looking for (for a detailed description of the methods, please see the online supplement to Sasano et al.¹⁴). Infarction caused an increase in cardiac enzymes 24 hours after balloon occlusion (creatin kinase-MB fraction 49 ± 32 ng/ml, troponin I 79 ± 8 ng/ml). Echocardiographic measurement of left ventricular ejection fraction (EF) showed an initial drop from the pre-infarction value of $68 \pm 3\%$ to $57 \pm 6\%$ one week after infarction. EF continued to decrease in the weeks after infarction, finally settling at $42 \pm 2\%$ on repeated weekly studies 3–5 weeks after infarction. We interpret these data to demonstrate an initial decrement in EF from the infarct, a subsequent further decrease from LV remodeling, and stabilization in EF as the infarct scar matured. Pathological analysis after sacrifice showed anterior-septal infarction with a thin surviving rim of endocardium on triphenyl tetrazolium chloride staining in the initial 7 animal cohort that we used to validate the model. Histological study of the anterior septal scar border in those initial 7 animals revealed surviving strands of myocardium interwoven with fibrotic scar (Figure 1A).

As of this writing, 50 animals have undergone the infarct procedure with weekly EP study for 5 weeks after infarction. Results of the weekly EP study are as follows: 0% had inducible sustained monomorphic ventricular tachycardia (SMVT) and 6% had inducible ventricular fibrillation (VF) on the baseline study before infarction. After infarction, 20% had inducible SMVT and 0% had VF at week 1, 62% had SMVT and 6% had VF at week 2, 80% had SMVT and 4% had VF at week 3, and 90% had SMVT and 0% had VF at weeks 4 and 5 (excluding animals that received gene therapy at the 4 week time point that we will discuss below). For each animal with inducible VT, after the animal became inducible the arrhythmia was consistently inducible and consistent in morphology and cycle length on all subsequent weekly EP studies (Figure 1B).

All animals with inducible arrhythmias had intracardiac electrogram recording of sinus rhythm and their induced arrhythmias using a 64-pole basket inserted into the LV cavity. We found fractionated, low amplitude electrograms in the anterior wall, anterior septum and apex during sinus rhythm in all animals. We recorded 48 VT morphologies in the 45 inducible animals. We found that activation was earliest on the septal side of the infarct scar in 47 of the 48 VT

morphologies, suggesting that the VT circuit almost always resided on that side of the scar (Figure 1C).

In a group of 6 animals, we performed comprehensive mapping of the VT circuit 5 weeks after infarction with both endocardial and epicardial interrogation using a 3-dimensional mapping system (RPM, Boston Scientific). We used voltage mapping techniques to identify dense scar and border zone where fibrotic scar intermingled with surviving myocardium. We used conventional EP mapping techniques of activation, entrainment and pace mapping during VT to identify the components of the VT circuit. In all 6 animals, we found the VT circuit to be a micro-reentrant area 1–2 cm in diameter that was located on the septal border of the scar (Figure 1D). The identified reentrant loop was continuously activated, and the remainder of the ventricles activated in a uniform wavefront emanating away from the VT circuit. In all mapped VTs, epicardial activation occurred later than endocardial activation, suggesting that the arrhythmia circuit either was located at the endocardial surface or was at least closer to the endocardium than the epicardium.

Comparison of the pig model to human data

To assess validity of our model, we looked to the literature on myocardial infarction and ventricular tachycardia in humans. We were particularly interested in 3 areas: time to scar maturity, pathology of the mature human infarct scar, and location of VT circuits in relationship to the isolated LAD infarct scar. The time course of scar development after infarction has been described by several investigators over the last century. Mallory et al. described “active absorption [of necrotic muscle] can be demonstrated to be taking place in infarcts up to 6 weeks [after MI]. Macrophages remain for a time after actual absorption has ceased. As the infarct becomes older they decrease in number, and in infarcts 1 to 2 years old they have practically disappeared... Basophilic [immature] fibroblasts have been found in infarcts ranging in age from 4 to 23 days... At three weeks the collagen is moderately prominent, particularly at the periphery,... By 6 weeks the whole scar is definitely contracted.”¹⁶ In addition, Fishbein et al. observed that “the time required for complete healing of myocardial infarcts in man (ie, absence of necrotic fibers) is quite variable... In the present study, necrotic fibers were not observed in any infarcts more than 35 days old.”¹⁷ These data suggest that there really is no definable time point where the scarred region is truly quiescent. Based on these data, reasonable transition points include an early time after the completion of the acute injury where inflammation, resorption of necrotic tissues, fibroblast recruitment and preliminary generation of fibrotic tissue occur; a later time where necrosis has resolved and scar tissue is in place, and a continual phase of scar remodeling that occurs over years. As such, a reasonable time point for study of the so-called mature scar would seem to be the 5–6 week period where necrosis has resolved and some reasonable stability of the scar substrate seems to be in place.

The pathological substrate for VT has been described by several investigators. Bollick et al. compared gross and microscopic pathology in autopsy samples of patients with old infarcts and VT to patients with old infarcts but no history of ventricular arrhythmias. They observed that the VT group had predominately large, patchy infarcts with irregular spared endocardium.¹⁸ In general, they found that human transmural infarcts generally consisted of fibrotic endocardium, a heterogeneous area of spared subendocardium that contained surviving myocytes, and a densely fibrotic mid-myocardial and epicardial region. Deneke et al. among others have shown that radiofrequency ablation lesions disrupt VT circuits by destroying myocardial tissue in this spared subendocardial area. Perhaps the most extensive human data on pathology of human infarction and VT mechanisms comes from a series of studies published by de Bakker et al. 15–20 years ago.^{19,20} In an initial study, they mapped VT circuits *in vivo* during cardiac surgical procedures. Of 136 mapped VTs in 72 patients, they localized 105 of the tachycardias to focal areas in the border zone less than 1.4 cm² in diameter (countering

a common misconception that reentrant VT circuits are necessarily large, encircling the entire infarct scar). In microelectrode recordings of this tissue, they found two different AP morphologies: a relatively normal ‘fast’ morphology with normal resting membrane potential, rapid upstroke, normal amplitude and repolarization, and a ‘slow’ morphology with slightly diminished resting potential, decreased upstroke velocity and amplitude and longer refractory period. They mapped the tachycardia activation sequence and compared it to tissue architecture, observing that VT consistently traveled through areas where extensive fibrosis infiltrated between myocytes. Comparing these literature reports to our pig data suggest that the gross and microscopic pathology of our animal model is quite similar to what is known about the human situation.

Perhaps the most intriguing finding from the pig infarct-VT model is the localization of VT circuits predominately to the septal side of the infarct scar. We looked for comparable human literature to assess the validity of this finding. A report by Miller et al. used intraoperative mapping to locate VT circuits in 108 patients.²¹ Only patients with single areas of infarction were considered to avoid confounding the results with multiple scars in single patients. An anterior infarct scar was present in 73 patients who had 128 mapped VT circuits. In all but 6 of these, the origin occurred on the septal side of the anterior infarct scar. Thirty-five of the patients had inferior infarct scars, accounting for 54 VT circuits. All but 5 of these circuits mapped to the basal side of the infarct scar. Thus, in humans anterior scar correlated most commonly with septal VT, and inferior scar correlated with basal VT. The intent of the Miller study was to compare VT location to 12-lead ECG morphology of the arrhythmias. As such, they do not directly address our question, but their data suggest that our observation in the pig model is consistent with the human condition.

Comparison to existing animal models and speculation on VT mechanism

The most extensively studied large mammalian model of infarction and ventricular tachycardia actually studies the healing phase days after infarction rather than the mature healed scar several weeks after infarction that we report in the pig model. The model was originally described by Harris in 1950, who reported that two stage ligation of the LAD in dogs (initial partial occlusion followed 30 minutes later by full occlusion) created a reproducible substrate for ventricular arrhythmias several days after the infarction.²² Arrhythmia inducibility in this model lessened over time, and most animals became uninducible after healing of the scar.²³ Investigation of border zone myocytes 4–5 days after infarction showed AP morphologies with reduced resting membrane potential, decreased upstroke velocity and shortened action potential duration, similar to the de Bakker’s “slow” morphology from the human study.²⁴ Electrophysiological abnormalities included decreased sodium and L-type calcium current density with altered kinetics, decreased transient and delayed repolarizing potassium currents, and decreased conduction velocity with connexin lateralization^{25–28}. Investigations at later time points in the dog model showed that alterations in AP morphology resolved by 28 days post-MI. The potassium currents normalized by 60 days post-MI, but reduction in the calcium current persisted through at least 60 days post-MI, with kinetic alterations that included a slower recovery from inactivation and a shift toward negative voltage in activation and inactivation.²⁹

Further definition of the VT mechanism in large mammalian models is limited because there is little data beyond the dog healing infarct model. Sporadic work in small mammal models has shed some light on border zone electrophysiology. Litwin et al. found decreases in peak $I_{Ca,L}$ with normal channel kinetics and decreases in the sodium-calcium exchanger current in border zone myocytes isolated 8 weeks after infarction in the rabbit heart.³⁰ Pinto et al. found reduced calcium currents with a shift in the inactivation curve toward negative voltage and no change for inactivation or recovery kinetics in myocytes isolated from the border zone in cats

2–4 months post-infarct,³¹ and Aimond found decreased $I_{Ca,L}$ with normal kinetics in myocytes isolated from rats 4–6 months post-infarction.³²

Overall, the picture of EP alterations in the mature infarct scar is still relatively incomplete. From the available evidence, we can speculate that the mechanism of reentry includes a composite of alterations in cellular excitability, repolarization and connectivity leading to slowing of conduction velocity and heterogeneities in cellular refractory properties. These functional alterations are the fundamental components of reentrant circuits.

Gene therapy to eliminate the arrhythmogenic substrate in the scar border

Given the reproducible septal location of the VT circuit and the reentrant characteristics of the arrhythmia, we hypothesized that localized, uniform prolongation of cellular refractory period, targeted to the septal scar border, would disrupt reentry by creating block at higher activation frequencies and thereby eliminate the ability of that tissue to support VT without causing proarrhythmic side effects throughout the rest of the heart. To achieve this focally targeted modification, we used gene transfer technology with adenovirus vectors. We had previously shown that simultaneous perfusion of adenovirus through the LAD and companion great cardiac vein caused gene transfer to 80% of myocytes in the anterior-septal region.³³ We tested this gene delivery method 3 weeks after MI in 5 animals. The LAD perfusion catheter was placed approximately in the same position that the balloon catheter had previously been inserted to create the infarction. In the post-MI animals, this method achieved gene transfer to approximately 45% of the myocytes in the target region (Figure 2A).

We tested the ability of gene transfer to modify the arrhythmogenic substrate by using KCNH2-G628S as a transgene. This mutation was originally identified with the long QT syndrome. It has been shown to eliminate the I_{Kr} current in with dominant negative effects. The dominant negative element was important because we needed a transgene that would alter the behavior of the endogenous potassium channels. We compared 5 animals receiving KCNH2-G628S to 5 animals receiving the reporter gene β -galactosidase and an additional 5 animals who did not undergo any gene transfer. We have previously shown that β -galactosidase gene transfer does not cause any measurable electrophysiological effects,²³ so these 2 additional groups served as controls. We tested ventricular arrhythmia inducibility weekly after MI and only used animals that had reproducibly inducible VT for this study. We tested the functional effects of transgene expression 7 days after gene transfer. In follow-up EP testing, we could no longer induce any ventricular arrhythmias in the KCNH2-G628S group, while both control groups remained easily and consistently inducible (Figure 2B). Correlating with this positive outcome, we noted that the KCNH2-G628S group also had a 20% increase in local refractory period within the anterior septum and no change in refractory period outside the target area (Figure 2C). The control groups had no change in refractory properties of any cardiac region when compared to pre-gene transfer values. All animals continued to have slow conduction through the border zone, suggesting that the mechanism of efficacy in the KCNH2-G628S group was an increase in cellular refractory properties that prevented activation at rates fast enough to support VT.

Safety testing in this cohort of animals included continuous monitoring for sustained arrhythmias using ICDs, daily quantitation of premature ventricular contraction frequency with telemetry recordings, pacing maneuvers to elicit triggered arrhythmias *in vivo* and early afterdepolarizations in myocytes isolated from the gene transfer region after animal sacrifice, and 12-lead ECG recordings of QT interval. We saw no change in QT interval, no spontaneous arrhythmias, and no difference in PVC frequency between groups. We were not able to induce triggered arrhythmias in any of the animals, and we saw no early afterdepolarization in spite of a more than doubling of the action potential duration in the KCNH2-G628S-expressing

isolated myocytes. The number of animals included in this study was small, but these data are encouraging for both safety and efficacy.

Summary

We have shown that 2 ½ hour balloon occlusion in pigs causes a dense transmural infarction that reliably creates the substrate for inducible VT. The pathological substrate for this arrhythmia is a heterogeneous area of fibrosis and surviving myocytes along the septal border of the infarct scar. VT inducibility typically is possible 3 or more weeks after infarction in these animals, and the characteristics of the pathology and the EP study are similar to those described previously in human studies. Simultaneous perfusion of the LAD and GCV with adenovirus gene transfer vectors can effectively modify approximately half of the cells in the VT-supporting region, and gene therapy with a dominant negative I_{K_r} -knock out mutation safely and effectively eliminated VT inducibility in the model. Extensive efficacy and safety testing in larger numbers of animals with gene transfer vectors capable of long-term gene expression is necessary to truly understand the potential benefit to humans. Our data present hope that this strategy may one day completely eliminate ventricular arrhythmias in patients after myocardial infarction.

Acknowledgements

Funding for this work came from the National Institutes of Health (R01 HL67148, R01 HL93486).

Drs. Sasano, Kelemen, Greener and Donahue declare research support related to this work including donation of defibrillators and leads from St. Jude Medical, Medtronic and Boston Scientific, and donation of the 3D mapping system and related equipment from Boston Scientific.

Dr. Donahue holds a patent for the general concept of gene therapy for arrhythmias and has an association with Excigen.

Abbreviations

VT, ventricular tachyarrhythmias; MI, myocardial infarction; EF, ejection fraction; ICD, implantable cardioverter defibrillator; LAD, left anterior descending coronary artery; VF, ventricular fibrillation; SMVT, sustained monomorphic ventricular tachycardia.

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A.

B.

C.

D.

Figure 1. Ventricular tachycardia after myocardial infarction in the porcine model

A. Gross (left) and microscopic (right) pathology of the model. The picture on the left shows a slice through the middle of the left ventricle from a representative animal. Tissue was harvested 5 weeks after infarction and stained with 2,3,5-Triphenyl-2H-tetrazolium chloride (TTC) to contrast the white infarcted area from the red surviving tissue. The Hematoxylin- and eosin-stained microsection was taken from the septal border of a representative animal 5 weeks after MI. This section reveals surviving strands of myocardium surrounded by fibrotic scar in the anterior septum. **B.** ECG examples showing identical VT morphology and cycle length from one week to the next in a representative animal. **C.** Photograph of intracardiac 64-electrode basket placement (left) and basket electrograms (right). The photograph shows the basket with spline D in a mid-septal position, E in an anterior septal position, and F in a straight anterior position. The electrogram taken during VT shows progressive diastolic activation through the anterior septum suggesting that the VT originates in this region. **D.** Representative

VT activation map. The view is antero-septal. The area to the right of the solid line had bipolar voltage less than 1.5 mV on separate voltage mapping, and the area to the right of the dotted line had bipolar voltage less than 0.2 mV. Earliest activation is orange-red, and late activation is pink. The dashed line represents the likely VT circuit based on the activation data. The area marked with “*” had concealed entrainment with post-pacing interval of 0 ms when pacing into VT. (with permission from Sasano et al.¹⁴).

Figure 2. *KCNH2*-G628S gene transfer in the MI-VT model

A. X-gal staining to identify *lacZ* gene transfer. (left) Gross tissue shows intense blue staining indicative successful gene transfer and *lacZ* expression in the anterior septal target area. (right) Microscopic sections taken from the target region exhibit blue, *lacZ* positive myocytes. **B.** Graph showing VT inducibility before and 7 days after gene transfer with either *KCNH2*-G628S or controls *lacZ* or no virus. Prior to gene transfer, VT was repeatedly inducible in all animals. After gene transfer, no arrhythmias could be induced in the *KCNH2*-G628S infected animals. All control animals remained inducible. The ECG tracing at the right shows a representative *KCNH2*-G628S animal with easily inducible VT before gene transfer and no arrhythmias when pacing down to refractoriness after gene transfer. **C.** Measurement of

effective refractory period (ERP) from the indicated regions. Prolongation of APD90 and ERP is isolated to the septal border of the infarct scar. Non—non-infarcted basal lateral wall. MS—mid-anterior septal infarct border. DS—distal anterior septal infarct border. Lat—anterior lateral infarct border. * $p < 0.05$. (with permission from Sasano et al.¹⁴).