Electrophysiologic Characterization of the Arrhythmogenic Substrate in Reentrant Atrial and Ventricular Arrhythmias

Insights from the Clinical and Experimental Electrophysiology Laboratories

CORY MICHAEL TSCHABRUNN

Doctor of Philosophy Candidate
School of Health Sciences
City University London

July 2016

City, University of London
Northampton Square
London
EC1V 0HB
United Kingdom

T +44 (0)20 7040 5060

THE FOLLOWING PARTS OF THIS THESIS HAVE BEEN REDACTED FOR COPYRIGHT REASONS:

THE FOLLOWING PARTS OF THIS THESIS HAVE BEEN REDACTED FOR DATA PROTECTION REASONS:

TABLE OF CONTENTS

List of Tables and Figures

Preface

This thesis will present a series of research studies conducted over the last 7 years during my tenure as a Research Assistant at the Hospital of the University of Pennsylvania under the supervision of Professor Francis Edward Marchlinski from August 2009 – September 2012 and subsequently in my current position as Technical Director of Experimental Electrophysiology at Beth Israel Deaconess Medical Center – Harvard Medical School under the supervision of Professor Mark Eric Josephson and Dr. Elad Anter. I will forever be grateful, beyond words, for their unwavering support and trust throughout my atypical career pathway in cardiac electrophysiology.

I would like to extend my deepest gratitude to the many other mentors, teachers, colleagues, and friends that have supported me and my career in cardiac electrophysiology for the last 14 years. Dr. Anastasios Manaris and members of the medical and nursing staff at Southside Hospital; Drs. Eric Rashba, Roger Fan, Ibrahim Almasry, and Saverio Barbera of Stony Brook University Medical Center; and Dr. Haris Haqqani, Ms. Erica Zado, and Ms. Carolyn Siwinski of the University of Pennsylvania.

I would also like to express my sincerest appreciation to Dr. Michele Baker of Boston and Dr. Mark Haddad of City University London for their patience, guidance, and kindness during the construction of this thesis.

Declaration

I declare that I grant power to the University Librarian to allow this thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgment and to copyright relating to the individual papers contained within the thesis.

Written permissions to include the full text manuscripts discussed and the adapted/reproduction of figures from other materials was acquired from each of the applicable publishers. These documents were provided separately to the University administration.

Abstract

This thesis encompasses an overview and critical analysis of 11 publications of clinical and translational cardiac electrophysiology research that has been executed over the last seven years. The focus of this dissertation and the selected papers is on the use of electroanatomic mapping technology to define the arrhythmogenic substrate in patients with structural heart disease and ventricular arrhythmias. Such advancements in elucidating the mechanisms and pathophysiology underlying scar-related ventricular tachycardia have yielded improved clinical outcomes for patients with drug-refractory ventricular arrhythmias.

Chapter 1 describes the epidemiologic background and introduces the concept of intracardiac mapping and the technological evolution that has provided the basis for this current body of work. Chapter 2 and Chapter 3 provide a detailed description of how electroanatomic mapping studies have provided critical insight into disease pathogenesis in patients with dilated non-ischemic cardiomyopathy arrhythmogenic right ventricular cardiomyopathy (ARVC). The clinical impact and relevance of these studies are discussed based on conventional electroanatomic mapping technologies to define abnormal physiological substrates. Chapter 3 also addresses important considerations regarding percutaneous epicardial mapping and ablation that have been derived from extensive clinical experience. Chapter 4 and Chapter 5 describe the evolution of mapping technologies and the use of high-resolution mapping system technologies. These chapters discuss the potential clinical advantages of these technologies during substrate and activation mapping, particularly in post-infarct ventricular scar and VT. Finally, Chapter 6 concludes this thesis with final thoughts on the broader context of the lessons that have been learned from the studies that are presented in this thesis and implications for future work.

Abbreviation List

AF: atrial fibrillation

ARVC: arrhythmogenic right ventricular cardiomyopathy

CMR: cardiac magnetic resonance

ECG: electrocardiogram

EGM: electrogram

EPS: electrophysiology study

ICD: implantable cardiac defibrillator

LAD: left anterior-descending

LGE: late gadolinium enhancement

LV: left ventricle

MI: myocardial infarction

PES: programmed extra stimulation

RV: right ventricle

SCD: sudden cardiac death

VF: ventricular fibrillation

VT: ventricular tachycardia

Chapter 1

Introduction and Review of Literature

1.1 Overview

The field of cardiac electrophysiology has seen a tremendous evolution over the last four decades, evolving from the intellectual and research curiosity of a select few to a powerful clinical and therapeutic discipline. The development of catheter ablation and new technologies have made non-pharmacological therapies a reality, and it is now the treatment of choice for most cardiac arrhythmias, including ventricular tachycardia.[1] Much of the current understanding of the electrophysiologic and electroanatomic substrates that underlie scar-related ventricular tachycardia (VT) was derived from studies that are performed within the electrophysiology laboratory. Through this experience, much has been learned about the arrhythmia mechanisms, underlying pathophysiological substrate, and strategies that are required to facilitate successful catheter ablation in patients with structural heart disease and recurrent VT. The ability to localize and define the associated abnormalities that are critical to the manifestation of VT in different disease substrates has provided important insight into disease pathogenesis and enhanced the therapeutic effectiveness of these procedures. The work in this thesis evaluates results from 11 published clinical and experimental electroanatomic mapping studies. Critical analysis of this work demonstrates the clinical utility, limitations, and technical considerations of intracardiac mapping to identify the underlying electrophysiologic substrate in patients with scar-related VT.

Chapter 1 describes seminal and historic investigations beginning in the 1970s that provided robust characterization of the arrhythmogenic substrate, reentrant mechanism, and responses to electrical stimulation in patients with infarct-related, monomorphic ventricular tachycardia. Utilizing these same principles and electroanatomic mapping technologies that are available in clinical electrophysiology laboratories, significant advances elucidating the electrophysiologic and electroanatomic substrate in patients with non-ischemic cardiomyopathies and VT have recently been made. Unlike the substrate that is associated with post-infarct VT, patients with NICM have regions of tissue abnormality that are localized in a non-regional manner, resulting in areas of interest that may be more diffuse and patchy. Particularly, abnormalities that are localized to the perivalvular regions and basal left ventricle with variable degrees of endocardial, mid-myocardial, and/or epicardial tissue involvement have been reported.[2,3] Although the reason for these variable scar patterns is unclear,

characterization of the underlying arrhythmogenic substrate is necessary, but challenging in this pathophysiologic setting.

1.2 List of Publications for Each Chapter (in order of discussion)

Chapter 2 – Electrophysiologic Substrate in Patients with Dilated Non-Ischemic Cardiomyopathy and Ventricular Tachycardia

Haqqani HM, **Tschabrunn CM,** Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Isolated Septal Substrate for Ventricular Tachycardia in Nonischemic Dilated Cardiomyopathy: Incidence, Characterization and Implications. Heart Rhythm. 2011 Aug8(8);1169-76.

Frankel DS, **Tschabrunn CM**, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical Ventricular Tachycardia Morphology in Left Ventricular Non-Ischemic Cardiomyopathy Predicts Poor Transplant Free Survival. Heart Rhythm. 2013 May;10(5): 621-6.

Bala R. Ren JF, Hutchinson MD, Desjardins B, **Tschabrunn CM**, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):667-73.

Chapter 3 – Electrophysiologic Substrate in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy and Ventricular Tachycardia

Haqqani HM, **Tschabrunn CM,** Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, **Tschabrunn CM**, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Long-term Outcome with Catheter Ablation of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2015 Dec 8;89(6):1413-21.

Tschabrunn CM, Haqqani HM, Zado ES, Marchlinski FE. Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

Tschabrunn CM, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Percutaneous Epicardial Ventricular Tachycardia Ablation After Non-Coronary Cardiac Surgery or Pericarditis. Heart Rhythm. 2013 Feb;10(2):165-9.

Chapter 4 – High Resolution Catheter and Mapping Technologies: Insight from Clinical Laboratory Investigations

Anter E, **Tschabrunn CM**, Josephson ME. High-resolution Mapping of Scar-related Atrial Arrhythmias Using Smaller Electrodes with Closer Interelectrode Spacing. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

Anter E, Li J, **Tschabrunn CM**, Nezafat R, Josephson ME. Mapping of a Post-infarction Left Ventricular Aneurysm-Dependent Macroreentrant Ventricular Tachycardia. Heart Rhythm Case Rep. 2015 Nov 1;1(6):472-6.

Chapter 5 – High Resolution Mapping of Ventricular Scar: Insight from Experimental Laboratory Investigations

Tschabrunn CM, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Swine Model of Infarct-related Reentrant Ventricular Tachycardia: Electroanatomic, Magnetic Resonance, and Histopathologic Characterization. Heart Rhythm. 2016 Jan;13(1):262-73.

Tschabrunn CM, Roujol S, Dorman NC, Nezafat R, Josephson ME, Anter E. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016 Jun;9(6) [Epub Ahead of Print].

1.3 Epidemiology and Clinical Management

Monomorphic ventricular tachycardia most commonly occurs in patients with coronary artery disease and prior myocardial infarction, but it can also develop in the setting of non-ischemic cardiomyopathy (NICM).[4] The initial clinical presentation of sustained monomorphic ventricular tachycardia (VT) may include palpitations, angina, exacerbation of heart failure, pre-syncope, syncope, and/or sudden death. The incidence of sudden cardiac death (SCD) in the United States occurs as high as 462,000 cases annually and is frequently attributed to circulatory collapse after initiation of ventricular arrhythmias.[5] Approximately 30% of coronary artery disease (CAD) patients develop an initial episode of sustained monomorphic VT within the first year following myocardial infarction with a cumulative incidence of 3-5% per year. Recently, the incidence of VT in the first year following MI has been reduced to ~1% due to aggressive revascularization and pharmacologic therapies that result in smaller infarctions with infrequent aneurysm formation.[4] Patients with NICM are characterized by mechanical and/or electrical ventricular dysfunction in the absence of significant coronary artery disease and thus represent a heterogeneous group with variable infiltrative, genetic, infectious, and idiopathic ideologies.

The clinical management of sustained monomorphic ventricular tachycardia in patients with structural heart disease (SHD) generally involves one or more of the following therapeutic options: 1) implantable cardioverter-defibrillator (ICD), 2) antiarrhythmic drugs, and 3) ablation. In the United States, the majority of patients with recurrent VTs are managed with ICD therapy. This approach is largely based on the findings of secondary prevention ICD trials that demonstrate a reduction of mortality in patients with structural heart disease and life-

threatening ventricular arrhythmias.[6–8] Importantly, ICD therapy is not a preventive therapy and is typically utilized in conjunction with antiarrhythmic and/or ablation therapies.

There are three main indications for antiarrhythmic drugs in the chronic treatment of ventricular tachycardia: adjunctive therapy in patients with ICD and frequent ICD therapies; to slow the VT cycle length to enhance tolerance, such that it may be amenable to pacing interventions; and lastly, as an alternative to an ICD in patients who choose not to have one or who are not good candidates (e.g., because of marked comorbidities). While amiodarone is the most effective antiarrhythmic in terms of the prevention of VT episodes, long-term use is associated with serious adverse effects and increased mortality.[9] Sotalol has been shown to reduce episodes of MMVT in patients with SHD and is a reasonable initial pharmacologic therapy in patients with normal renal function and a baseline QT interval.[10,11] Dofetilide is also an alternative, but only class I agents and amiodarone can slow the VT cycle length.

Catheter ablation for sustained VT in the setting of SHD is an important alternative or adjunct to pharmacological therapy. Catheter ablation after the first presentation of sustained VT is associated with a significant reduction of ICD shocks versus antiarrhythmic drug therapy in patients with post-infarct VT.[12] The Multicenter Thermocool Ventricular Tachycardia Ablation trial reported the outcome in 231 patients who underwent VT ablation with an open-irrigated catheter.[13] In this population of post infarction VT with a median LV ejection fraction of 25%, the targeted VT was successfully ablated in 81% of patients. Although the frequency of episodes was markedly reduced, only 49% of patients remained VT free at the six-month follow-up.[13] Catheter ablation has also been successfully used in NICM patients and typically entails a more complex procedure involving epicardial mapping and ablation.[3] The long-term effectiveness of catheter ablation in the NICM population is less understood than in the post-infarct population. Of note, a recent, large retrospective analysis of 2061 patients with scar-related VT demonstrated one year of freedom from VT recurrence in 72% of post-infarct patients and 68% of NICM patients.[14] In this same study, the overall procedure complication rate was 6%, including 0.1% deaths, 0.3% requiring cardiopulmonary resuscitation, and a 1.7% incidence of hemopericardium.

1.4 Pathophysiology

The pathophysiology of scar-related monomorphic ventricular tachycardia includes structural and electrical remodeling, which results in inhomogeneous scarring with variable degrees of surviving myocardial tissue that is contiguous with dense fibrosis, forming the “arrhythmogenic substrate”.[15–18] This arrhythmogenic substrate is characterized by zones of slow conduction due to non-uniform anisotropy, resulting in fixed and/or functional regions of conduction block. These zones facilitate reentry as they generate enough time for tissue in the circuit to recover its excitability and allow the excitation wavefront to reenter the initial site of the block, creating a circuit.[19–21]

Most of the current understanding of the pathophysiologic and electrophysiologic substrates that underlie monomorphic VT has been derived from studies that are performed with patients who have coronary artery disease and prior myocardial infarction. The electrophysiologic substrate for monomorphic VT gradually develops over the first two weeks after myocardial infarction, and once established it appears to remain indefinitely.[22] During the infarct healing process, necrotic myocardium is replaced with fibrous tissue that surrounds surviving myocardial fibers (Figure 1.1).

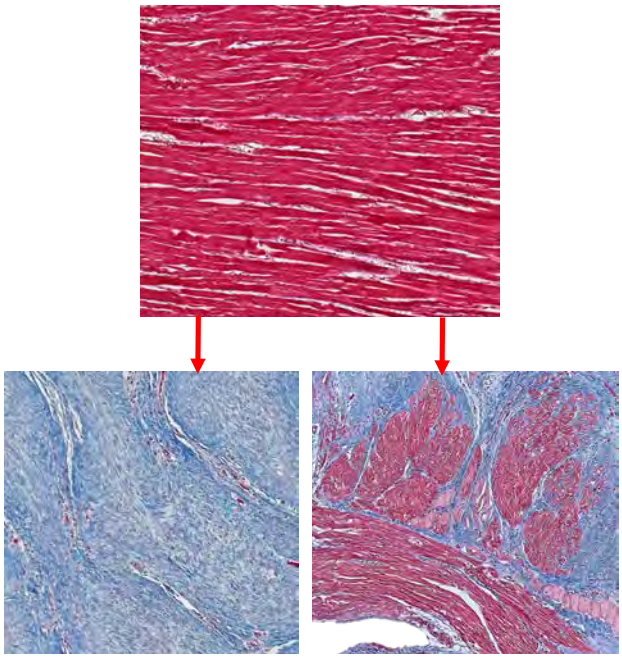

Figure 1.1: Structural Remodeling Following Myocardial Infarction

Mason-trichrome stained histology section in normal and post-infarct tissue. The blue stained tissue indicates the extent of fibrosis. Survived layer of myocardial fibers in disarray occurs at the borders of the scar. The viable tissue demonstrates loss of the parallel bundle orientation with myocardial fiber disarray and variable degrees of fibrosis.

In addition, reduction in the number of gap junctions coupled with altered cellular distribution results in slow, non-uniform anisotropic conduction, which may promote reentry (Figure 1.2).[18,23] Other electrophysiological consequences of infarction include abnormalities in refractoriness, inexcitability, and enhanced automaticity, all of which can contribute to arrhythmogenicity. However, abnormalities of conduction are most prominent and provide the electrophysiologic substrate for VT.[19]

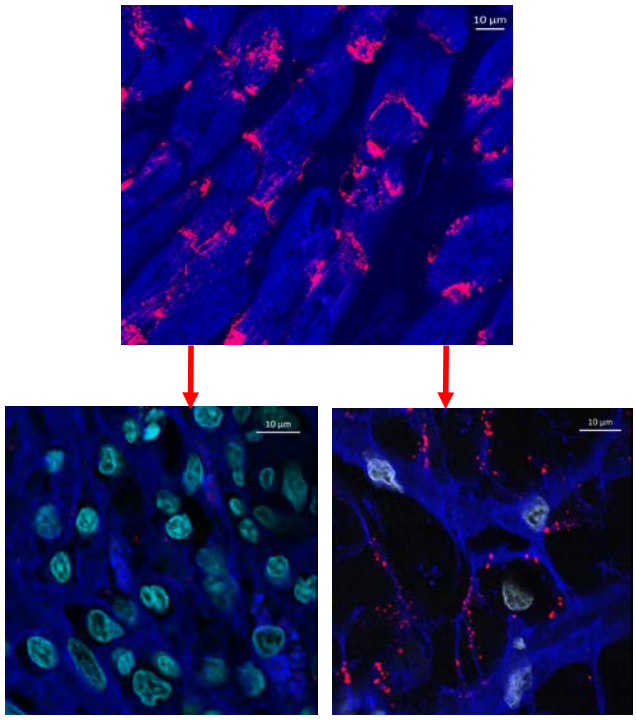

Figure 1.2: Electrical Remodeling Following Myocardial Infarction

Connexin-43 antibody immunofluorescence in normal and post-infarct tissue. Following myocardial infarction, gap junction activity becomes absent or significantly reduced and lateralized in the infarcted region

1.5 Reentrant Circuit

This pathophysiologic substrate facilitates reentry as it generates enough time for the tissue in the circuit to recover its excitability and allow the excitation wavefront to reenter the circuit. Clinical and experimental investigations provide convincing evidence for reentry as the underlying mechanism of post-infarction VTs in human.[20,24] In patients with NICM, 80% of VTs are caused by scar-related reentry, 20% are due to bundle branch reentry or focal mechanisms.[25] Evaluation of the VT mechanism has important therapeutic implications in post-infarct and NICM related substrates. In particular, distinguishing arrhythmias that are

caused by triggered activity from those due to reentry effects the selection of an appropriate antiarrhythmic drug, anti-tachycardia pacing protocol, and ablation strategy.

Reentrant circuits typically have a consistent relationship with the anatomic substrate. They arise in areas of fibrosis that contain surviving myocardial strands with the tissue's inherent inhomogeneous anisotropy that leads to a zigzag course of activation.[19] A discrete, protected zone of slow conduction is contained within the dense scar and this zone serves as the critical isthmus, allowing reentry to occur. The reentrant circuit has several components which include entrance, common pathway (critical isthmus), exit, outer loop(s), inner loop(s), and bystander sites (Figure 1.3). The wavefront enters the reentrant circuit at the entrance site and then propagates through the critical isthmus during electrical diastole. As the critical isthmus is usually composed of a small amount of myocardial tissue with conduction abnormalities and is bounded by anatomical or functional barriers that prevent the spread of the electrical signal, except in the orthodromic direction, propagation of the wavefront in the protected isthmus is electrocardiographically silent. The wavefront leaves the protected isthmus to depolarize the remainder of the ventricles, producing the QRS complex. The reentrant wavefront can then return back to the entrance of the common pathway through an outer or an inner loop. The outer loop is the path through which the reentrant wavefront propagates while simultaneously activating the rest of the myocardium. An inner loop is contained within the scar and can serve as an integral part of the reentrant circuit or function as a bystander pathway. If conduction through the inner loop is slower than conduction from exit to entrance sites through the outer loop, it is a bystander pathway. Alternatively, if the inner loop allows faster conduction back to the entrance site, it serves as an internal part of the reentrant circuit.[4]

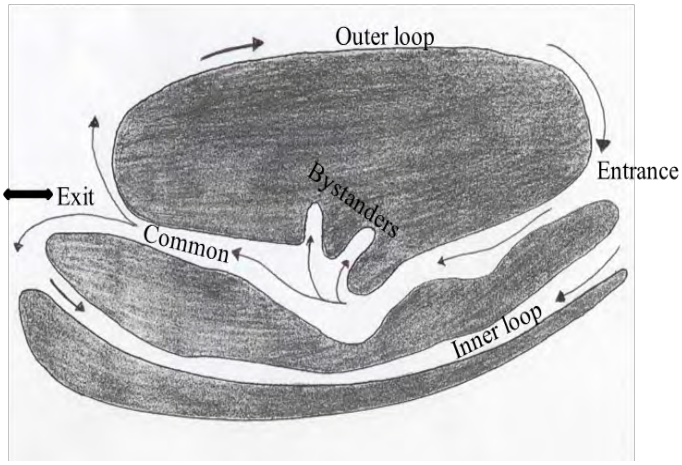

Figure 1.3: Schematic of Reentrant Ventricular Tachycardia Circuit

1.6 Data from Intraoperative Studies

Intraoperative and endocardial mapping studies that were carried out by Mark Josephson and his team at the University of Pennsylvania in the 1970s provided substantial insight into the mechanisms and underlying arrhythmogenic substrate in patients with VT and prior myocardial infarction. These initial studies utilized endocardial catheter mapping techniques, multi-site programmed stimulation, and evaluation of VT response to drugs and electrical stimulation to demonstrate the reentrant arrhythmia mechanism and subendocardial tissue involvement in coronary artery disease patients.

The definition of normal versus abnormal signal characteristics were defined using a non-deflectable catheter with a 2mm tip electrode, separated by 5mm from a 1mm ring electrode during sinus rhythm and VT. These efforts evaluated the electrogram characteristics in patients with tolerated VT as well as patients with non-tolerated VT and cardiac arrest. These reports were the first to define normal and abnormal electrogram signal amplitude, duration, morphology, and activation patterns.[26]

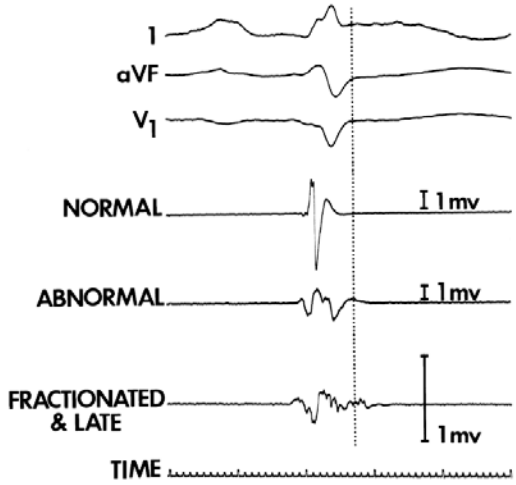

Figure 1.4: Normal and Abnormal Electrograms

Example of normal, abnormal, fractionated, and late activation electrograms from a patient with healed myocardial infarction and sustained ventricular tachycardia.

Reproduced with permission from Josephson's Clinical Cardiac Electrophysiology: Techniques and Interpretations 3rd Edition

Activation mapping was performed in patients with healed myocardial infarction and sustained VT in the electrophysiology lab and operating room to determine the relationship between abnormal electrograms that were identified during sinus rhythm and the location of reentrant VT circuits. These investigations discovered that the majority of all electrograms (>85%) at critical VT sites (based on pre-QRS or mid-diastolic continuous electrical activity identification criteria) had abnormal electrograms during sinus rhythm that demonstrated low amplitude (<3.0mV) and/or long duration (>70ms) signals. A small percent of signals was profoundly abnormal and displayed either fractioned, split potentials (electrograms separated by 30ms by an isoelectric interval), delayed activation extending beyond the QRS, and late potentials separated by a 30-50ms isoelectric interval from the QRS (Figure 1.4). While these abnormal signals reflect abnormal signal propagation that is not seen in normal regions of tissue (high specificity), they were not seen in all patients with ventricular tachycardia and therefore, they carried a modest predictive value of approximately 30% for defining the "site

of origin" during sinus rhythm. Histopathologic evaluation of ventricular tissue with electrogram abnormalities demonstrated myocardial fiber disarray with bundles of survived myocytes encased in fibrous tissue that were located primarily in the subendocardial surface of the heart.

These studies also found that patients with sustained monomorphic VT had lower tissue excitability in areas of low amplitude and fractioned electrograms with prolonged dispersion of recovery due to abnormalities of activation. These areas often demonstrated early activation adjacent to areas of late activation; this feature is advantageous to promote reentry. All of these features are known to represent the electrophysiological milieu for reentrant ventricular tachycardia. Patients who require treatment for VT underwent a 2-3cm subendocardial resection, where abnormal electrograms were identified. This resulted in the normalization of 50% of adjacent EGMs and the elimination of VT in the majority of patients, providing the strategic foundation for future catheter based therapies.[27–31]

1.7 Electroanatomic Mapping Technologies

The development of electroanatomic mapping (EAM) technology during the 1990s transformed the field of cardiac electrophysiology, as it allowed visual localization of the mapping catheter within a 3-dimensional space.[32] This facilitated, for the first time, the ability to record signals at multiple sites and assess activation during sinus rhythm and arrhythmias during catheter-based studies. This groundbreaking technology continued to evolve and was widely adopted as the electrophysiologist's "GPS system" inside of the heart and allowed accurate localization and annotation of abnormal electrograms during sinus rhythm.

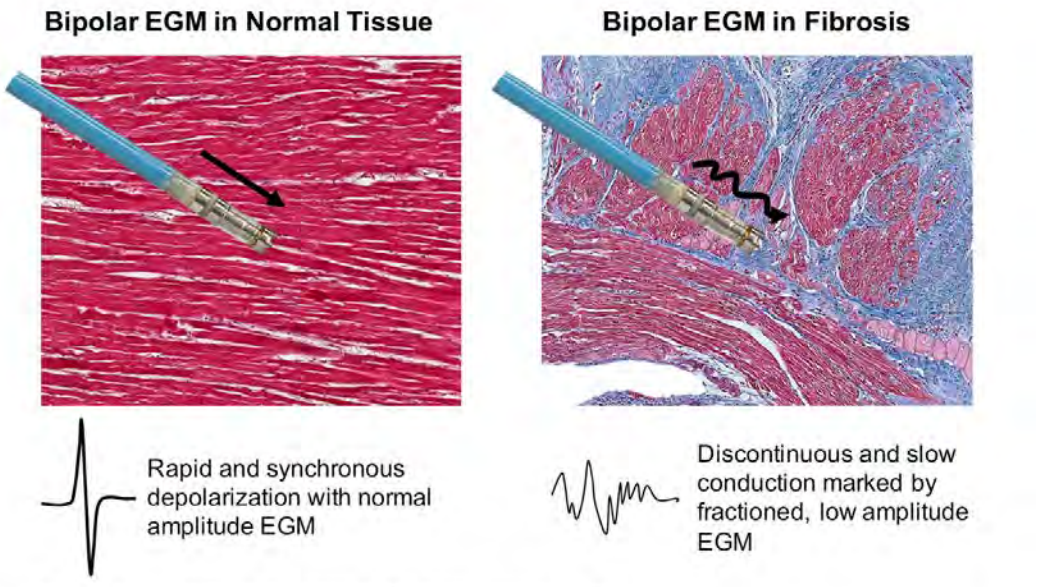

Figure 1.5: Comparison of Bipolar Electrograms (EGM) in Normal vs. Abnormal Tissue

The ability to localize regions of low bipolar amplitude, abnormal signals, and the presumed scar using this technique led to the development of substrate mapping and ablation as the primary approach for the treatment of scar-related VTs. This initial concept was based on the idea that channels of viable myocytes within a dense scar could be recorded during sinus rhythm, representing isthmuses of reentrant circuits. Pace mapping at the junction of these channels and the "border zone" produced QRS morphologies that were similar to recorded VTs. This led investigators to develop ablation strategies, in which lesions are applied perpendicular to these channels and/or their borders with the hope of blocking propagation through the channels, resulting in the elimination of VT.[33] As was the case in early intraoperative studies, these abnormal electrogram features that were identified during catheter-based electroanatomic mapping is indicative of abnormal myocardium with multicomponent, delayed signals that represent slow or delayed activation and that could serve as the prerequisite for reentrant VT (Figure 1.5).

Bipolar Voltage Criteria

The most common feature that has been analyzed in clinical studies is electrogram peak-to-peak voltage. This has been evaluated for bipolar (mapping catheter tip to ring electrode) and unipolar (mapping catheter tip to Wilson central terminal) recordings. In a case control study, bipolar voltage cutoff values of normal vs abnormal substrates in patients presenting for catheter ablation of infarct-related VT using an electroanatomic mapping system.[33] These initial studies utilized a standard linear ablation and mapping catheter with a 4mm tip electrode, 1mm ring electrode, and 2mm interelectrode spacing. A statistical cut off was utilized to develop normal bipolar voltage criteria with >95% electrograms in healthy ventricular tissue, recording a bipolar voltage >1.5mV (Figure 1.6). Abnormal regions were delineated as the "scar border zone", which is defined as bipolar voltage amplitude between 0.5-1.5mV; "dense scar" is defined as voltages <0.5mV; these electrograms were filtered at 10-400Hz. These cutoff values have also been validated in animal infarct models.[34] Typically, areas with low bipolar voltages are characterized by

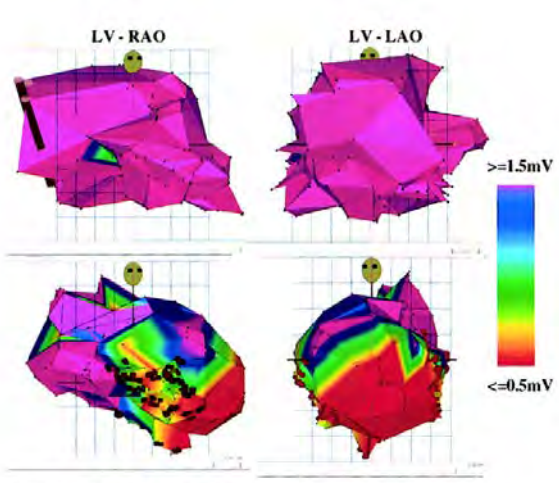

Figure 1.6: Bipolar Voltage Mapping

Left Ventricular Bipolar Voltage Mapping to Identify Normal and Abnormal Regions of Tissue. Adapted with permission: Marchlinski FE, et al. Circulation 2000; Mar 21 101(11):1288-96.

markedly abnormal fragmented, split, and late electrograms, which are usually not found in regions of normal bipolar voltage.

Unipolar Voltage Criteria

The limited field of view of bipolar signals is an issue of particular importance when attempting to characterize the substrate in patients with non-ischemic cardiomyopathies (NICM). The abnormal substrate in these patients is fairly equal, but variably distributed to endocardial, mid-myocardial, and in some cases isolated to epicardial locations. In general, substrate abnormalities that are involved in reentrant VT circuits typically involve perivalvular regions with increased prevalence of intramural and/or epicardial substrate abnormalities. In this setting, unipolar voltage mapping can provide additional value to identify the location and extent of abnormal substrate, beyond the bipolar electrogram field of view. Similar to the development of normal and abnormal bipolar voltage criteria, prior studies have developed a statistical cutoff value for unipolar electrograms, where >95% of all signals are >8.27mV in the left ventricle (Figure 1.7). Low unipolar voltages are usually indicative of epicardial regional involvement with a high positive and negative predictive value in patients with no endocardial abnormalities identified with bipolar voltage mapping.[35]

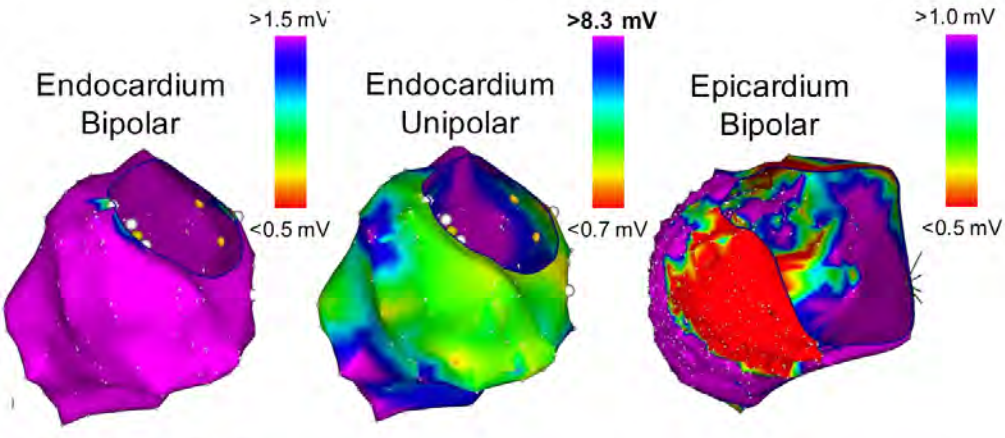

Figure 1.7: Unipolar Voltage Mapping

Unipolar voltage mapping can be used to identify abnormal epicardial left ventricular substrate in patients with non-ischemic cardiomyopathy and ventricular tachycardia. Adapted with permission: Hutchinson MD, et al. Circ Arrhythm Electrophysiol. 2011;4:49-55

1.8 Conclusion

Adverse structural and electrical remodeling following myocardial infarction or during variable processes of different non-ischemic cardiomyopathies can promote the manifestation of reentrant monomorphic ventricular tachycardia. Intracardiac mapping can be used to detect and characterize regions of abnormal ventricular tissue that are critical to the reentrant VT

circuit. These regions serve as therapeutic targets, initially during intraoperative surgical procedures and recently with catheter ablation techniques. As such, efforts to accurately identify these arrhythmogenic areas continues to have an important role in scar-related VT ablation.

Chapter 2

Electrophysiologic Substrate in Patients with Dilated Non-Ischemic Cardiomyopathy and Ventricular Tachycardia

2.1 Introduction

Chapter 2 encompasses a critical review of clinical electroanatomic mapping studies performed in patients with dilated non-ischemic cardiomyopathy and VT. Chapter 2.2 describes the incidence, electrophysiologic characterization, and clinical implications of isolated septal substrate; Chapter 2.3 discusses apical LV extension and the prognostic value of LV endocardial mapping; and Chapter 2.4 describes the utility of other imaging techniques to localize abnormal regions of LV tissue.

The research investigations that are discussed in this Chapter were carried out in the clinical electrophysiology laboratories of the Hospital of the University of Pennsylvania in Philadelphia, Pennsylvania. All of the patients provided written informed consent prior to the clinical electrophysiologic procedures, in accordance with the University of Pennsylvania Health System's institutional guidelines.

2.2 Incidence and Characterization of Isolated Septal Substrate

*Haqqani HM, **Tschabrunn CM,** Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Isolated Septal Substrate for Ventricular Tachycardia in Nonischemic Dilated Cardiomyopathy: Incidence, Characterization and Implications. Heart Rhythm. 2011 Aug8(8);1169-76.*

Previous studies in patients with LV NICM and VT have characterized the basal peri-annular LV endocardial and epicardial VT substrate using electroanatomic mapping techniques.[2] This abnormal substrate is typically isolated to the basolateral region or involves both the basolateral and basal septal LV. As the clinical experience of LV NICM VT cases expanded, occasional cases without basal peri-annular abnormalities were seen and appeared to represent a rare sub-type of NICM substrate, requiring further evaluation. The objective of this study was to determine the incidence and electrophysiologic characteristics of patients with isolated septal involvement in the NICM VT patient cohort at the University of Pennsylvania. Of 266 consecutive NICM VT patients, 31 (11.6%) were identified with isolated or minimal involvement beyond the septum based on EAM and/or cardiac magnetic resonance imaging.

Major Findings

1. Majority of low-voltage and abnormal electrograms localized to the LV or RV endocardium with minimal involvement of the septal epicardial tissue

2. Possibility of an exclusive, deep intramural VT substrate within the interventricular septum that may only be evident on imaging or with unipolar voltage mapping
3. Multiple monomorphic VT morphologies with left and/or right bundle branch block, variable axis, but with characteristic V_2 transition due to peri-septal breakthrough
4. Limited efficacy (66% acute success) of ablation to eliminate all inducible VTs
5. Extensive septal ablation may permanently damage the conduction system.

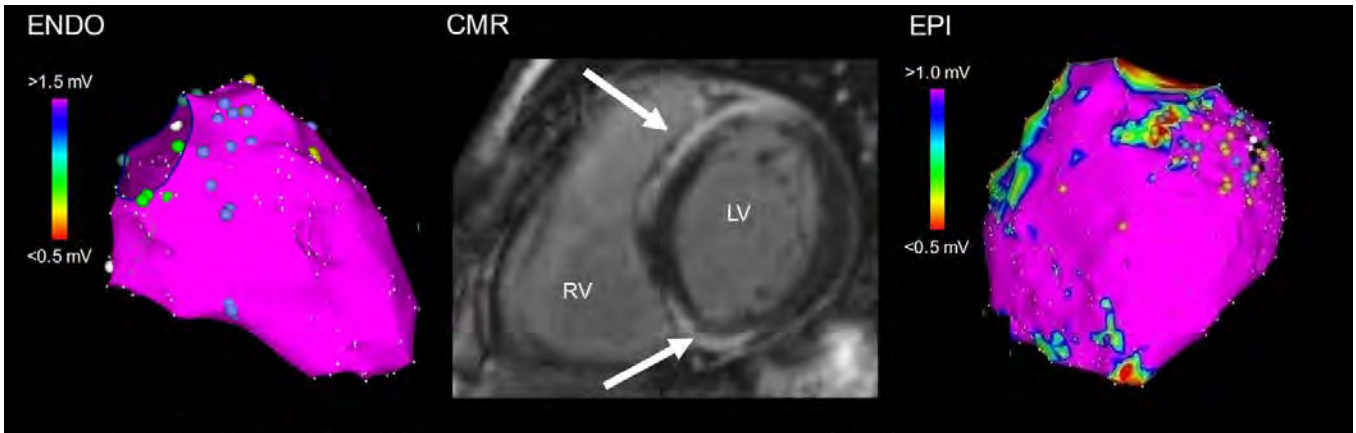

Figure 2.1: Voltage Maps and Cardiac Magnetic Resonance Imaging in Patient with Isolated Septal Substrate

Normal left ventricle endocardial and epicardial voltage maps in a patient with mid-septal late gadolinium enhancement (white arrows) on cardiac magnetic resonance imaging and ventricle tachycardia.

Study Limitations

This was a single center, nonrandomized study representing a consecutive group of NICM patients. During this time, the evolution of CMR imaging, epicardial mapping, and irrigated ablation may have affected the study results.

Clinical Implications

This is the first report to describe the presence of endocardial/epicardial EAM abnormalities, VT characteristics, procedural outcome, challenges, and complications that are specific to this subset of NICM patients with isolated septal involvement. This study incorporated EAM and CMR imaging techniques to describe clinical characteristics and challenges, particularly regarding the identification of the arrhythmogenic substrate using conventional bipolar voltage criteria and the ability of radiofrequency ablation to reach deep intramural substrates. Isolated or predominant septal substrate for scar-related VT in NICM represents an uncommon but challenging cohort of patients. Biventricular endocardial low-voltage zones extending from the basal septum (with or without patchy epicardial involvement) are characteristic, but the septal scar may be intramural and only identified with CMR imaging or with unipolar voltage map evaluation (Figure 2.1). The additional risk that is associated with epicardial access and mapping should be avoided as it provides limited value. Instead, effort should be focused on

characterization of the septal RV and LV endocardium. Multiple procedures may be required for successful VT ablation, with the potential to affect the conducting system.

Since the publication of this study, isolated VTs involving mid-septal substrate continues to be a challenge requiring multiple procedures and aggressive ablation from the RV and LV septum to eliminate VT circuits that involve deep mid-septal substrate. In addition, since this phenomenon was introduced and quickly recognized as a major challenge, efforts to develop more aggressive ablation therapies have been underway, which may extend further within this region beyond conventional tools. Two potential technologies that may bridge this gap include a proprietary radiofrequency ablation needle catheter that can be deployed directly within the ventricular tissue (Figure 2.2), and a bipolar radiofrequency ablation technique for more directed and deeper lesions. Both have been utilized in a limited and select group of patients with modest success.[36,37]

Figure 2.2: Needle Ablation Catheter

Adapted with permission: Sapp JL, et al. Circulation. 2013;128:2289-2295

2.3 Left Ventricular Apical Substrate and Ventricular Tachycardia

*Frankel DS, **Tschabrunn CM**, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical Ventricular Tachycardia Morphology in Left Ventricular Non-Ischemic Cardiomyopathy Predicts Poor Transplant Free Survival. Heart Rhythm. 2013 May;10(5): 621-6.*

As discussed earlier, the area of bipolar low-voltage and abnormal electrograms that are consistent with a "scar" in patients with LV NICM and VT typically involves the mitral annular region with variable degrees of apical extension. The objective of this study was to compare LV endocardial and epicardial electroanatomic substrates and transplant free survival in NICM patients with clinical and/or induced sustained VTs that are suggestive of an apical exit site versus those without apical VTs. Apical VT exit morphology was defined as left bundle morphology with precordial transition $\geq V_5$ or right bundle morphology with precordial transition $\leq V_3$. Patients with NICM and monomorphic VT who require catheter ablation between May 2008-April 2011 were categorized accordingly. Of 76 total patients, 32 (42%) were identified as having ≥1 VT ECG morphology that was suggestive of an apical exit site.

Major Findings

1. Patients with apical VT morphologies had larger areas of abnormal electrograms, extending beyond the basal LV toward the apex.

2. During clinical follow-up, these patients had a higher incidence of death, cardiac transplantation, or LVAD implantation due to progressive and end-stage heart failure.

Study Limitations

Although validation of this association had not been previously reported, one would hypothesize that patients with apical VT morphologies are likely to have apical extension and involvement from the basal mitral annulus, either in a continuous or patchy distribution. These findings are consistent with other studies that have evaluated scar size with CMR imaging and found higher mortality in patients with high scar burdens independently of LVEF.[38] Nonetheless, this was a moderately-sized, single-center study with limited follow-up duration in patients with NICM, and should not be applied to other disease substrates that were not included in this study cohort.

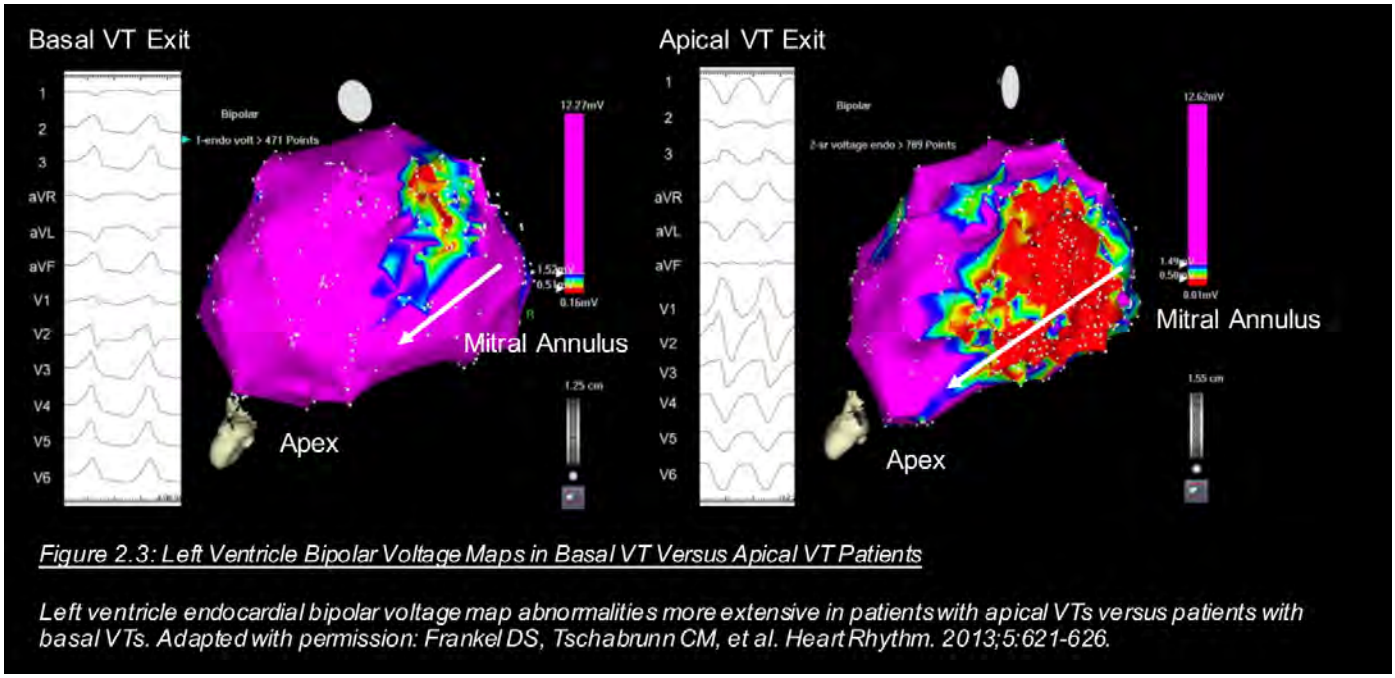

Figure 2.3: Left Ventricle Bipolar Voltage Maps in Basal VT Versus Apical VT Patients

Left ventricle endocardial bipolar voltage map abnormalities more extensive in patients with apical VTs versus patients with basal VTs. Adapted with permission: Frankel DS, Tschabrunn CM, et al. Heart Rhythm. 2013;5:621-626.

Clinical Implications

The presence of an apical VT morphology is a simple, noninvasive marker that provides useful prognostic information. Patients with NICM and apical VTs have larger areas of scarring, extending further from the base toward the apex and worse transplant/LVAD-free survival, despite similar LVEF (Figure 2.3). Particular attention should be paid to optimal heart failure management in these patients, with a more guarded prognosis. Despite a mean follow-up of less than one year, more than 25% of the patients died or required an LVAD/heart transplant, emphasizing the advanced heart failure in this patient cohort. At the time of publication, this was the first study that demonstrated the association between VT localization and clinical outcomes in patients with NICM with multivariate analysis. In the multivariate analysis model,

LVEF and endocardial bipolar low-voltage percentage independently predicted adverse clinical outcomes. A subsequent study published by the Penn group evaluated the incidence and characteristic of LV NICM scar progression in 12 patients that underwent repeat LV endocardial mapping, and 6 out of 12 patients had markedly increased unipolar and bipolar low voltage areas that were indicative of ongoing disease progression and pathogenesis. In four cases, this progression extended towards the apex.[39] Taken in conjunction with the apical VT study results, it is possible that the development of a new apical VT may be indicative of a progressive substrate towards the LV apex and warrants further consideration of potential early heart failure interventions. Multicenter studies with longer follow-up are required to determine the reproducibility of these findings.

2.4 Detection of Epicardial Substrate with Intracardiac Echocardiography

*Bala R. Ren JF, Hutchinson MD, Desjardins B, **Tschabrunn CM**, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):667-73.*

Intracardiac echocardiography (ICE) is routinely utilized during electrophysiology procedures to facilitate real-time imaging of cardiac anatomy, catheter position, and lesion formation, and to monitor for complications. There is limited information on the ability of ICE to identify abnormal substrate during VT ablation. The objective of this study was to evaluate the feasibility of ICE to identify echogenic tissue regions at the mid-myocardial or epicardial LV regions, which are representative of abnormal ventricular substrate in patients with NICM and recurrent VT. Eighteen patients were identified that underwent LV endocardial and epicardial mapping with ICE imaging that identified increased echogenicity in the lateral LV wall. A control group of 30 patients with structurally normal hearts were included for validation.

Major Findings

1. All of the 18 patients with NICM and ICE defined lateral LV echogenicity correlated to epicardial abnormalities identified during electroanatomic mapping marked by fractionated and low bipolar voltage electrograms.
2. There was no identification of ICE increased echogenicity in a control group of 30 patients with structurally normal hearts.

Study Limitations

This was a small feasibility study, which was limited to the evaluation of the LV lateral wall in patients with NICM and VT and did not include other regions of the LV. While this technique continues to be utilized by operators who are experienced in ICE imaging in conjunction with

mapping and imaging modalities, there are no extensive evaluations to determine the sensitivity and specificity of ICE imaging as a diagnostic modality for this purpose.

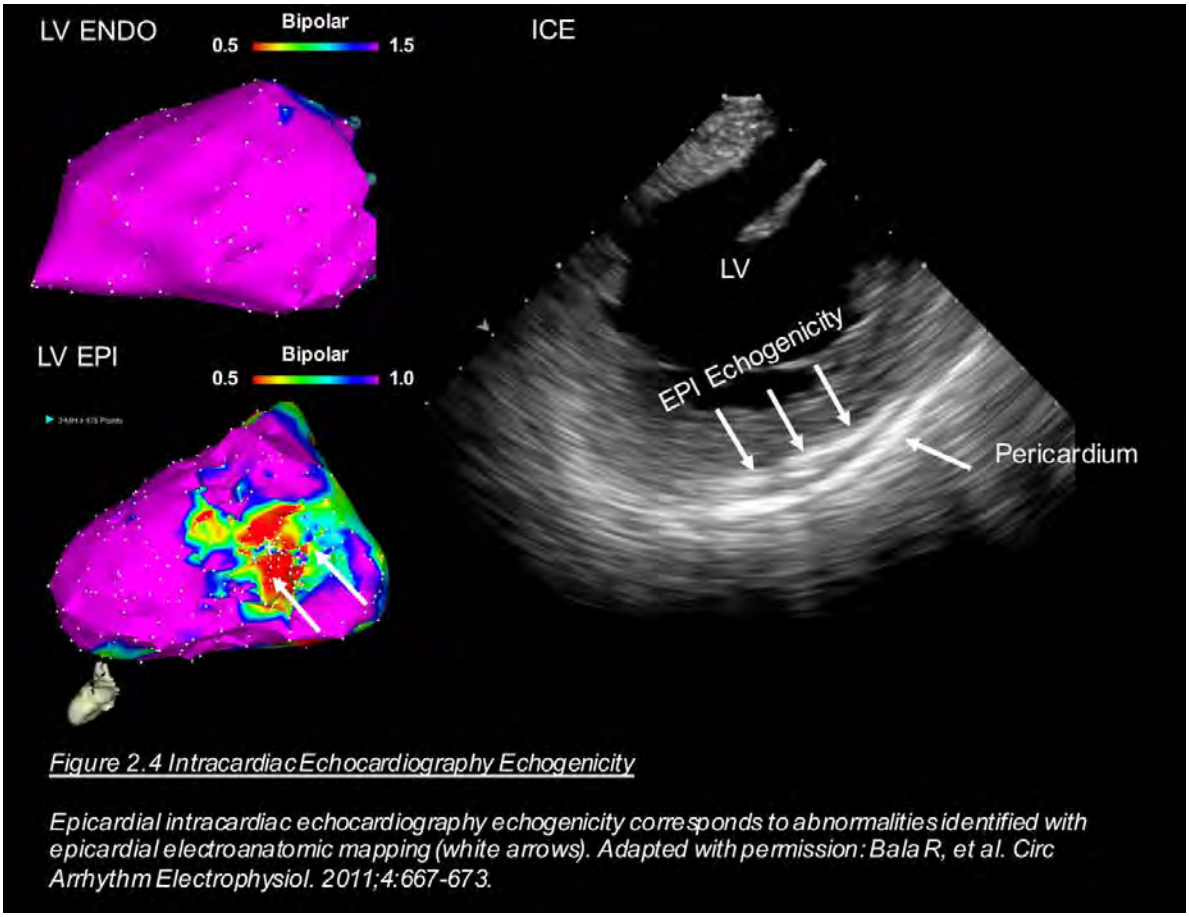

Figure 2.4 Intracardiac Echocardiography Echogenicity

Epicardial intracardiac echocardiography echogenicity corresponds to abnormalities identified with epicardial electroanatomic mapping (white arrows). Adapted with permission: Bala R, et al. Circ Arrhythm Electrophysiol. 2011;4:667-673.

Clinical Implications

The findings from this initial series of patients suggests that ICE imaging may provide an additive and important role in identifying abnormal substrate and facilitating VT ablation. Increased echogenicity on ICE imaging coupled with normal or small areas of low voltage on LV endocardial electroanatomic mapping suggest the need for detailed epicardial mapping/ablation (Figure 2.4). Electroanatomic mapping is currently the gold standard for identification of abnormal epicardial substrate, and the validation of these regions to the ICE echogenic findings is a major strength of this study. The use of ICE imaging for this purpose has particular utility in patients presenting with NICM and VT as MRI imaging in patients with ICD implants is not widely performed. ICE imaging identified both midmyocardial and epicardial echogenicity in 10 of the 18 patients, and these findings were confirmed in five of these patients with CMR imaging. In three patients, epicardial abnormalities were not as extensive as the CMR midmyocardial LGE. The CMR and ICE data indicates a greater midmyocardial than epicardial substrate abnormality identified with voltage mapping. These data are likely representative of the limitations of bipolar voltage mapping to detect

abnormalities beyond preserved sub-epicardial layers, and it illustrates the importance of additional mapping and imaging techniques in order to identify mid-myocardial abnormal myocardial substrates. A more recent study in 22 patients (12 post-infarcts and 12 non-ischemic) performed 3D reconstruction of ICE images using the Carto Sound module and also found that ICE imaging can provide important information about the VT anatomical substrate in conjunction with EAM. However, further evaluation is required to determine the true clinical benefit during VT ablation.[40]

2.5 Conclusions

There is no current consensus on the optimal ablation strategy for patients with NICM and VT, but previous studies support the concept of an underlying anatomical substrate that facilitates reentry. These important clinical studies that utilize electroanatomic mapping technology provide critical insight into the electrophysiologic substrate underlying VT in patients with NICM. These data represented, at the time of publication, new information to the electrophysiology community and was validated and expanded by investigations at other centers. Chapter 3 describes insights from clinical electroanatomical mapping studies in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) and VT.

Chapter 3

Electrophysiologic Substrate in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy and Ventricular Tachycardia

3.1 Introduction

The pathogenesis of arrhythmogenic right ventricular cardiomyopathy (ARVC) is distinguished by fibrous and adipose tissue replacement of ventricular myocardium. Though several hypotheses have been proposed for the underlying cause of ARVC/D, it is primarily believed to be an inherited cardiomyopathy, resulting from gene mutations that encode desmosomal proteins, the organelle responsible for cell-cell adhesion. Desmosomal dysfunction in patients with ARVC/D leads to inadequate cell adhesion and subsequent myocyte detachment and apoptosis.[41,42] This process predominantly affects the right ventricular free wall and extends inward from the epicardium toward the endocardial surface in most patients.[42–44] The replacement of functional RV myocardium with fibrosis serves as the underlying substrate for the development of reentrant ventricular arrhythmias due to inhomogeneous conduction during sinus rhythm with slow and discontinuous electrical propagation.[20,45]

Three-dimensional electroanatomic mapping has been instrumental in facilitating a more robust understanding of the complex electrophysiologic substrate that is present in patients with ARVC. Identifying low voltage electrograms with long-duration, split, fractionated, and/or late potentials can localize regions of abnormal myocardial tissue that serves as the substrate for VT.[46] Identification of these key areas has been correlated with relevant histopathologic findings in patients with ARVC, verifying the presence of cardiomyocyte loss with fibrofatty replacement that is consistent with the disease.[47] The ability to localize and define the associated abnormalities that are essential for VT enhanced the effectiveness of catheter ablation procedures. In addition, assessment of the anatomic substrate during electrophysiology procedures has shed light on controversies pertaining to disease pathogenesis.

This chapter discusses insight and outcome implications in ARVC patients, as well as the identification of special considerations in epicardial mapping and ablation. Chapter 3.2 discusses the endocardial and epicardial substrate in patients with ARVC, Chapter 3.3 describes implications of layered and/or confined epicardial substrate, and Chapter 3.4 discusses the long-term catheter ablation outcome in ARVC-VT patients. Chapter 3.5 focuses on epicardial mapping techniques, including the challenges associated with pericardial adhesions. The research investigations that are discussed in this Chapter were all carried out

in the clinical electrophysiology laboratories of the Hospital of the University of Pennsylvania in Philadelphia, Pennsylvania. All of the patients provided written informed consent prior to the clinical electrophysiologic procedures in accordance with the University of Pennsylvania Health System's institutional guidelines.

3.2 Endocardial and Epicardial Substrate Characterization

Endocardial Mapping

Advances in 3D electroanatomic mapping enabled a more thorough understanding of the complex electrophysiologic substrate in patients with ARVC/D and VT. Abnormal RV endocardial regions can be localized with electroanatomic mapping by identifying regions of low bipolar RV endocardial voltage (<1.5 mV) and long-duration, low-amplitude, fractionated potentials. These key areas have been correlated to relevant histopathologic findings (myocyte loss with fibrofatty replacement) and critical VT circuits, confirming the involvement of these areas in the arrhythmogenic mechanism. The endocardial distribution of electroanatomic scars in patients with VT and ARVC/D typically extends from the tricuspid valve and/or the pulmonary valve to the RV free wall. Low-voltage abnormalities can also be found on the septal aspect of the perivalvular region(s), but typically not on the RV apex.[45]

Although ARVC/D is known to primarily involve the RV, involvement of the left ventricle (LV) is more frequent than previously recognized. Left ventricle abnormalities have been documented with electroanatomic mapping and typically involve the basal perivalvular region, which is characteristic of other non-infarct related cardiomyopathies.[45] Consideration of endocardial LV involvement is of particular importance if right bundle branch block VTs with positive R waves in the precordial leads are seen, as this suggests an LV VT exit site of interest.

Epicardial Mapping

Despite peri-procedural advances with irrigated ablation catheter technology and criteria to identify RV endocardial bipolar electroanatomic voltage abnormalities, the endocardial ablation approach provides modest long-term arrhythmia freedom. The epicardial to endocardial scarring process associated with ARVC/D often results in a more extensive abnormal epicardial substrate that may not be amenable to endocardial ablation alone (Figure 3.1). Insight from percutaneous epicardial mapping and ablation procedures in patients with ARVC/D and VT have demonstrated the important role of the epicardium. Abnormal epicardial low-voltage areas are typically much larger than the corresponding endocardial region, with extensive networks of late activation and fractioned signals.[46,48] Due to the widespread extent

of confluent scarring in these patients, it is common to identify multiple VT circuits that may involve both endocardial and epicardial surfaces. In addition, the dense mid-myocardial/sub epicardial fibrosis can create an effective barrier for the endocardial to epicardial spread of activation. The resultant layered and delayed activation of the epicardium from the edges of the scar creates the milieu for an isolated VT circuit that is entirely confined to the epicardium and requires epicardial access and direct ablation for elimination.[49] In patients that have failed endocardial ablation, repeat ablation targeting the epicardial circuits was associated with superior long-term success rates.[46] As such, patients often require epicardial access for mapping and ablation to achieve a successful outcome.

Although identification of abnormal epicardial substrate is best achieved through a percutaneous pericardial puncture, analysis of unipolar endocardial voltage maps with the associated larger field-of-view provides information that pertains to the degree of epicardial abnormality present. Areas of unipolar voltage of <5.5 mV are associated with epicardial abnormalities. Unipolar voltage abnormalities that are identified during RV endocardial mapping and that far exceed the bipolar endocardial substrate are highly suggestive of a more extensive epicardial > endocardial substrate that is consistent with the ARVC/D substrate in patients with VT.[48] Additional clues to the requirement for epicardial mapping and ablation include surface ECG morphologies of VT, suggesting epicardial exits (QS complex in the inferior leads and/or right precordial leads), the presence of an isolated epicardial scar on magnetic resonance or intracardiac echo imaging, and/or prior failed endocardial ablation. [3,48]

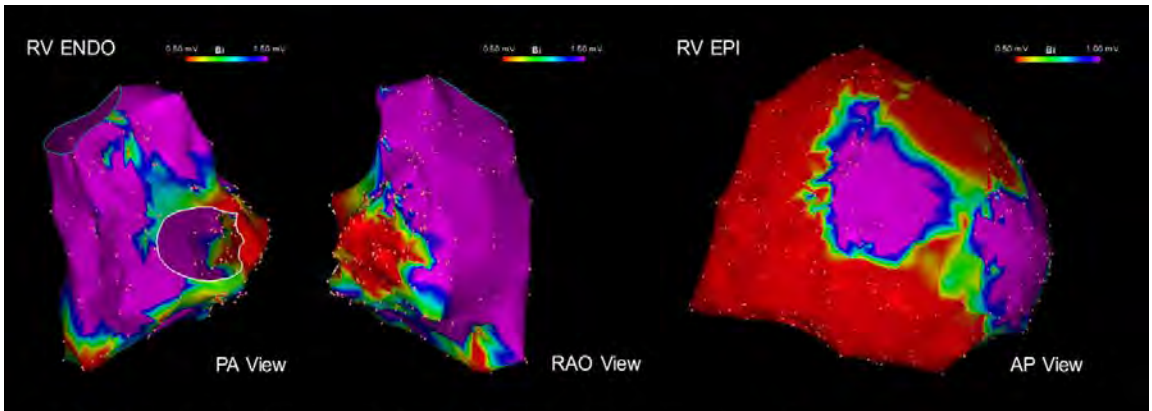

Figure 3.1: Right Ventricle Voltage Maps in Arrhythmogenic Right Ventricular Cardiomyopathy Patient

Right ventricle endocardial bipolar voltage abnormalities (0.5-1.5mV) in the characteristic peri-tricuspid valvular and free wall regions. Epicardial low bipolar voltage (0.5-1.0mV) abnormalities are significantly greater than the endocardium due consistent with the epicardial to endocardial scarring process of arrhythmogenic right ventricular cardiomyopathy.

3.3 Implications of Layered Epicardial Activation

*Haqqani HM, **Tschabrunn CM,** Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.*

A unique opportunity to understand the three-dimensional substrate underlying VT in non-ischemic cardiomyopathies is presented by patients with ARVC. Patients requiring ablation for VT in this context generally have significantly more epicardial scarring than endocardial scarring, but may also have substantial intramural fibrosis. This would increase the likelihood of conduction block to the endocardium and independent activation of the epicardium in VT by circuits that are unable to traverse the intramural RV. In sinus rhythm, the footprint of such a schema would be the independent, laminar activation of the endocardium and epicardium.

The purpose of this study was to evaluate whether confluent epicardial or intramural scarring in patients with ARVC and VT can prevent transmural endocardial to epicardial activation during VT and/or sinus rhythm, indicating the possibility of VT circuits confined to the epicardial surface. This study included 18 consecutive patients with VT and ARVC between 2007-2010 at the University of Pennsylvania that underwent RV endocardial and epicardial mapping. A control group of six patients without structural heart disease that underwent RV endocardial and epicardial mapping during idiopathic ventricular arrhythmia ablation was included.

Major Findings

1. Sinus rhythm endocardial RV activation in the absence of structural heart disease progresses smoothly from the earliest breakthrough in the apical anteroseptal endocardium toward the basal regions.
2. Reference patients without structural heart disease also show evidence of epicardial RV activation in a similar sequence to the endocardium with relative activation timing, which is suggestive of direct transmural endocardial-to-epicardial depolarization.
3. Endocardial RV activation in ARVC is altered by extensive fibrosis that characterizes this disease, such that it takes proportionately longer but occurs in an overall similar sequence because of the largely periannular endocardial substrate distribution.
4. Epicardial RV activation is altered and activated in a delayed fashion, with a pattern that often appears independent of subjacent endocardial activation, suggesting that the dense confluent fibrosis characteristic of ARVC may potentially compartmentalize the endocardium from the epicardium.

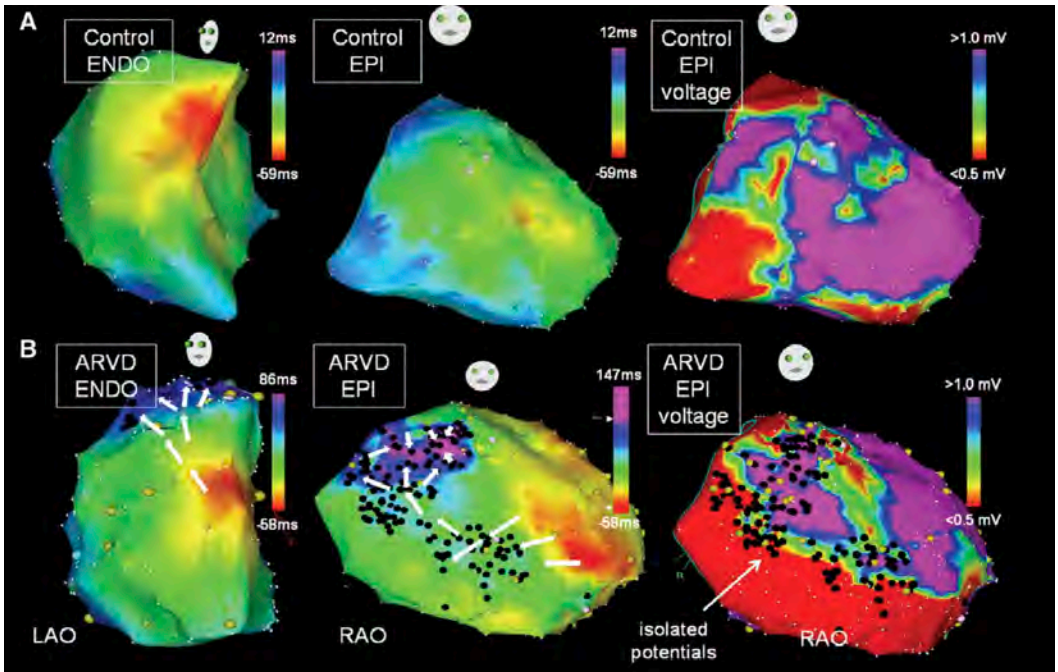

Figure 3.2: Endocardial Activation, Epicardial Activation, and Epicardial Bipolar Voltage Maps in Control and ARVC Patients

Panel A (Control Patient): activation can be seen to smoothly progress back toward the infundibulum and inferior tricuspid annulus. No evidence of endocardial (not shown) or epicardial scarring. Panel B (ARVC Patient): Extensive epicardial low voltage abnormalities and late potential activity (black dots). Although activation breakouts were in a similar region to the control patient, wavefront propagation is significantly altered by the sheets of scarring, particularly on the epicardium, where very delayed activation into the scar is seen. Reproduced with permission: Haqqani HM, Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

Study Limitations

This study has several important limitations. The endocardial and epicardial activation sequence have been determined in ARVC patients undergoing VT ablation, many of whom had already undergone prior ablation which may have altered activation and study results. Inaccuracies in determining local activation may have affected the results, including those related to the size of the mapping bipolar, the orientation of the catheter shaft, and the difficulty in absolutely distinguishing far-field activation from local activation in fractionated signals.

Clinical Implications

This is the first study to examine the transmural RV activation pattern in a group of control patients without structural heart disease and in patients with ARVC. Normal human RV activation progresses smoothly from apex to base on the endocardium and epicardium, likely with direct transmural epicardial activation. Right ventricular activation in ARVC is modified by the presence of confluent scar with a delayed epicardial activation sequence, which is suggestive of possible independent rather than direct transmural activation. (Figure 3.2) This may predispose VT circuits that are contained entirely within the epicardium in ARVC, and it explains the frequent need for direct epicardial ablation to successfully eliminate VT.

In the presence of dense fibrosis that is seen in ARVC, successful endocardial ablation of VT may be less probable, given the poor transmural penetration of current ablation energy sources. This limitation is likely to occur when burning in the thickened, densely scarred RVs that are seen in this disease. Though no randomized comparisons are available, the incorporation of epicardial mapping appears to be associated with better outcomes for ARVC-related VT ablation than endocardial ablation alone. This is presumably related to the increased ability to directly ablate the substrate for confined epicardial VT circuits.[46]

Although there is much data on the normal sequence of ventricular activation in patients with and without structural and conduction system disease, no studies have performed simultaneous contact mapping of the ventricular endocardium and epicardium to examine the sequence and relationship of activation of the two surfaces, and there have not been any data describing the effect of structural disease on this relationship. Control group findings from this study suggests that normal human RV activation occurs in an apex-to-base fashion, from its initial breakout at the myocardial border of the distal right bundle branch back toward the infundibulum and basal annuli. A similar sequence occurs on the epicardium, which is consistent with the results that were obtained by Wyndham et al., with surgical mapping of patients with coronary disease.[50] In that study, a constant anterior RV epicardial breakout was also seen and the latest activation was heterogeneous in a precise location, but was generally in the basal regions of the RV. A near simultaneous activation (delayed by only 5.2±1.9ms) was observed at sequential fiducial points along the course of activation of the endocardium and epicardium. This suggests that progressive transmural activation of the epicardium from subjacent endocardial points (rather than independent epicardial laminar activation) was occurring; the absence of a Purkinje network on the human epicardium would be expected to slow conduction relative to the endocardium to a significantly greater extent than observed. The finding that the latest epicardial site is activated within a mean of only 16ms of the completion of endocardial activation further supports this hypothesis.

The majority of patients exhibited a reverse centripetal pattern of activation of a confluent epicardial scar region from the periphery, progressing to collision in the center (Figure 3.3). Such a pattern essentially excludes the possibility of direct sinus rhythm transmural endocardial-to-epicardial RV activation in these patients. It is probable that this independent layered activation of the epicardium in sinus rhythm predisposes the existence of VT circuits that are partly or even completely confined to the epicardium, as the intramural fibrotic process provides a limited number of possible breakthrough sites to the endocardium that are

insufficient to short circuit the reentrant VTs.

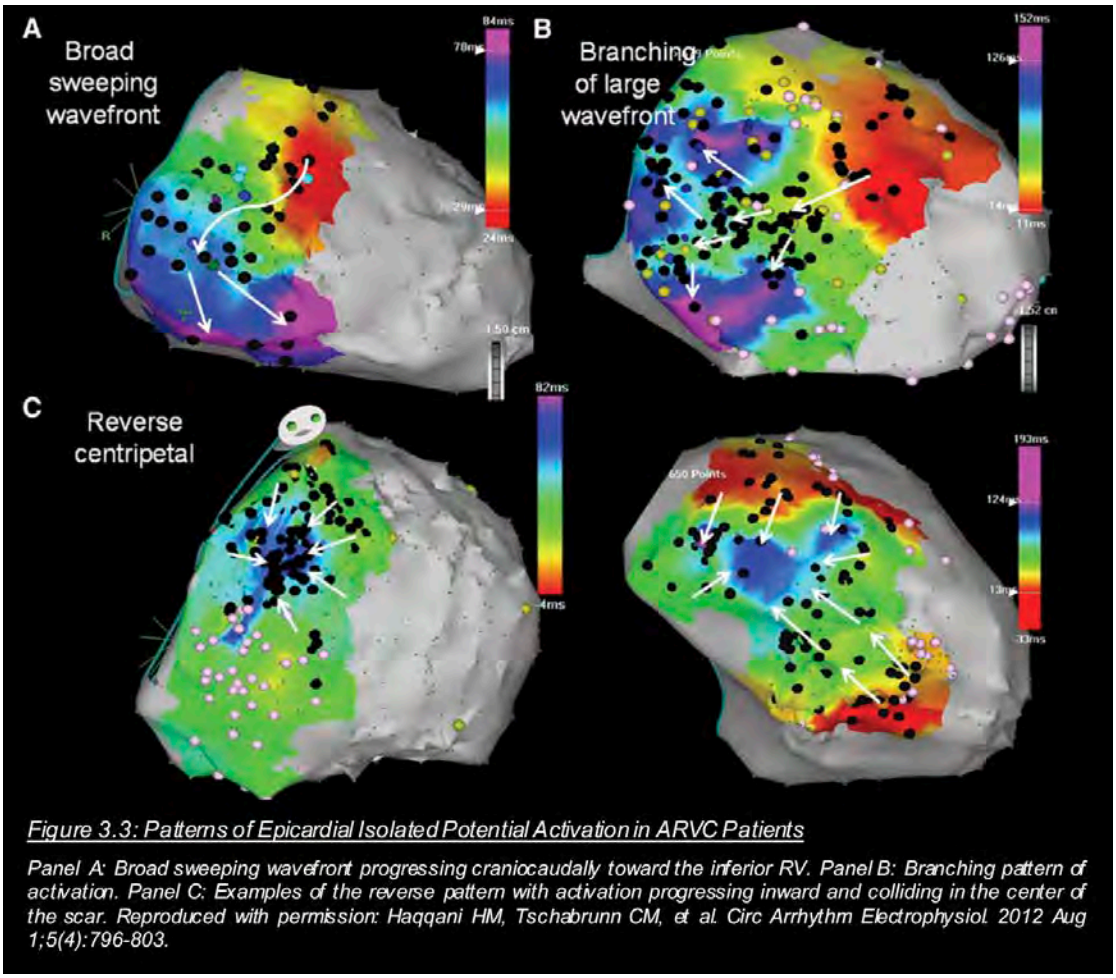

Figure 3.3: Patterns of Epicardial Isolated Potential Activation in ARVC Patients

Panel A: Broad sweeping wavefront progressing craniocaudally toward the inferior RV. Panel B: Branching pattern of activation. Panel C: Examples of the reverse pattern with activation progressing inward and colliding in the center of the scar. Reproduced with permission: Haqqani HM, Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

Normal human RV activation progresses smoothly from apex to base on the endocardium and epicardium, likely with direct transmural epicardial activation. RV activation in ARVC is modified by the presence of a confluent scar with a delayed epicardial activation sequence that is suggestive of possible independent rather than direct transmural activation. This may predispose VT circuits that are contained entirely within the epicardium in ARVC, and it explains observations of the need for direct epicardial ablation to successfully eliminate VT. In the presence of the type of dense fibrosis that is seen in ARVC, successful endocardial ablation of such VT may be less probable given the poor transmural penetration of current ablation energy sources. This limitation is particularly likely when burning in the thickened, densely scarred RVs that are seen in this condition. Though no randomized comparisons are available, the incorporation of epicardial mapping appears to be associated with better outcomes for ARVC-related VT ablation than endocardial ablation alone. This is likely to be related to the increased ability to directly ablate the substrate for confined epicardial VT circuits when approaching these with a transpericardial, rather than a transmural, strategy.

3.4 Long-term Clinical Outcomes of Catheter Ablation

*Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, **Tschabrunn CM**, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Long-term Outcome with Catheter Ablation of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2015 Dec 8;89(6):1413-21.*

Catheter ablation of ventricular tachycardia (VT) in arrhythmogenic right ventricular cardiomyopathy improves short-term VT-free survival. The purpose of this study was to determine long-term outcomes of VT control, and the need for antiarrhythmic drug therapy after endocardial (ENDO) and adjuvant epicardial (EPI) substrate modification in patients with arrhythmogenic right ventricular cardiomyopathy.

Major Findings

1. VT free survival was 71% with a mean follow-up of 56 months; an additional 15% experienced a single VT recurrent episode, and no patient received long-term amiodarone therapy.
2. Approximately half of the patients required more than one procedure and 37% received only endocardial ablation.
3. In patients with ARVC, long-term VT control can be achieved in the majority of cases with a strategy of endocardial ablation with adjuvant epicardial VT ablation.

Study Limitations

This was an observational, non-randomized study that summarizes a single-center experience spanning >15 years. The choice for the specific ablation approach (i.e., ENDO-only versus ENDO–EPI) was not randomized and, as expected, the acute ablation end points evolved over the multiyear study period. Patients who underwent ENDO-only ablation were enrolled earlier in the experience and, as a result, also had a longer follow-up, which may potentially act as a bias. In addition, the year of enrollment may have influenced the decision to perform EPI ablation, as operator threshold for proceeding with EPI ablation was expectedly lower than in 2003. Patients who had their ablation before 2003 were more likely to experience a clinical recurrence and then have persistent inducible VT, whereas patients with ablation since 2003 had an EPI ablation if they had inducible VT after extensive ENDO-only ablation before a clinical recurrence.

Clinical Implications

Prior studies evaluating the benefits of radiofrequency catheter ablation of VT in the setting of ARVC have only reported short-term and mid-term outcomes in a relatively small series of patients, frequently combining the results from multiple centers. The cumulative evidence arising from such studies and our own large single-center experience suggests that an ENDO

and EPI substrate–based ablation strategy is important for optimizing the management of recurrent VT in patients with ARVC.

These data support the clinical importance of an aggressive and comprehensive ENDO substrate modification as part of intraprocedural management strategy. This study supports the notion that ENDO-only ablation may still provide a clinical benefit in selected ARVC cases, as the long-term results were achieved with more than one third of patients undergoing ENDO-only procedures. For instance, ENDO ablation may be particularly critical to target the most basal aspect of the typical ARVC perivalvular substrate, which cannot be fully addressed with EPI ablation because of the presence of major coronary vessels. Importantly, in this study, EPI ablation only was reserved for patients who still had spontaneous or inducible VT after extensive ENDO ablation. Currently, this EPI ablation is typically performed in the same setting. As such, ENDO ablation represented an important aspect of the procedure and preceded EPI ablation. Therefore, the results of this study do not support a first-line EPI-only ablation approach in patients with ARVC, although adjuvant EPI ablation is often required to achieve long-term VT control.

Given the exceptionally high VT burden in this patient population, with a median of 4 (and ≤14) distinct clinical/inducible VTs per patient, it is important to emphasize the relevance of a comprehensive and extensive substrate-based ablation strategy that incorporates ENDO and, if still inducible, EPI ablation to achieve the long-term VT control that is reported in the present study. These data, from over a >10-year experience with EPI VT ablation, demonstrates the need to be more comprehensive in the extent of substrate ablation, particularly when epicardial access is obtained. This was done even more aggressively, as the researchers' clinical experience evolved to minimize the need for repeat ablation procedures that were initially commonly observed. It should be emphasized, however, that this strategy of performing noninvasive programmed stimulation before discharge and bringing patients back to the electrophysiology laboratory if inducible VT is found is still advocated. Early repeat ablation to minimize the potential for late adhesion formation that may limit accessibility is advisable.

3.5 Special Considerations During Epicardial Access, Mapping, and Ablation

Feasibility, Safety, and Challenges of Repeat Epicardial Access and Mapping

***Tschabrunn CM**, Haqqani HM, Zado ES, Marchlinski FE. Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.*

Percutaneous epicardial mapping and ablation has been increasingly utilized since it was first described by Sosa, et al. in 1996.[51] The feasibility and risk of de novo epicardial access procedures is relatively low. In some cases, repeat epicardial mapping and ablation may be needed, requiring a repeat percutaneous access attempt to the pericardium in the same patient. The objective of this study was to define the feasibility to safely obtain repeat pericardial access, the presence of pericardial adhesions, along with the incidence of mapping limitations and potential clinical impact. Patients that underwent epicardial mapping between June 2002 and April 2011 at the University of Pennsylvania and required a subsequent pericardial access for mapping, and ablation of VT was included in the analysis. Thirty patients were identified who required two or more epicardial procedures for recurrent VT.

Major Findings

1. Repeat pericardial access followed by epicardial mapping/ablation can be performed safely in the majority of cases.
2. Significant pericardial adhesions from the prior procedure, limiting catheter manipulation, was noted in seven (23%) patients. A steerable sheath was used in six of these cases to aid in cautious blunt dissection with the deflected catheter curve.
3. Adhesions were easily disrupted in five patients using careful blunt catheter dissection, and complete epicardial mapping was limited in only two patients.
4. Comparison of several index procedure characteristics between non-adhesion and adhesion groups, including number of epicardial lesions delivered, epicardial ablation time, post-procedure intravenous, and/or oral non-steroidal anti-inflammatory medications appeared to predict the development of pericardial adhesions.

Study Limitations

This is a study of a selected patient cohort in a single center with extensive experience performing percutaneous pericardial access and epicardial mapping. Procedural findings are based on the subjective judgment of the density of adhesions that were reported by the primary operator.

Clinical Implications

This study describes the largest population of patients undergoing repeat percutaneous pericardial access for catheter ablation of VT. Successful repeat pericardial access was acquired in all 30 patients. One patient required an additional puncture during the repeat procedure due to significant adhesions and pericardial space compartmentalization that precluded full epicardial mapping over the RV with the initial puncture directed toward the inferior septum and LV (Figure 3.4). The subsequent puncture, directed over the anterior RV, allowed successful mapping and ablation of these patients epicardial RV VT.

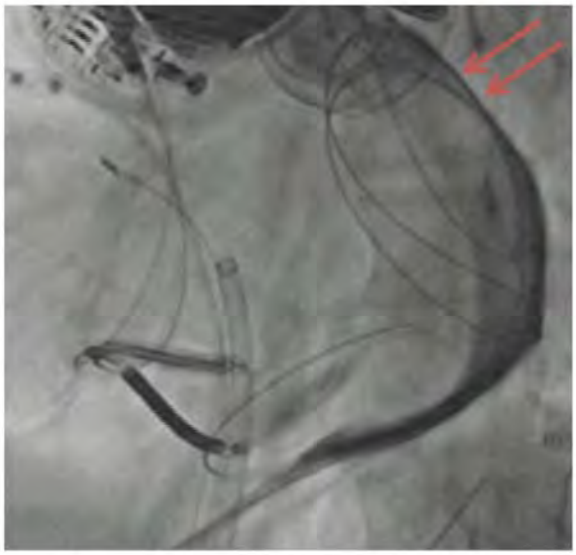

Figure 3.4: Epicardial Compartmentalization Due to Pericardial Adhesions

Adapted with permission: Tschabrunn CM, et al. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

This study demonstrates the safety and efficacy of repeat percutaneous pericardial access for recurrent epicardial VT. It demonstrates that in the vast majority of cases, repeat access can be obtained and that typically, no adhesions are encountered. Importantly, those adhesions can be effectively disrupted without complication when encountered, using the deflected mapping catheter and a steerable sheath that allows for detailed mapping and repeat ablation with a good long-term outcome. Uncommonly, adhesions that are encountered can be dramatic and produce compartmentalization of the pericardial space. The dense adherence may also be seen at the site of prior extensive epicardial ablation, which does not preclude successful mapping and ablation of other VT, although it may preclude repeat targeting of the original VT ablation sites.

Most VT can be successfully mapped and ablated from the endocardial surface. However, when this is not possible, percutaneous epicardial mapping and ablation may be required to target and eliminate the VT. In some cases, recurrent arrhythmia may require repeat epicardial procedures to obtain complete elimination of VT. There is little data available on the safety and efficacy of repeat epicardial procedures. Brugada et al. described one case where repeat pericardial access was required the day after the initial procedure and was obtained without incident.[52] Roberts-Thomson et al. reported a study with 15 patients requiring repeat epicardial mapping and successful percutaneous pericardial access was achieved in 87% of patients; however, no information about pericardial adhesions was reported.[53]

In this study, repeat pericardial access was obtained in each patient, regardless of whether or not intrapericardial steroid was administered during the initial procedure.[54] Adhesions can typically be disrupted with blunt catheter dissection, allowing the operator to access the site of interest (Figure 3.5). This has been done safely in the consecutive patients who are presented in this series by operators who are experienced in percutaneous pericardial access and mapping techniques. However, this experience is still limited and caution should be employed. Operators should be prepared to handle problems that are encountered with appropriate surgical backup available. Significant adhesions may be present from previous procedures; however, these can usually be disrupted mechanically without complication. By allowing for complete epicardial mapping, successful repeat VT ablation can be achieved in the majority of patients.

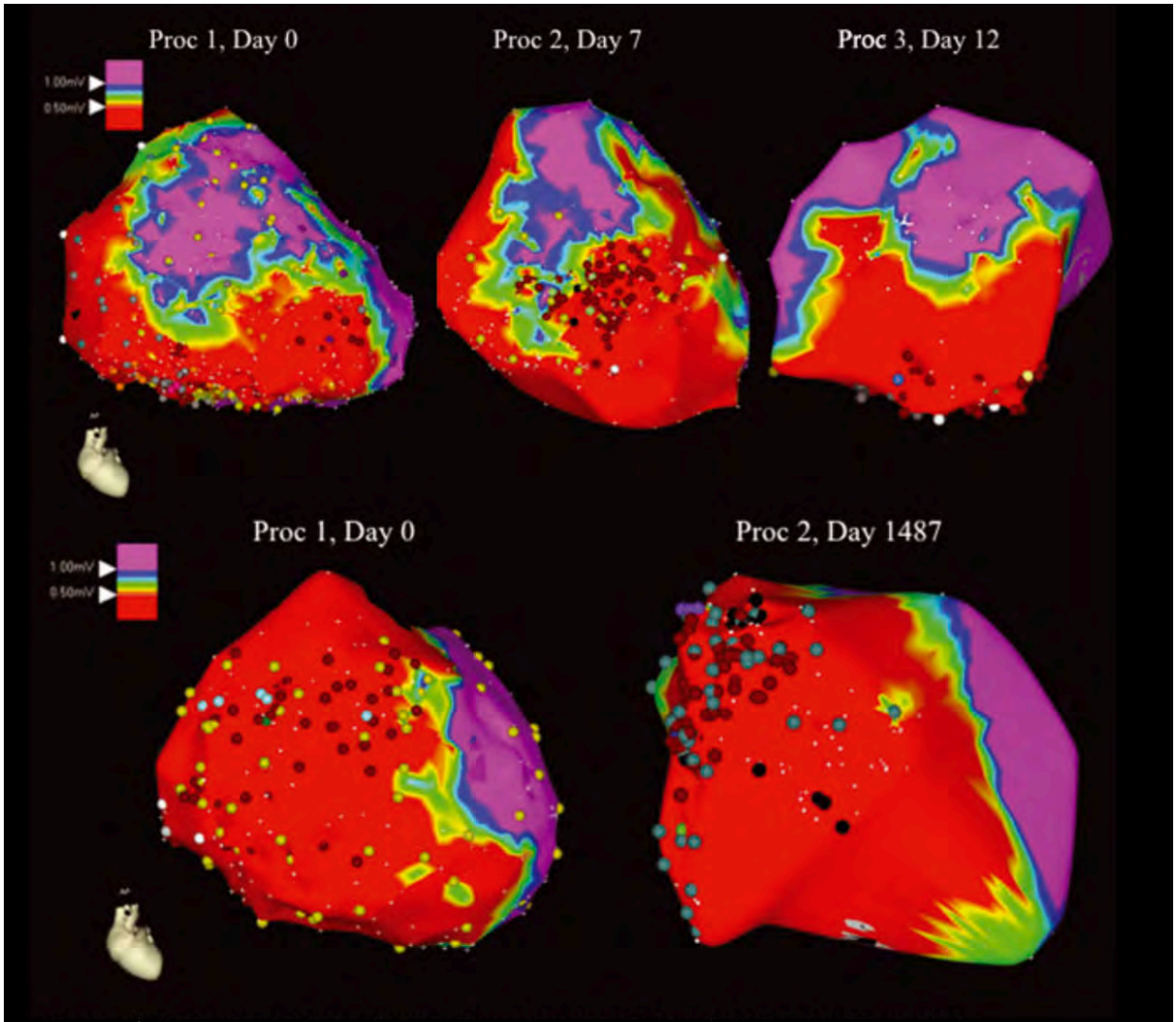

Figure 3.5: Early and Late Repeat Percutaneous Epicardial Mapping Examples

Adapted with permission: Tschabrunn CM, et al. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

Feasibility, Safety, and Challenges of Percutaneous Epicardial Access & Mapping Following Noncoronary Cardiac Surgery or Pericarditis

Tschabrunn CM, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Percutaneous Epicardial Ventricular Tachycardia Ablation After Non-Coronary Cardiac Surgery or Pericarditis. Heart Rhythm. 2013 Feb;10(2):165-9.

As described earlier, percutaneous epicardial mapping and ablation may be required to target and eliminate VT. In some cases, patients with prior cardiac surgery or pericarditis may require epicardial access to facilitate successful VT ablation. There is little data available on the safety and efficacy of epicardial procedures in these patients. Furthermore, there are varying reports on how often the pericardial space can be accessed in these patients and on how significantly adhesions limit epicardial mapping and ablation.

The objective of this study was to evaluate the safety and efficacy of percutaneous pericardial access and mapping/ablation in patients with prior non-coronary cardiac surgery or pericarditis. Patients that underwent an epicardial access attempt between June 2002 and June 2011 at the University of Pennsylvania were evaluated. In ten patients, epicardial access was attempted for recurrent VT. Two patients had previously treated pericarditis and the remaining eight patients had undergone sternotomy for variable indications. Of note, six out of ten of these patients were referred urgently due to VT storm.

Major Findings

1. Successful percutaneous pericardial access was achieved in all patients, but significant adhesions were encountered, limiting free movement of the ablation catheter in each case.
2. Similar to the adhesion disruption technique described in Chapter 2.6, adhesions could typically be disrupted with blunt catheter dissection, which allowed limited epicardial mapping and ablation in all but one patient.
3. Although this was performed safely in this cohort, this experience is still limited and caution should be exercised. Furthermore, operators were experienced in epicardial access and mapping with surgical backup available if needed.

Study Limitations

This is a study of a selected patient cohort in a single center with extensive experience performing percutaneous pericardial access and epicardial mapping. Procedural findings are based on the subjective judgment of the density of adhesions reported by the primary operator. This strategy should be reserved for high-volume centers with adequate surgical backup available at all times.

Clinical Implications

This study described the largest population of successful percutaneous pericardial access for catheter ablation of VT in patients with prior non-coronary cardiac surgery or pericarditis (Figure 3.6). This experience offers a new strategy that may allow experienced operators to perform epicardial mapping and ablation in a group of patients where it was previously thought not to be possible.

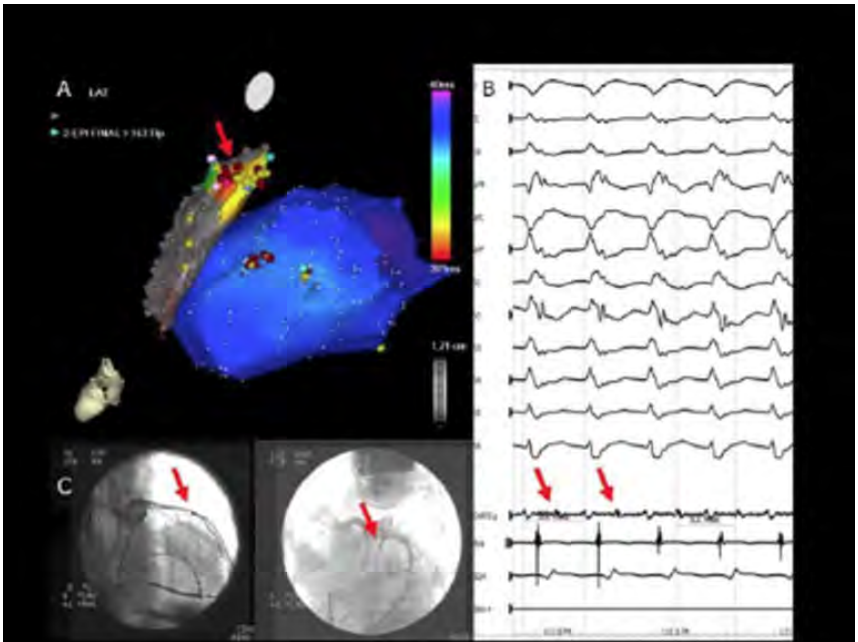

Figure 3.6: Epicardial Mapping in Patient with Prior Pericarditis and Epicardial VT

Reproduced with permission: Tschabrunn CM, et al. Heart Rhythm. 2013 Feb;10(2):165-9.

Although in the majority of these cases adhesions were successfully disrupted, this may not always be possible. Adhesions that are encountered can be dramatic and produce compartmentalization of the pericardial space that is resistant to blunt catheter dissection. Roberts-Thomson et al. described the largest study population of 13 patients with prior cardiac surgery or pericarditis requiring epicardial procedures. In their series, successful percutaneous pericardial access was achieved in only two of these cases (15%).[53] The long-term outcome in these patients was not provided. Sosa et al. have described five cases in which pericardial access was obtained in patients with previous cardiac surgery. In this series, mapping and ablation were limited, owing to adhesions and no data on long-term outcome or failed access attempts were provided.[55] There is some reports that suggests that performing a surgical pericardial window in the electrophysiology laboratory may assist with disrupting the

dense adhesions in these patients.[56] However, this is more invasive than mechanical disruption with the ablation catheter/steerable sheath. In the single case from our series where the ablation catheter was unable to break the adhesions, the surgical window was also unable to create a channel in the pericardial space. This suggests that both strategies may be limited in some patients with dense adhesions. The ability to access and map the epicardium in this series is significantly higher than previously reported. This is attributed to having access to the steerable sheath and experienced operators with expertise at performing epicardial procedures.

3.6 Conclusions

The development of fibrosis in ARVC is characterized by a unique epicardial to endocardial disease process that requires a specialized approach for arrhythmia treatment in the electrophysiology laboratory. Although the association between ARVC/D and the development of ventricular arrhythmias has become increasingly clear over the last two decades, our understanding of the arrhythmia mechanisms underlying electrophysiologic substrate and treatment strategies was significantly limited. These and other clinical studies performed in the electrophysiology laboratory allowed detailed characterization of the electrophysiologic and electroanatomic substrate underlying ventricular tachycardia in patients with ARVC/D. Through increased understanding of the disease process, catheter ablation has evolved to become an effective and preferred therapy for the majority of these patients. In addition, we demonstrated the safety and feasibility of percutaneous pericardial access and mapping in patients that underwent prior epicardial mapping, non-coronary cardiac surgery, or pericarditis. These studies described a new technique to disrupt pericardial adhesions using a deflected mapping catheter and a steerable sheath to facilitate epicardial mapping and ablation.

Chapter 4

High Resolution Catheter and Mapping Technologies: Insight from Clinical Laboratory Investigations

4.1 Introduction

Bipolar amplitude is influenced by several factors including: 1) conduction velocity, 2) fiber orientation and curvature, 3) relationship of fiber orientation to the propagating wavefront (non-uniform anisotropy), 4) tissue contact (Figure 4.1), and 5) characteristics of the recording catheter (electrode size, orientation relative to tissue, and interelectrode spacing). The notion that electrode size and interelectrode spacing characteristics impact bipolar signal morphology and spatial resolution is not a new concept. Schaefer et al. demonstrated the mathematical relationship between electrode distance from the recording source (i.e. tissue) and the implications of unipolar and bipolar electrogram characteristics in 1951.[57] This initial work also introduced the concept that bipolar electrodes reduce far-field contamination, and this effect was maximized as interelectrode distance decreased. Durrer et al. validated this concept in 1957 in a canine left ventricle experimental model.[58]

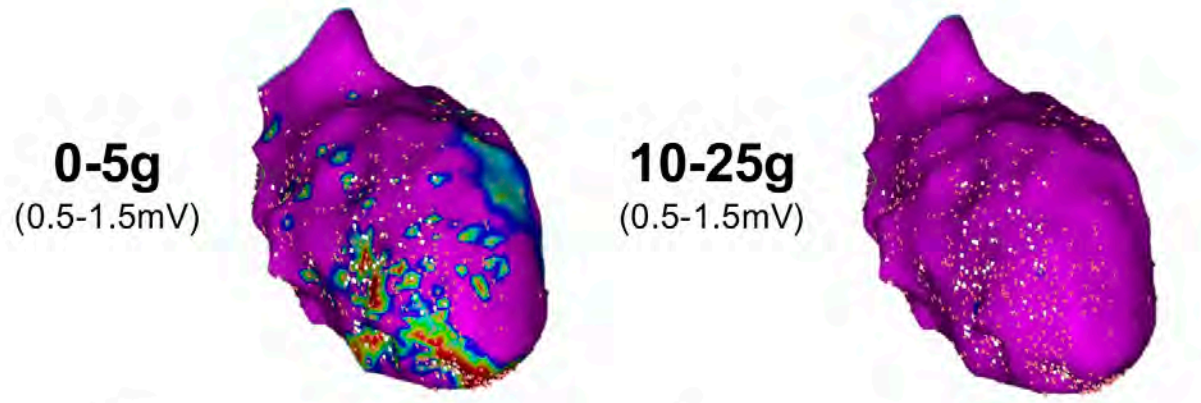

Figure 4.1: Influence of Catheter Tissue Contact on Bipolar Voltage

Endocardial left ventricular voltage maps in patient without structural heart disease. Areas of inadequate tissue contact (0-5g) more likely to record bipolar amplitude electrograms <1.5mV.

In more recent work, Stinnett-Donnelly et al. showed, using computational and in-vitro models, that electrode spatial resolution is impacted by electrode diameter, electrode length, interelectrode distance, and distance from the current source (tissue), and spatial resolution degrades with the increase of any of these four factors.[59] The angle of incidence (orientation of

the catheter relative to the tissue) also has major implications that can impact the degree of signal cancellation and electrogram spatial resolution. Previous experimental studies have showed that electrograms in a nonparallel orientation (distal electrode in contact with tissue and proximal electrode not in contact) results in near simultaneous activation of the distal and proximal unipolar electrograms.[60] This results in the bipolar summation that is subjected to significant cancellation, even in normal tissue (Figure 4.2). This is further complicated in the setting of tissue fibrosis due to non-uniform anisotropy and a significantly smaller degree of tissue mass being activated.

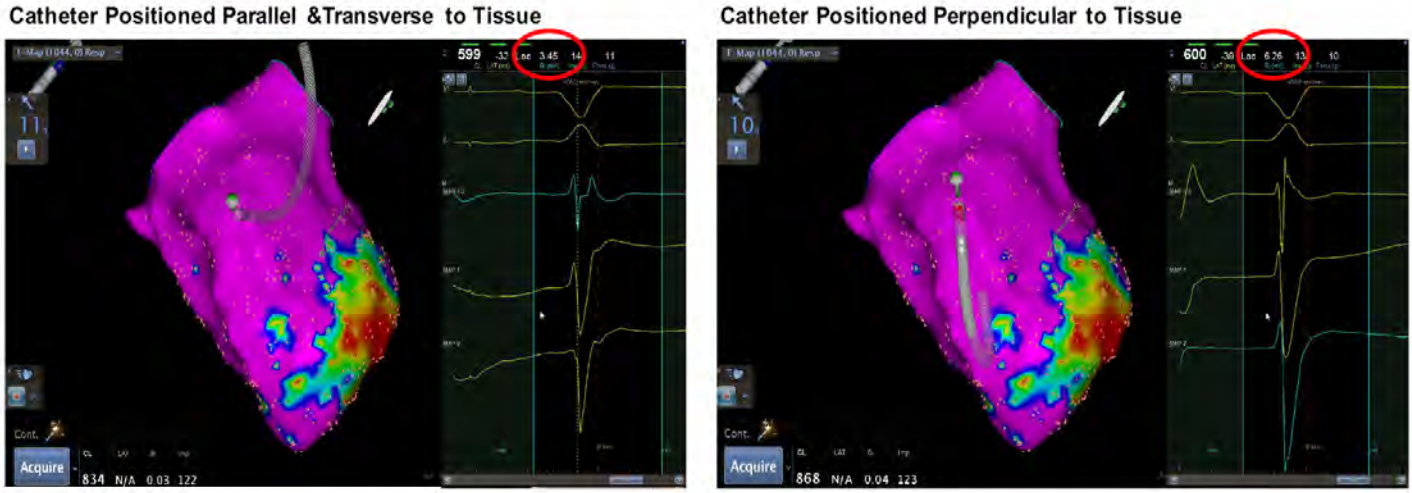

Figure 4.2: Influence of Catheter Orientation on Bipolar Voltage

Demonstration of how catheter orientation and angle of incidence relative to the tissue influences bipolar voltage. When the catheter is positioned in a nonparallel orientation (distal electrode in contact with tissue and proximal electrode not in contact) there is near simultaneous activation of the distal and proximal unipolar electrograms that results in bipolar summation and significant cancellation. There is less cancellation when the catheter is positioned perpendicular to the tissue with both distal and proximal electrodes in contact with tissue, resulting in a larger bipolar amplitude.

Conventional mapping catheters with a distal electrode that is larger than 3.5mm, longer center-to-center interelectrode spacing, and predisposition to variable extremes in angle of incidence inherently limits the spatial resolution of bipolar electrograms. This chapter discusses the initial critical insight from clinical studies that were performed using high-resolution mapping catheters and technologies. Chapter 4.2 compares the mapping resolution of standard and high-resolution mapping catheters in the right and left atria, and Chapter 4.3 presents a case report of high-resolution reentrant VT activation mapping. The research investigations discussed in this Chapter were carried out in the clinical electrophysiology laboratories of the Beth Israel Deaconess Medical Center (BIDMC) - Harvard Medical School in Boston, Massachusetts. All of the patients provided written informed consent prior to the clinical electrophysiologic procedures in accordance with BIDMC institutional guidelines.

4.2 High Resolution Mapping of Atrial Scar and Arrhythmias

*Anter E, **Tschabrunn CM**, Josephson ME. High-resolution Mapping of Scar-related Atrial Arrhythmias Using Smaller Electrodes with Closer Interelectrode Spacing. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.*

Atrial fibrillation (AF) ablation is an acceptable therapeutic option for patients with symptomatic AF refractory to medications.[62,63] Pulmonary vein isolation is the cornerstone of the procedure and is associated with a reasonable clinical outcome in patients with paroxysmal AF.[64] However, in patients with persistent AF, pulmonary vein isolation is less effective and additional substrate ablation is frequently performed (linear ablation lines and/or complex fractioned electrogram ablation), but without evidence of any clinical benefit.[65] [66] This approach often results in the development of post-ablation, scar-related, organized atrial tachycardias (AT).[67] The mechanism of these arrhythmias is usually re-entry involving pre-existing and/or ablation related scar tissue. These circuits are typically challenging to map because of significant scar coupled with fractionated and multicomponent electrograms, limiting local time annotation. In addition, entrainment and post-pacing interval mapping techniques may be difficult to perform and interpret because of high output pacing and lack of capture in these areas of low voltage.

The standard catheter for mapping these arrhythmias is a linear catheter with a 3.5-mm distal electrode separated by 2 mm from a proximal 2-mm electrode, resulting in a center-to-center interelectrode spacing of 4.75 mm. As such, each bipolar electrogram represents an underlying tissue diameter that ranges from 3.5 to 7.5 mm, depending on the angle of incidence (from perpendicular to parallel to the tissue, respectively). Catheters with 1-mm electrodes, 2-mm interelectrode spacing, and 3-mm center-to-center interelectrode spacing record electrograms from a significantly smaller underlying tissue diameter, ranging from 1 to 4.0 mm (also dependent on catheter orientation relative to the surface). These catheters may have advantages for mapping scar-related arrhythmias, including (1) higher mapping resolution that can identify heterogeneity within the area of low voltage, localizing channels of surviving bundles; (2) smaller electrodes with closer interelectrode spacing are subjected to less signal averaging and cancellation effects, and may thus record higher bipolar voltage amplitude with shorter electrogram duration, allowing more accurate time annotation; and (3) pacing with capture at lower output because of increased electric density (Figure 4.3).

The objectives of this study were to (1) establish normal voltage amplitude cutoffs in the atria for both 3.5-mm electrode tip catheters and 1-mm multielectrode-mapping catheters, and (2) compare their mapping resolution in scar-related organized AT.

Major Findings

1. Bipolar voltage amplitude in healthy atria is similar between 3.5- and 1-mm electrode catheters with a fifth percentile of 0.48 and 0.52 mV, respectively
2. Mapping resolution within areas of low voltage and scar is enhanced with 1-mm electrode catheters.
3. Electrode size and interelectrode spacing were major determinants of mapping resolution within areas of low voltage and scar mapping using activation, and overdrive pacing techniques was more accurate using 1-mm electrode catheters.

Study Limitations

This single center study included a relatively small cohort of patients. Although mapping data with the linear catheter was confirmed by contact force measurement, such data were not available for maps made with the multielectrode-mapping catheter. However, although differences in tissue contact can affect bipolar voltage amplitude, this is unlikely to account for the differences between the catheters because 1) all of the maps that were performed with multielectrode-mapping catheters had similar volumes compared to maps that were made with linear catheters, and 2) points were only accepted if they were within 5mm of the original shell that was made with the linear catheter. The clinical impact of mapping with small electrode catheters on long-term clinical outcomes is outside of the scope of this study and remains unanswered.

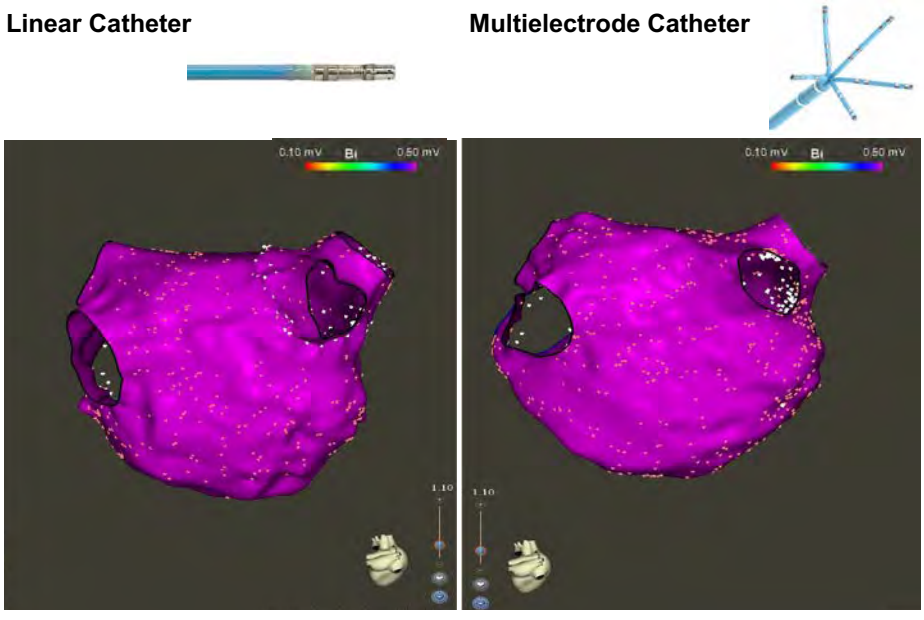

Figure 4.3: Linear and Multielectrode Catheter Left Atrial Bipolar Voltage Maps

Left atrial bipolar voltage maps (0.10-0.50mV) acquired with both the linear and multielectrode catheters in a patient undergoing de novo pulmonary vein isolation with a structurally normal heart. Adapted with permission: Anter E, Tschabrunn CM, Josephson ME. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

Clinical Implications

This study established the normal bipolar voltage distributions in the right and left atria for both a linear catheter with 3.5-mm distal electrode and 1-mm multielectrode-mapping catheter. In addition, this study compared the mapping resolution in low voltage and scars with both catheters. Accurate detection and characterization of atrial scars with electroanatomic mapping is essential for catheter ablation of atrial arrhythmias. Limited data exists on the normal voltage distribution in the atria. Kapa et al. have defined the normal bipolar voltage distribution in the left atrium using a 3.5-mm Thermocool catheter. In ten patients with paroxysmal AF, the mean bipolar voltage amplitude was 1.44±1.27 mV, and 95% of all points demonstrated a bipolar voltage amplitude >0.45 mV.[68]

In this study, the normal atrial electrogram characteristics of two commonly used catheters were established: a standard mapping/ablation catheter (Thermocool) and a multielectrode-mapping catheter (Pentaray). This study demonstrated that 95% of all electrograms in the right and left atria had a bipolar voltage amplitude >0.48 mV. In addition, the distribution of electrogram duration was measured in healthy atria and 95% of all electrograms had a duration <58ms Although the resolution of mapping between the catheters was similar in healthy atrial tissue (Figure 4.3), they significantly diverged in low voltage and scar tissue (Figure 4.4).

Linear Catheter **Multielectrode Catheter**

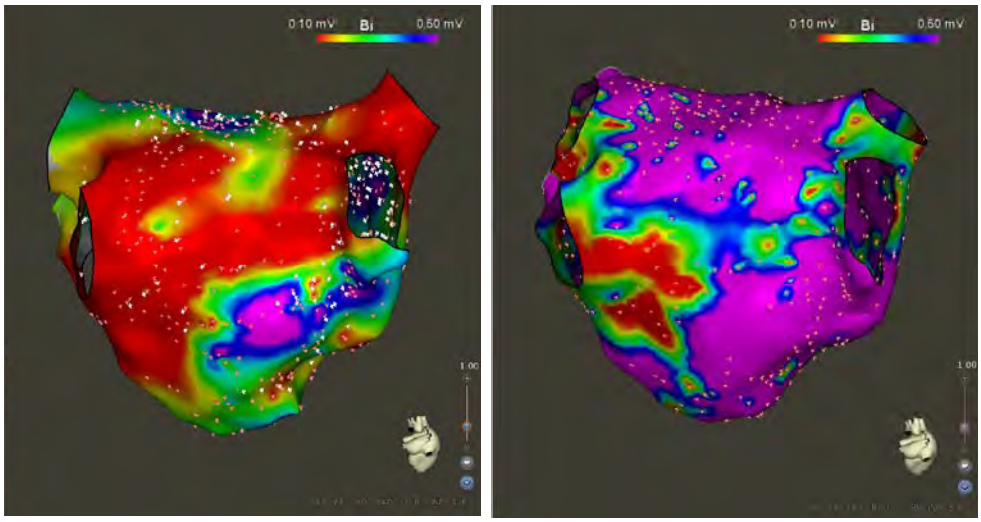

Figure 4.4: Linear and Multielectrode Catheter Left Atrial Bipolar Voltage Maps in Scar

Left atrial bipolar voltage maps (0.10-0.50mV) acquired with both the linear and multielectrode catheters in a patient with prior left atrial ablation and scar. Bipolar voltage map acquired with the mapping with the multielectrode catheter demonstrates smaller low-voltage area. Adapted with permission: Anter E, Tschabrunn CM, Josephson ME. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

The resolution of electric mapping is influenced by multiple parameters, including electrode size, interelectrode spacing, angle of incidence (catheter orientation relative to the surface), the vector of wave propagation, and filtering. Their combined effect is associated with significant variations in the recorded bipolar voltage amplitude at any single recording point. While these changes may not be as clinically important in normal healthy tissue a bipolar voltage amplitude variation between 0.5 and 4.0 mV represents normal tissue; such variations in areas of low voltage and scars are significant and determine the feasibility to identify surviving myocardial channels and isthmuses that are often present in zones of low voltage.

Further analysis demonstrated that mapping density alone is not responsible for the differences in mapping resolution within a scar and that smaller electrodes and closer interelectrode spacing are significant determinants of mapping resolution. Smaller electrodes have smaller electric fields of view and smaller antenna, and as such are subjected to less averaging and cancellation effects. A bipolar electrode pair with closer interelectrode spacing records signals from smaller tissue diameters and is therefore more sensitive to detect surviving myocardial fibers in zones of generally low voltage channels. It also has a more distinct electrogram with a shorter electrogram duration that allows more accurate annotation of activation time (Figure 4.5). Lastly, the pacing output threshold within the zone of low voltage and scar is lower with small electrode catheters, presumably because of the increased electric current density at the electrode-tissue interface. This technique can facilitate successful ablation of scar-related atrial tachycardia.

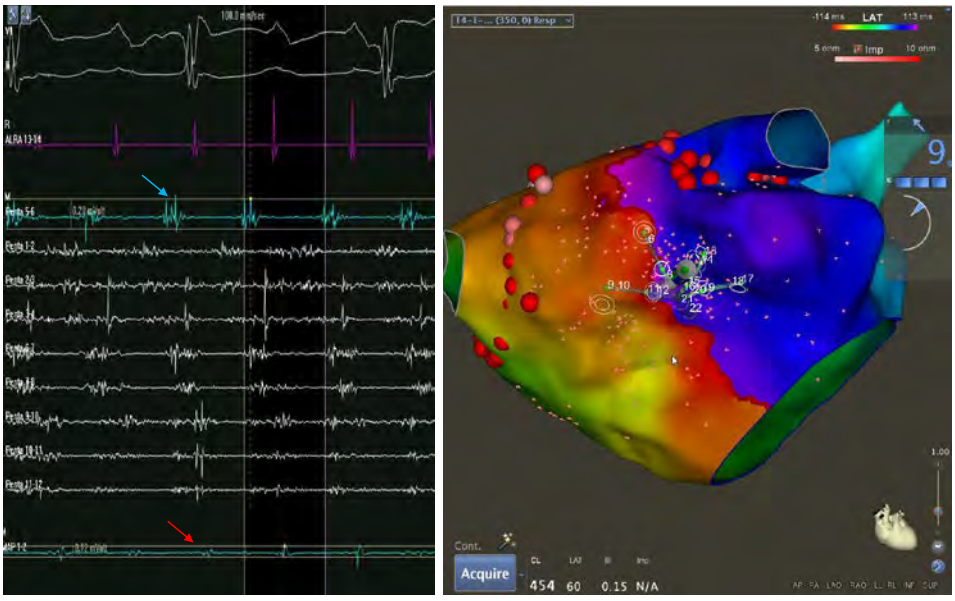

Figure 4.5: Atrial Activation Mapping with Linear and Multielectrode Catheters

In a patient with macro-reentrant left atrial flutter, the linear catheter recorded low, far-field, signals with amplitude of 0.12 mV (red arrow). The multielectrode catheter recorded sharp, near-field, signals with bipolar amplitude range of 0.18–0.28 mV (blue arrow) that allowed superior annotation of local activation. Adapted with permission: Anter E, Tschabrunn CM, Josephson ME. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

4.3 High Resolution Activation Mapping of Reentrant Ventricular Tachycardia

*Anter E, Li J, **Tschabrunn CM**, Nezafat R, Josephson ME. Mapping of a Post-Infarction Left Ventricular Aneurysm-Dependent Macroreentrant Ventricular Tachycardia. HeartRhythm Case Rep. 2015 Nov 1;1(6):472-6.*

Activation mapping of ventricular tachycardia (VT) is rarely accomplished due to limited temporal and spatial resolution, unacceptably long mapping time, and hemodynamic instability. Entrainment mapping is a reasonable approach to identifying targets for ablation in patients with tolerated post-infarction reentrant VTs. However, it often does not allow delineation of the entire VT circuit. Introduction of newer mapping technologies that are capable of rapid and high-resolution electroanatomical mapping may allow detailed activation mapping of macroreentrant VTs, enhancing our understanding of a macroreentrant circuit's geometry and electrophysiology to facilitate ablation.

Case Report

A 77-year-old man with a history of hypertension, hypercholesterolemia, diabetes, and multi-vessel coronary artery disease with prior inferior MI was transferred to our institution for the management of recurrent monomorphic VT. Six-weeks earlier, he underwent coronary artery bypass graft surgery and a thin-walled large aneurysm at the base of the inferior wall was identified. The aneurysm contained thin fibrous, non-contractile material that was associated with dyskinetic wall motion abnormality, which was consistent with a contained ruptured wall from prior transmural MI, and a pericardial patch was placed during surgery. The patient recovered well from surgery with a left ventricular ejection fraction of 35-40% on transthoracic echocardiography one month later. Unfortunately, he began to develop frequent and recurrent episodes of sustained monomorphic VT that was refractory to pharmacologic therapy (amiodarone, quinidine, and mexiletine) and required external shocks due to hemodynamic compromise. The VT cycle length was 360msec and it had a left bundle branch block pattern with left superior axis, suggestive of a basal inferior wall exit (Figure 4.6).

The high resolution Rhythmia^{TM} mapping system with its proprietary Orion^{TM} mini-basket catheter (Boston Scientific, Cambridge, MA) was used to perform high resolution activation mapping of the VT. Activation mapping is automated and is determined based on the combination of the bipolar and unipolar electrograms and timed at the maximal (-) dV/dt of the local unipolar electrogram. The mini-basket catheter was placed in the aneurysm and the clinical VT was induced with single extra stimuli from the right ventricle apex. Pacing from the RVA during VT showed ECG fusion, which is consistent with a reentrant mechanism. The entire reentrant circuit was mapped and it demonstrated a continuous loop around the base

of the aneurysm. During a mapping time of 7 minutes and 12 seconds, 4264 activation points were acquired.

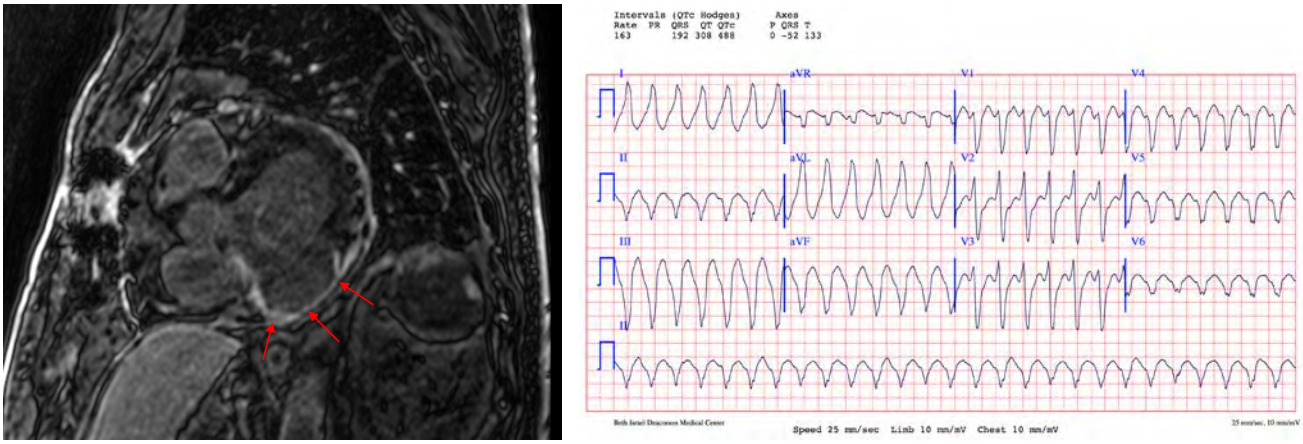

Figure 4.6: Cardiac Magnetic Resonance Imaging and 12-Lead Electrocardiogram of VT in Patient with Prior Myocardial Infarction

Cardiac magnetic resonance imaging with late gadolinium enhancement demonstrates infero-basal aneurysm and fibrosis. The patient developed recurrent monomorphic ventricular tachycardia with a left bundle branch block morphology and superior axis suggestive of a left ventricle infero-basal site of origin. Adapted with permission: Anter E, et al. HeartRhythm Case Rep. 2015 Nov 1;1(6):472-6.

The area of slowest conduction velocity was at the junction between the base of the aneurysm and the mitral annulus. This area served as the protected common pathway of the tachycardia that propagated clockwise around the edge of the aneurysm. A fractionated mid-diastolic signal was recorded at this site. Entrainment from this site showed a concealed QRS fusion with a post-pacing interval that was identical to the tachycardia cycle length and with a stimulus to QRS interval of 182ms (50% of the tachycardia cycle length) that was the same as the EGM to QRS interval, which is consistent with a protected isthmus site (Figure 4.7). A single radiofrequency ablation application at this site slowed and terminated the tachycardia. The local electrogram at the termination site demonstrated atrial and ventricular signals that were consistent with a mitral annulus site. Following termination of the tachycardia, pacing medial to the ablation lesion resulted in clockwise propagation around the edge of the aneurysm with QRS morphology that is similar to the VT. Pacing lateral to the ablation lesion resulted in counterclockwise propagation around the edge of the aneurysm with QRS morphology opposite to the VT with a right inferior axis, which is consistent with a block across the isthmus line. Following ablation at the isthmus site, the VT was not inducible.

Clinical Implications

This case report demonstrates the feasibility of utilizing the Rhythmia mapping system to perform high resolution activation mapping of an entire reentrant VT circuit in a patient with inferior infarction and aneurysm. This demonstrated that the macroreentrant circuit circulated

around the edge of the aneurysm with the area of slowest conduction velocity at the edge of the aneurysm adjacent to the mitral annulus. This was confirmed to be a central isthmus site and entrainment mapping ablation at that site resulted in slowing and termination of the VT with a single radiofrequency ablation application.

Macroreentrant circuits around the edge of an LV aneurysm have been described with a wavefront propagation that can be clockwise or counterclockwise. However, a detailed activation map of such arrhythmias has been limited by inadequate spatiotemporal resolution. New mapping technologies utilizing catheters with small multi-electrodes in conjunction with automated annotation of local activation time allow rapid mapping of reentrant electrical circuits in unprecedented detail. This mapping technology may be particularly useful for mapping reentrant VTs and may facilitate rapid mapping of VTs that were previously considered “unmappable” because of hemodynamic instability or circuit complexity. It may also improve the current understanding of circuit geometry and physiology that can better guide targeted ablation strategy.

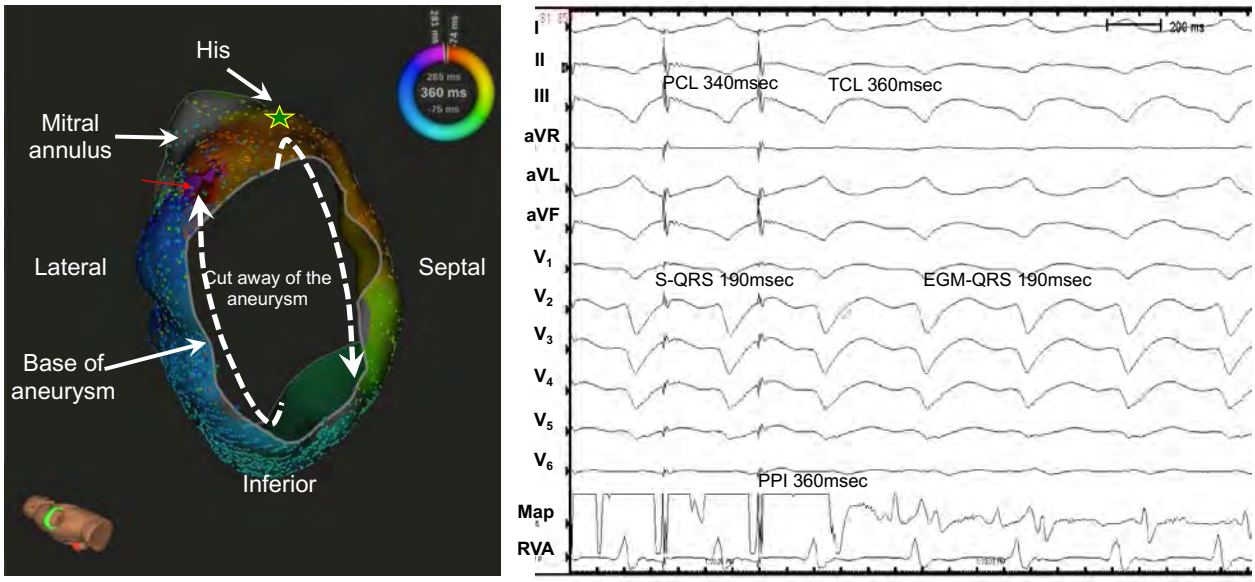

Figure 4.7: High Resolution Activation Map and Entrainment of Sustained Ventricular Tachycardia

Adapted with permission: Anter E, et al. HeartRhythm Case Rep. 2015 Nov 1;1(6):472-6.

4.4 Conclusions

Multielectrode mapping catheters using smaller electrodes with closer interelectrode spacing offer several advantages for mapping scar-related atrial and ventricle substrate and arrhythmias, including: 1) higher mapping resolution that may identify heterogeneity within the area of low voltage during sinus rhythm mapping, allowing localizing “channels” of surviving

myocardial bundles; 2) smaller electrodes with closer interelectrode spacing are subjected to less signal averaging and cancellation effects, and may thus record electrograms with higher bipolar voltage amplitude and short electrogram duration, allowing more accurate local activation time annotation; and 3) pacing with capture at lower output due to increased electrical current density.

Chapter 5

High Resolution Mapping of Ventricular Scar: Insight from Experimental Laboratory Investigations

5.1 Introduction

Attempts to use voltage amplitude alone to define barriers and recognize channels are inherently influenced by the catheter design and technology. Standard mapping catheters have several limitations for mapping scar-related VTs. These catheters have a 3.5mm distal tip electrode that is separated by 1mm from a proximal 2mm electrode, resulting in center-to-center interelectrode spacing of 3.75mm. As such, each bipolar electrogram represents a recording from an underlying tissue diameter ranging from 3.5mm to 6.5mm, depending on the angle of the catheter (from perpendicular to parallel to the tissue, respectively). This mapping resolution may not be adequate to identify surviving myocardial bundles (including isthmuses) within the area of low voltage since there may be cancellation effects of bipolar electrograms recorded within these areas.[69] In addition, electrograms recorded using these relatively large electrode catheters often record long, fractionated, and multicomponent signals because of the underlying pattern of activation. The presence of such fractioned electrograms limits accurate annotation of local activation time during activation mapping and interpretation of entrainment mapping.

Multielectrode-mapping catheters have smaller electrodes and closer center-to-center interelectrode spacing in comparison to conventional linear mapping catheters. This results in increased mapping resolution as each point represents electrical activity of a smaller tissue size. This may allow for the identification of surviving myocardial bundles “channels” within an area of heterogeneous scarring, that may be “contaminated” by surrounding fibrosis with the large distal electrode of the linear catheter. In addition, mapping with multielectrode catheters also contains more electrogram points, and points acquired with increased variability in the angle of incidence and the relationship to the vector of propagation. They are therefore less subject to the individual confounding effects of bipolar voltage amplitude measurement.

This chapter describes the evaluation of high resolution technologies in a human-like large animal model of a post-infarct scar. Chapter 5.2 describes the development and validation of the swine model that was used for this purpose, Chapter 5.3 compares the standard and multielectrode mapping catheters in conjunction with CMR imaging and histopathology, and Chapter 5.4 introduces unpublished data from high-resolution VT activation mapping studies that were

performed using the same model. The research investigations discussed in this Chapter were carried out in the experimental electrophysiology laboratory of the Beth Israel Deaconess Medical Center (BIDMC) - Harvard Medical School in Boston, Massachusetts under an approved institutional animal care and use committee protocol. All of the procedures were performed in accordance with BIDMC institutional guidelines.

5.2 Clinically Relevant Model of Post-Infarct Ventricular Scar and Reentrant VT

***Tschabrunn CM**, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Swine Model of Infarct-related Reentrant Ventricular Tachycardia: Electroanatomic, Magnetic Resonance, and Histopathologic Characterization. Heart Rhythm. 2016 Jan;13(1):262-73.*

Large animal models have been utilized to study post-infarct arrhythmogenic substrate and VT for decades. The selected animal species, designated coronary artery, and myocardial ischemia induction method have significantly varied across investigations. These experimental characteristics are critical to determining whether or not arrhythmias occur and they define their inherent characteristics when they do. Arrhythmias may not occur without the presence of surviving myocardial fibers in the infarcted region, and their spatial arrangement is important for developing a milieu to support reentry.[70] Despite significant advancements that have been made in this area, there is an ongoing need for human-like models of post-infarct reentrant VT. These models can assist in the development of improved methodologies to identify and differentiate an arrhythmogenic scar from a non-arrhythmogenic scar and to validate new diagnostic and therapeutic tools in the pre-clinical setting. The objective of this study was to develop and characterize a model of a healed myocardial infarction with human-like subendocardial reentrant VT utilizing a consistent experimental approach.

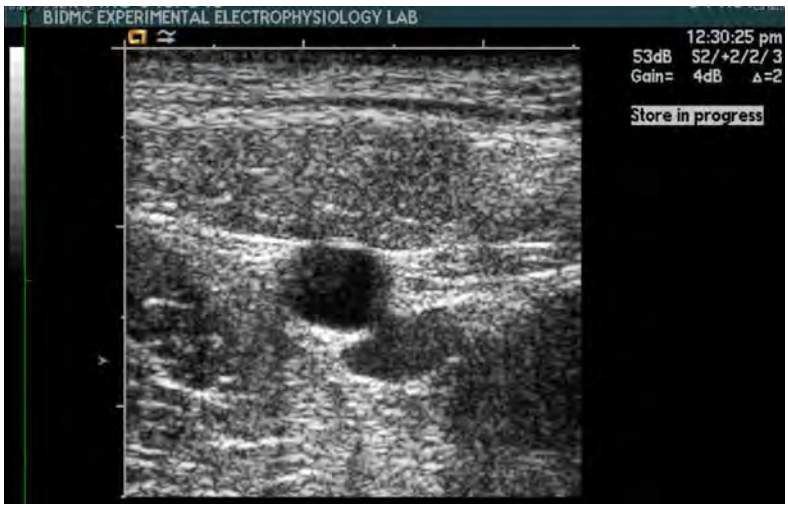

Figure 5.1: Vascular Ultrasound Guidance for Femoral Arterial and Venous Access

Vascular ultrasound was used to guide percutaneous femoral arterial and venous access rather than performing a more traumatic surgical cut-down that is typically utilized in experimental laboratories. This approach minimizes vascular complications and expedites animal recovery following the myocardial infarction procedure.

Post-infarct Model Development and Technique

This study implemented a number of specific techniques to maximize survivability. Animals were treated with amiodarone at a dose of 800 mg twice daily for 3-4 days before the infarction procedure to reduce the incidence of ventricular arrhythmias during the peri-infarct period. Percutaneous femoral arterial and venous access was guided by ultrasound (Siemens Acuson, Mountain View, CA) and obtained using a micropuncture needle (Cook Medical, Bloomington, IN) to minimize vascular trauma (Figure 5.1). After vascular access, 10,000 units of unfractionated heparin were administered intravenously with maintenance boluses (2000–3000 units) as needed to maintain activated clotting time (ACT) of 250–350 seconds. Intravenous lidocaine (50–100 mg bolus, 1 mg/min continuous drip) and metoprolol (1mg) were administered to reduce the incidence of malignant ventricular arrhythmias. Under fluoroscopic guidance, a 6F Hockey stick guide catheter (Cordis Corporation, Fremont, CA) was positioned in the left main ostium. A 0.18-in, 180-cm Choice PT angioplasty wire (Boston Scientific, Marlborough, MA) was carefully advanced into the left anterior descending (LAD) coronary artery. A rapid-exchange 2..5x12 mm angioplasty balloon (Apex, Boston Scientific, Marlborough, MA) was placed over the angioplasty wire in the mid-LAD. Serial coronary angiography was performed to position the angioplasty balloon immediately distal to the second diagonal branch of the LAD. The angioplasty balloon was inflated and maintained at 12–14 atm throughout the infarct procedure. After initial balloon inflation, repeat coronary angiography was performed to confirm adequate distal occlusion of the LAD. Uninterrupted coronary occlusion was maintained for 180 minutes, with confirmation of acute MI by ST-segment elevation in the precordial ECG leads (Figure 5.2).

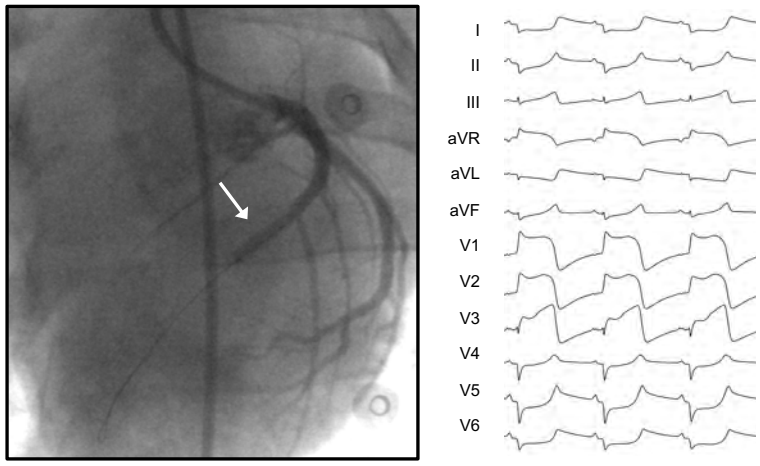

Figure 5.2: Induction of Experimental Myocardial Infarction

Anterior infarction induced with mid left anterior descending coronary artery balloon occlusion (white arrow). 12-lead electrocardiogram demonstrates ST segment elevations consistent with anterior infarction shortly after initiation of coronary occlusion. Adapted with permission: Tschabrunn CM, et al. Heart Rhythm. 2016 Jan;13(1):262-73.

Animals were recovered and survived for 6–8 weeks after the MI. Amiodarone at a dose of 800 mg twice daily was continued for another 5–6 days after the infarct procedure up to a total dose of 14,400–16,000 mg to minimize post-procedure arrhythmias. Thirty-four of the 35 animals (97%) survived the MI procedure. One animal developed refractory ventricular fibrillation 45 minutes after intracoronary balloon occlusion that persisted despite balloon deflation, defibrillation, and antiarrhythmic drug therapy. Thirty-one of the remaining animals (91%) completed the survival period of 47.7±2.4 days without complication. One animal developed a spontaneous episode of sustained monomorphic VT 6 days after the MI that resulted in congestive heart failure. This animal was successfully converted to sinus rhythm, but was subsequently euthanized because of cardiogenic shock. Two animals died suddenly 38 and 45 days after the MI procedure without preceding signs and/or symptoms of heart failure. The study demographics and experiments are detailed in Table 5.1.

Demographics	
Acute mortality	1 (3)
VF during infarct	8 (27)
Study completion	31 (91)
Postinfarct period (d)	47.7 ± 12.4
Final weight (kg)	62.8 ± 11.7
CMR imaging data	
LV end-diastolic volume (mL)	142 ± 37
LVEF (%)	36 ± 6.6
Total scar area (%)	12.5 ± 4.1
LV mapping	
LV chamber volume (mL)	149 ± 50
Low bipolar voltage (≤1.5 mV) area (%)	11.1 ± 3.5
Very low bipolar voltage (≤0.5 mV) area (%)	3.8 ± 1.8
Fractionated EGM density (%)	65.2 ± 9.6
ILP EGM density (%)	16.6 ± 3.8
VT	
VT induction	28/31 (90)
Distinct VT morphologies	2.4 ± 1.1 (range 1–4)
Tachycardia cycle length (ms)	256 ± 42 (range 185–356)
VT QRSd (ms)	137 ± 26
VT duration (s)	396 ± 186

Table 5.1: Experimental Results and Demographics (Total n=35)

Adapted with permission: Tschabrunn CM, et al. Heart Rhythm. 2016 Jan;13(1):262-73.

Major Findings

1. mid-LAD balloon occlusion for 180-minutes results in the reproducible development of a humanlike post-infarct arrhythmogenic scar in the majority of cases and the developed technique and methods yields excellent animal survivability.

2. This includes a transmural component of anterior/anteroseptal fibrosis with adjacent septal and lateral borders of preserved subendocardial tissue. These regions contribute to slow conduction and non-uniform anisotropy underlying reentrant VT.
3. Reproducible and sustained monomorphic reentrant VT can be induced in all swine that develop this arrhythmogenic substrate after the post-infarct healing phase. Only in rare cases can VT not be induced, which is most likely a reflection of a more favorable ventricular remodeling process.
4. Activation mapping during the VT is highly suggestive of a subendocardial VT circuit consistent with the aforementioned subendocardial substrate.

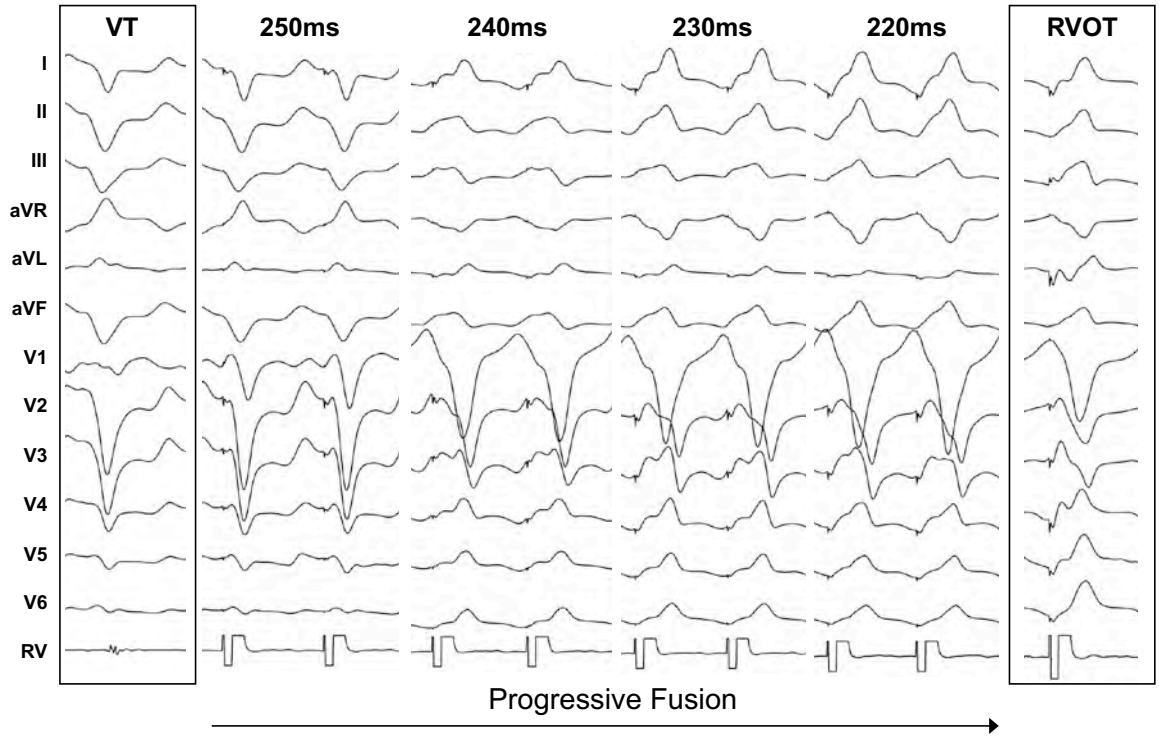

Figure 5.3: Overdrive Pacing During VT from RV Demonstrates Progressive Fusion

Adapted with permission: Tschabrunn CM, et al. Heart Rhythm. 2016 Jan;13(1):262-73.

Study Limitations

Although these findings demonstrate similar LV remodeling and arrhythmia mechanisms to humans, these studies were performed six to eight weeks after infarction and may differ from humans with healed MI beyond this time period. The process of LV remodeling in humans and probably in swine continues far beyond this time point. Nonetheless, no significant differences were found in the anatomical or electrophysiological substrate between animals that were evaluated at the six-week time point and the eight-week time point.

As the layer of surviving myocardial fibers in swine is in the subendocardium, signals were

only recorded from the endocardium. Continuous electrical activity was recorded that was consistent with a subendocardial reentrant circuit; however, e a midmyocardial or epicardial component of the circuit cannot be excluded. This requires simultaneous epicardial mapping or mapping using needle plunges. In addition, data on connexin-43 were not quantified, but limited analyses confirm the findings of previous, more detailed, investigations in this field.

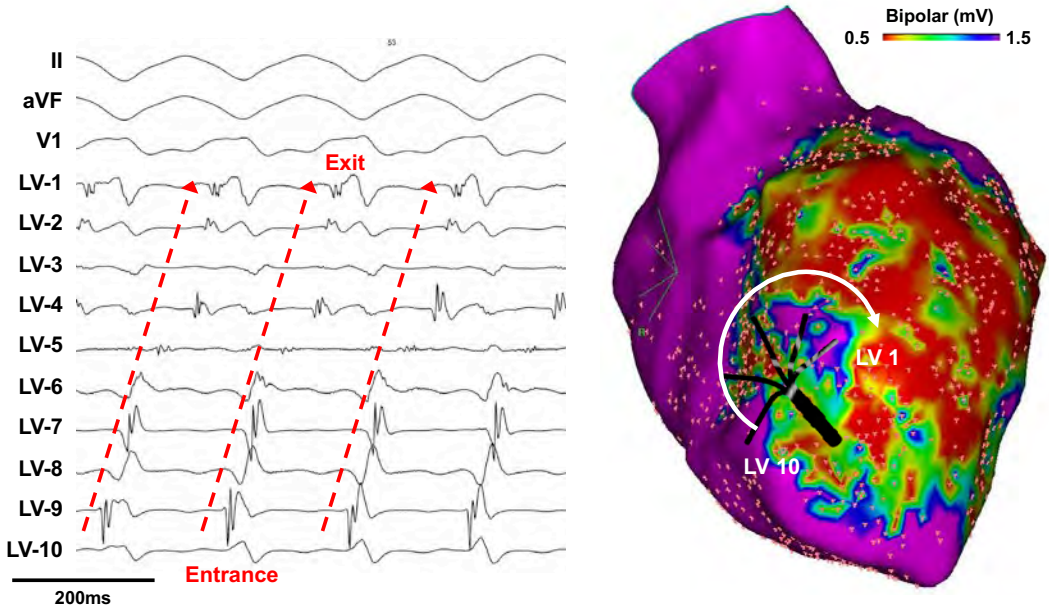

Figure 5.4: Multielectrode Recordings from LV Endocardium During VT Demonstrates Reentrant Excitation

Adapted with permission: Tschabrunn CM, et al. Heart Rhythm. 2016 Jan;13(1):262-73.

Arrhythmogenic Substrate and Reentrant Mechanism Characterization

Arrhythmias occurring in hearts with healing and healed infarcts are, to a large extent, the result of reentrant excitation; however, delayed afterdepolarization–dependent triggered activity is another possible mechanism of arrhythmia that is documented in both human and experimental models of infarction.[71] Sustained monomorphic VT was induced in all animals using programmed stimulation. The pattern of resetting response of the tachycardia to premature stimuli showed a mixed curve with a fairly short flat curve during long premature intervals and a longer increasing curve as the coupling interval was further decreased; this observation is consistent with a reentrant circuit. This observation suggests that the presence of a relatively small fully excitable gap, as reflected by a narrow window of the flat response curve (20–60ms), and a predominant partial excitable gap, as reflected by the increasing cycle length after the premature impulse (increasing curve). Overdrive pacing from the RV demonstrated entrainment with progressive fusion (Figure 5.3). In addition, activation mapping showed reentrant excitation with continuous diastolic electrical activity (Figure 5.4). These

collective responses to stimulation during VT suggests that the sustained ventricular arrhythmias induced in this model were predominantly reentrant.

Substrate assessment using CMR imaging (Figure 5.5), EAM, and histopathology in these swine showed a large infarct region with transmural anterior components and septal and lateral border zones with subendocardial and subepicardial preserved tissue. However, the subendocardial component was more heterogeneous with fibrosis and surviving fibers than the sub-epicardial layer. The geometrical arrangement of the surviving subendocardial myocardial bundles showed a greater extent of fiber disarray with loss of parallel orientation and redistribution of connexin-43 gap junctions in sampled regions, resulting in a greater degree of non-uniform anisotropy. Non-uniform anisotropic conduction was evident across the infarct region and marked by fractionated, split, and isolated late potentials during sinus rhythm. This is consistent with our subendocardial characterization of VT circuits and is demonstrated by continuous diastolic electrical activity during LV endocardial activation mapping.

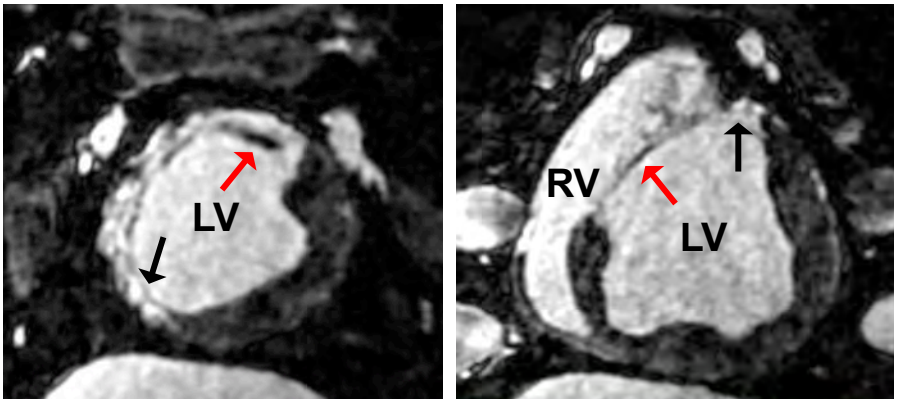

Figure 5.5: Post-Infarct Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging with late gadolinium enhancement (LGE) demonstrates variable LGE signal intensities were within the scar area including regions of dark signal representative of survived myocardial tissue (red arrows). These regions of viable tissue were predominantly preserved to the subendocardial rather than subepicardial tissue. Regions of confluent LGE signal intensity indicative of transmural scar were also observed (black arrows). Adapted with permission: Tschabrunn CM, et al. Heart Rhythm. 2016 Jan;13(1):262-73.

Comparison to Conventional Experimental Models

A number of animal models have been developed to study the arrhythmogenic substrate and mechanisms that are associated with post-infarct VT. These assorted species and methodologies have translated into variable results, including infarct size, location, and the extent of surviving myocardial fibers. The anatomical features that develop following infarct

healing are critical for determining whether arrhythmias occur and defining their inherent characteristics when they do occur. Arrhythmias may not manifest without the presence of surviving myocardial fibers in the infarcted region, and their spatial arrangement is important for developing the electrophysiologic milieu that can support reentry. For example, canine coronary occlusion has been used for decades as a model to investigate scar and ventricular arrhythmias. Surviving myocardial fibers are located on the epicardial and endocardial surface, with reentrant VT circuits more frequently involving the epicardial surface in the canine MI model. As such, reentrant VT circuits often involve the epicardial surface in the canine MI model.[72] In contrast, swine have a predominant endocardial/midmyocardial system and absent epicardial collateral system that is more favorable for a subendocardial reentrant VT model.

The mid-LAD ischemia reperfusion technique that was used in this study was adapted and based on the extensive experience reported by Sasano et al., who characterized the swine LV remodeling process with serial transthoracic echocardiograms (TEEs) and also performed programmed extra stimulation each week to evaluate the VT induction rate.[73] The authors reported a 100% monomorphic VT induction rate following 150-minute balloon occlusion after a four-week survival period. LV mapping with a 64-pole basket noncontact system showed the earliest activation at the subendocardial septal infarct border in the majority of VTs. Detailed endocardial and epicardial mapping was performed in six animals, but detailed voltage and VT circuit characteristics are not described, as this was not the primary objective of the authors. Histology from the septal “border zone” of this region demonstrated surviving strands of the myocardium surrounded by fibrotic tissue.

Ashikaga et al. performed a similar technique of 150-minute LAD balloon occlusion with a 10 to 12 week survival period, followed by CMR imaging and either endocardial (n=5) or epicardial (n=6) VT mapping.[74] The authors also reported a complex CMR substrate with preserved surviving tissue with a corresponding subendocardial and subepicardial substrate. The authors hypothesized that the majority of mapped VTs were subendocardial in nature, but did not perform endocardial mapping in swine that underwent epicardial mapping. This study also did not report bipolar voltage mapping or histopathologic correlates to CMR data. Tung et al. performed obtuse–marginal balloon occlusion for 90 minutes in swine and evaluated the distribution of fibrosis after a 12-week survival period with complete LV endocardial and epicardial voltage mapping, ex vivo CMR imaging, and histopathologic correlates.[75] While endocardial and epicardial abnormalities were present, VT induction was not performed. Our study also utilized an ischemia-reperfusion model in a large series of 35 swine. Unlike previous studies, we performed LAD balloon occlusion for 180 minutes, followed by a six to eight week

survival period including systematic assessment with CMR imaging, detailed electrophysiology study with high-resolution EAM, and histopathologic analysis. This multimodality characterization allowed the evaluation and confirmed the distribution, quality, and relevance of scarring in this preclinical setting. Reentrant monomorphic VT was reproducibly induced in 90% of animals.

Comparison to Human Physiology

The majority of sustained VTs in humans with healed MI originate in the subendocardial region, particularly in hearts with anteroseptal infarcts and ventricular aneurysms. The endocardial border zones of these infarcts contain bundles of ventricular muscle as well as Purkinje fibers. The surviving muscle bundles provide the necessary substrate for the formation of reentrant circuits due to the physical and electrical ventricular remodeling that occurs after an MI. The consequential non-uniform anisotropy properties create the necessary slow conduction that is required for reentry. Our swine model of healed infarct resembles the human pathophysiology with subendocardial arrhythmia origin and characteristics of non-uniform anisotropic conduction, as suggested by fractionated EGMs. In addition, swine frequently developed anteroseptal aneurysm after an MI, which is a known and common phenomenon that also occurs in humans.

5.3 High Resolution Mapping of Ventricular Scar

Tschabrunn CM, Roujol S, Dorman NC, Nezafat R, Josephson ME, Anter E. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

Three-dimensional (3D) electroanatomic mapping systems have been developed to assist with mapping and ablation of cardiac arrhythmias. These systems have become an essential tool for mapping scar-related VT and they are frequently used to evaluate the underlying substrate of scar-related VTs. However, evaluation of the substrate using standard mapping techniques is mystified by assumptions and misconceptions. Specifically, bipolar voltage is a measure of conduction time between two electrodes rather than a measure of the underlying tissue (healthy vs. scar). It is influenced by multiple variables including electrode size, interelectrode spacing, angle of incidence (catheter orientation relative to the surface), the vector of wave propagation, and filtering. Their combined effect is associated with significant variations in the recorded bipolar voltage amplitude at any single recording point. Bipolar voltage that is recorded with standard catheters can differentiate dense scar (<0.1mV) from healthy myocardium (1.55mV). However, they have insufficient sensitivity to characterize the architecture of complex and heterogeneous scar tissue.

As discussed in Chapter 4, multielectrode-mapping catheters have smaller electrodes and closer interelectrode spacing (Figure 5.6). This results in increased mapping resolution, as each data point represents the electrical activity of a smaller tissue size. This may allow for the identification surviving myocardial bundle "channels" within an area of heterogeneous scar tissue. The aims of this study were to: 1) define normal voltage amplitude and electrogram duration in the ventricle for 1mm multielectrode-mapping catheters (Pentaray®); 2) compare its mapping resolution in a scar to a standard 3.5mm electrode tip catheter (Thermocool®); and 3) evaluate its utility for mapping post-infarction reentrant VTs in a swine model.

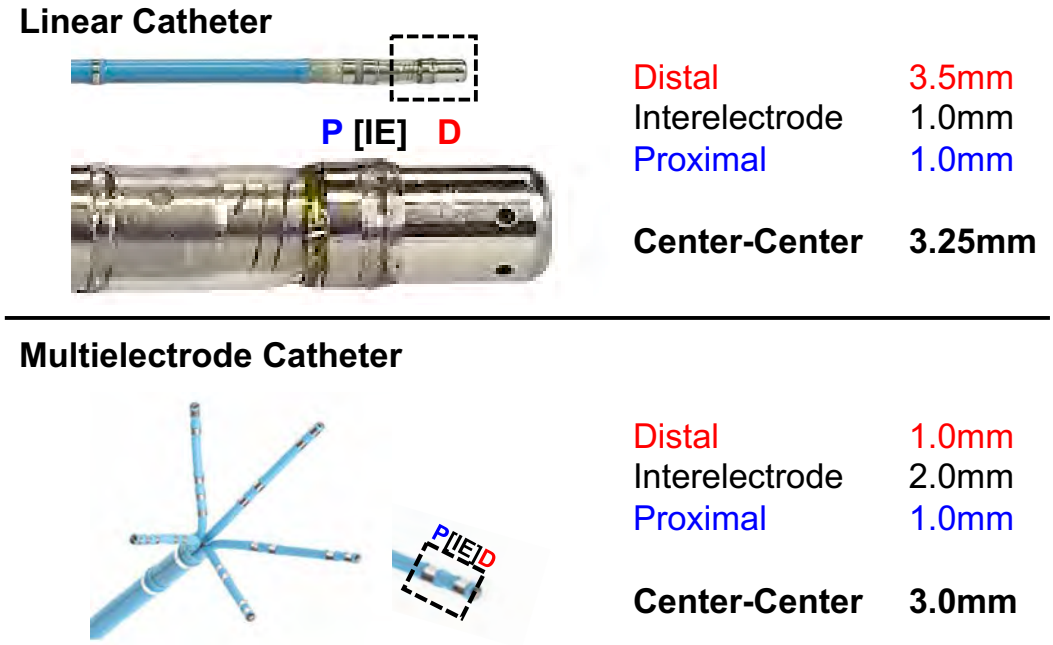

Figure 5.6: Design Comparison of Linear and Multielectrode Catheters. Adapted with permission: Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

Major Findings

1. Bipolar voltage amplitude in the healthy ventricle is similar between linear and multielectrode catheters with a 5th percentile of ~1.5mV.
2. Mapping resolution within areas of a low voltage and scar is enhanced with multielectrode catheters, identifying areas of preserved myocardial bundles ("channels") that are otherwise considered dense scar by standard linear catheters (Figure 5.7).
3. The increased mapping resolution of multielectrode catheters is primarily confined to tissue layers that are adjacent to the recording electrodes (endocardium and subendocardium).

4. Multielectrode catheters are advantageous for mapping scar-related reentrant VT, as their small and closely-spaced electrodes permit identification of distinct diastolic activity (including diastolic pathways) that may not be seen with standard linear catheters.
5. Multielectrode catheters allow pacing with the capture of low voltage tissue at a lower output than linear catheters.

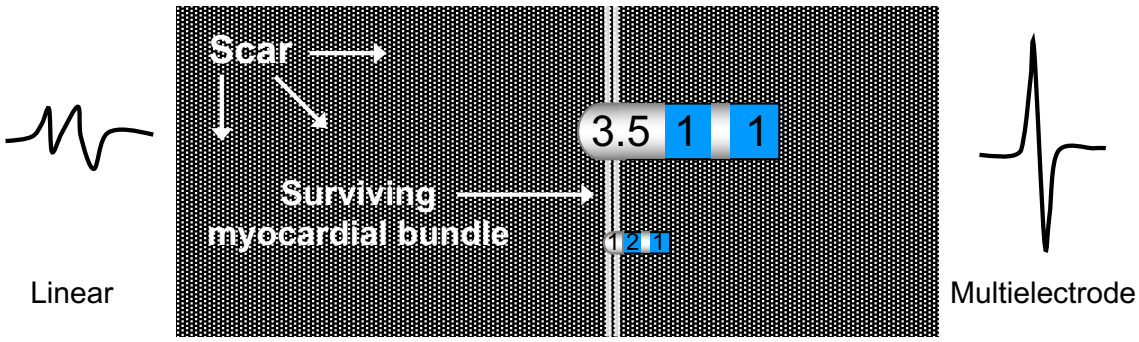

Figure 5.7: Schematic of Survived Myocardial Tissue Detection with Linear and Multielectrode Catheters. Adapted with permission: Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

Correlation Between Mapping, CMR Imaging, and Histopathology

All of the 11 swine with healed anterior myocardial infarction showed a large area of LGE at the anterior septum, which is consistent with anterior wall infarction. The distribution of the scar was complex with areas of transmural infarction along with areas of near transmural infarction, with either subendocardial or subepicardial (right ventricular) myocardial tissue preservation. The scar volume that was measured with CMR was significantly smaller than the corresponding EAM zone of bipolar voltage amplitude <1.5mV, as measured with both the linear and multielectrode catheters. In 4 out of 11 swine (37%), voltage maps that were made with linear and multielectrode catheters were similar. In these cases, the mean bipolar voltage amplitude within the low voltage area was similar between maps made with linear and multielectrode catheters. The seven swine that showed significant differences between maps made with linear and multielectrode mapping catheters were all characterized by a nearly transmural scar, with evidence of subendocardial myocardial tissue preservation.

In contrast, the four swine with similar voltage maps, made with linear and multielectrode mapping catheters, showed either a transmural scar or a scar that was limited to the subepicardium. In these cases, the tissue in proximity to the recording catheter was homogeneous, with either healthy or scarred myocardium. These data supports the

hypothesis that small multielectrode mapping catheters have increased resolution to detect heterogeneity within low voltage tissue that is in close proximity to the recording electrodes (i.e., surviving subendocardial bundles in a post infarction scar).

Histological analysis was consistent with the CMR analysis, showing complex scar architecture at the anterior-septum, with areas of transmural infarction along with areas of near transmural infarction, and with either subendocardial or subepicardial myocardial tissue preservation. Consistent with the CMR data, in the 7 out of 11 swine that showed significant differences between maps that were made with linear and multielectrode catheters, a thin layer of surviving myocardium bundles was identified in the subendocardium. In the four swine with similar maps between the catheters, the tissue layers in proximity to the recording catheter (endocardium) were homogeneous, showing either a thick layer of myocardium or collagen.

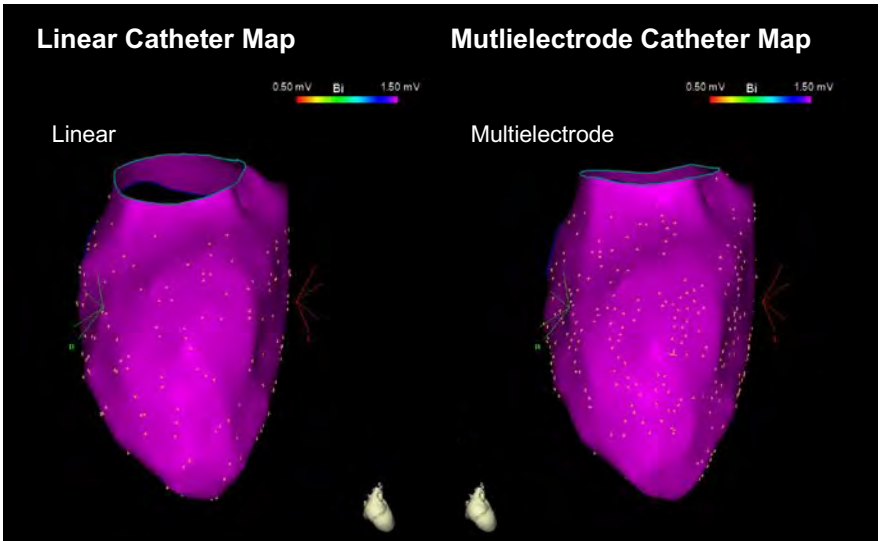

Figure 5.8: Linear and Multielectrode Catheter Left Ventricle Bipolar Voltage Maps

Left ventricle bipolar voltage maps (0.50-1.50mV) acquired with both the linear and multielectrode catheters in normal swine. Adapted with permission: Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

Study Limitations

This preclinical study was performed in swine and it utilized an established, human-like model of chronic anterior myocardial infarction. While bipolar voltage amplitude in healthy and scar tissue are similar between swine and human, this has not been validated for 1mm electrode catheters. However, limited experience in human with post-infarction VT is consistent with the findings of this study, showing improved mapping resolution with the ability to identify surviving

myocardial bundles with multielectrode catheters. The increased resolution of multielectrode mapping catheters appears to be confined to the tissue layers that are adjacent to the recording catheter (endocardium and subendocardium). Though this may be beneficial for patients with healed myocardium infarction and subendocardial scar, its potential in other substrates, in particular patients with non-ischemic cardiomyopathy with midmyocardial and sub-epicardial scarring, is not clear. Lastly, the differences in unipolar voltage amplitude were not compared. While this may be an interesting measure, smaller electrodes have a smaller field of view and may therefore be less sensitive to measure the effects of remote tissue layers.

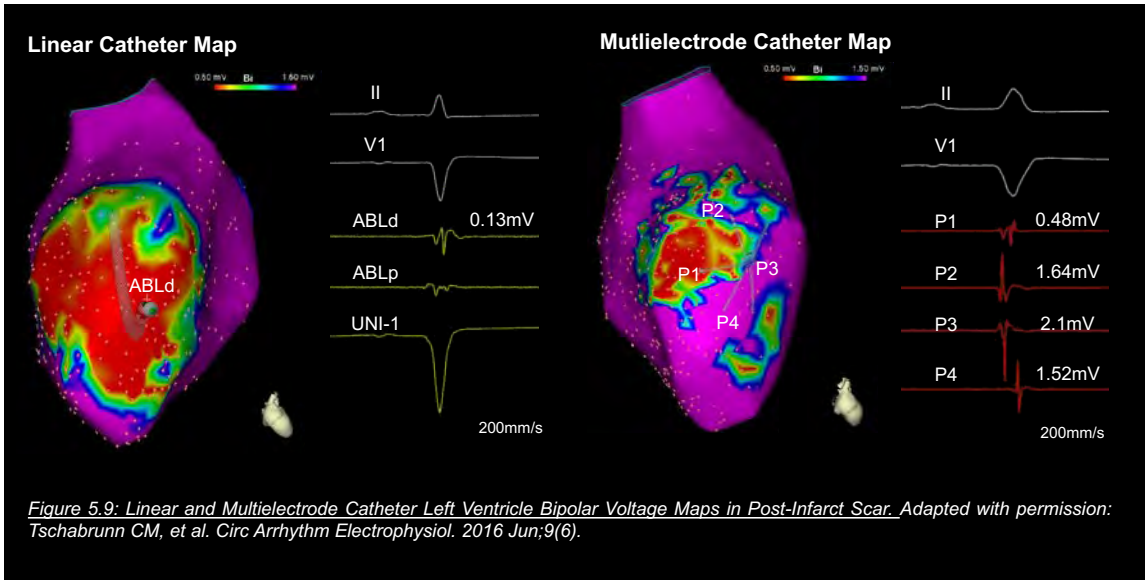

Figure 5.9: Linear and Multielectrode Catheter Left Ventricle Bipolar Voltage Maps in Post-Infarct Scar. Adapted with permission: Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

Clinical Implications

This study established the voltage distribution and electrogram characteristics of multielectrode mapping catheters (Pentaray®) in the ventricle of normal and post-infarction swine. In addition, it compared the mapping resolution between standard linear (Thermocool®) and multielectrode (Pentaray®) catheters within scar tissue during sinus rhythm and VT, using EAM, CMR, and histology.

While multielectrode catheters increased mapping resolution, this had little value in normal healthy myocardium as bipolar voltage variation between 1.5 and 5mV represent normal myocardium (Figure 5.8). In contrast, such voltage variations in the infarct and peri-infarct zone determined the feasibility of identifying subendocardial surviving myocardial bundles that formed conduction channels during sinus rhythm and during VT (isthmuses). We found that the improved mapping resolution of multielectrode catheter was most significant in areas of heterogeneous scar distribution and in a close proximity recording catheter. In these areas, the small and closely-spaced multielectrodes are subject to fewer tissue averaging effects,

allowing the detection of surviving myocardial bundles within an area of heterogeneous scar (Figure 5.9).

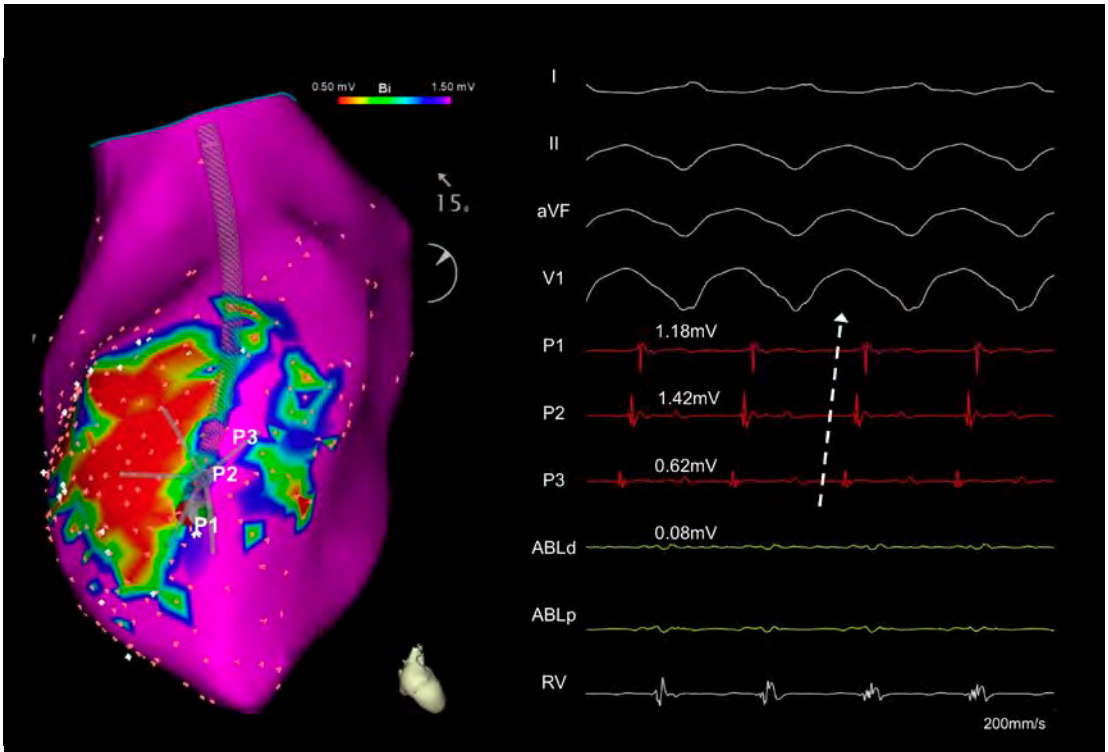

Figure 5.10: Ventricular Activation Mapping with Linear and Multielectrode Catheters

During reentrant monomorphic ventricular tachycardia, the linear catheter recorded low, far-field, signals with amplitude of 0.08 mV. The multielectrode catheter recorded sharp, near-field, signals with bipolar amplitude range of 0.62–1.42 mV that allowed superior annotation of local activation. Adapted with permission: Tschabrunn CM, et al. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

In eight of the ten induced VTs, the arrhythmia was stable enough to allow positioning of the multielectrode mapping catheter at “channels” of increased voltage amplitude, as detected by the multielectrode mapping catheter but not by the linear catheter. In all cases, the recording electrograms were triphasic and narrow, which is consistent with electrograms that are recorded during sinus rhythm. In addition, these electrograms occurred during diastole and showed a pattern of sequential activation that is consistent with propagation through the channel (Figure 5.10). In two hemodynamically tolerated VTs, entrainment from a channel detected with the multielectrode catheter but not with the linear catheter demonstrated an isthmus site. Ablation at this site resulted in rapid termination of the VT (Figure 5.11). Importantly, when the linear catheter was placed at these channels with diastolic activity, as recorded with the multielectrode catheter, low voltage, fractionated electrograms were

recorded. In addition, consistent with our findings in the human atria, pacing output threshold within low voltage areas is lower with multielectrode catheters due to increased electrical "current" density at the electrode-tissue interface. This may be advantageous for pace and/or entrainment mapping.

Berte and colleagues performed LV mapping with the 3.5mm electrode catheter (Navistar^{TM}) and multielectrode-mapping catheter (Pentary^{TM}) in both post-infarction sheep and patients with scar-related VT.[76] They also reported increased mapping density and higher prevalence of late abnormal ventricular activation (LAVA) using multielectrode mapping catheters. However, they reported increased bipolar low voltage areas with multielectrode catheters compared to linear 3.5mm electrode catheters. This difference may be related to inadequate tissue contact when mapping with multielectrode catheters. Furthermore, they did not compare the low voltage area with CMR and/or histopathology, precluding objective assessment of the true scar.

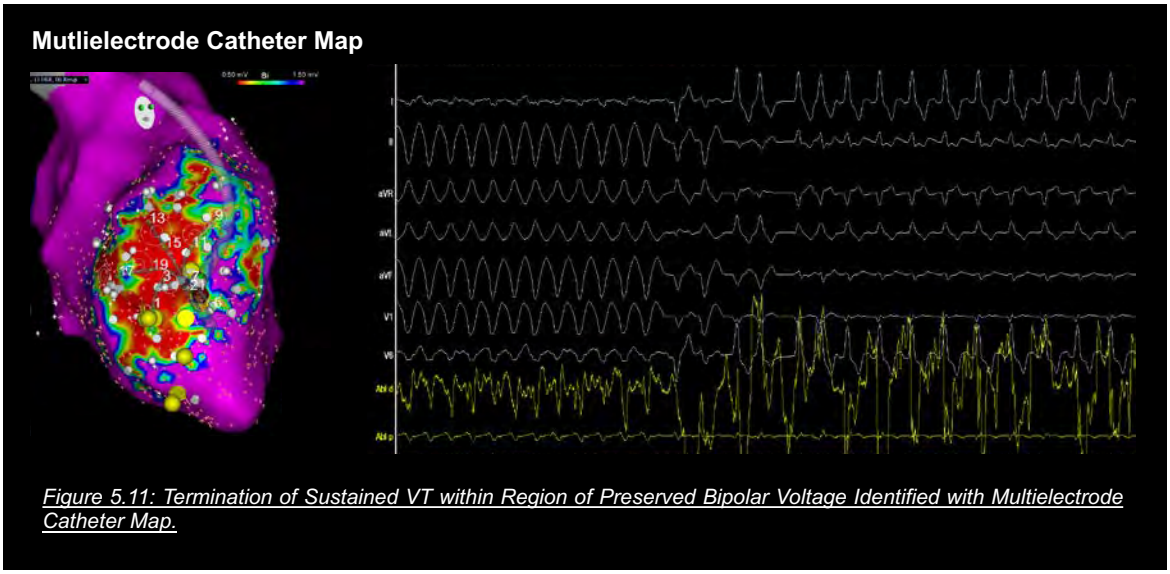

Figure 5.11: Termination of Sustained VT within Region of Preserved Bipolar Voltage Identified with Multielectrode Catheter Map.

5.4 Initial Insight from High Resolution Activation Mapping of Reentrant VT

Mapping reentrant VTs is a clinical challenge that is difficult to achieve. Activation and/or entrainment mapping can localize the circuit including its protected isthmus. However, this is often time-consuming and is limited to hemodynamically tolerated arrhythmias. As a result, ablation strategies are often limited to substrate mapping (low voltage, abnormal electrograms, and pace-mapping). One limitation of substrate-based mapping stems from the fact that lines of block, including the protected isthmus, may be partially functional with a relative paucity of abnormal electrograms during sinus rhythm. As such, activation mapping

of VT remains a desired strategy as it can identify isthmuses that are formed by fixed or functional lines of conduction block.

There has been increasing interest in developing technologies that allow detailed and rapid activation mapping of arrhythmias. This includes catheters with small and closely spaced multi-electrodes, accurate time annotation of multicomponent electrograms, and software allowing automated and rapid EGM acquisition. Activation mapping of monomorphic VT was performed in a prospective study that included 15 swine with chronic anterior wall infarction using the Rhythmia^{TM} high-resolution mapping system to: 1) examine the feasibility of mapping post-infarction reentrant VTs, 2) examine the electrophysiological properties of the isthmus, and 3) correlate the relationship between isthmus' determined by activation and entrainment mapping. Activation mapping of all hemodynamically tolerated monomorphic VTs was attempted. Activation was determined based on the combination of the bipolar and unipolar electrograms and timed at the maximal (-)dV/dt of the local unipolar electrogram. Specifically, at sites with multiple and/or fractionated bipolar potentials, the activation time was determined by the maximal (–)dV/dt of the corresponding unipolar electrograms. Data acquisition during VT were automatic using the following EGM acceptance criteria: 1) 12-lead electrocardiogram morphology match, 2) TCL stability (±5ms), 3) time stability of a reference electrogram positioned at the RVA, 4) beat-to-beat electrocardiogram consistency (≥3 beat with similar electrogram morphology and timing), and 5) respiratory stability that allows data acquisitions at a constant respiratory phase.

Mapping of a macroreentrant VT was considered complete when: 1) ≥ 90% of the TCL was mapped; 2) a channel of conduction “isthmus” was identified; and 3) mapping density at zones of slow conduction was adequate, limiting point interpolation between points to ≤3mm. The mechanism of the tachycardia was defined as macroreentry or focal (or microreentry) on the basis of the activation map. Macroreentrant circuits had a well-defined entrance site (inward curvature), common pathway (isthmus), and separate exit site (outward curvature). The entrance was defined as the site at which the orthodromic wavefront enters the common pathway (inward curvature), while the exit was defined as the site at which the orthodromic wavefront exits the common pathway (outward curvature). Focal tachycardia had a point source with centrifugal activation from this center. Fractionated signals during VT were defined as those with ≥5 deflections crossing the isoelectric baseline. Split potentials were defined as those with ≥2 separate deflections that are separated by an isoelectric interval ≥30ms. Split potentials could have occurred during the QRS or after the QRS (i.e., late potentials).

Following completion of the activation map, overdrive pacing was performed at selected sites of macroreentrant circuits, as determined by activation mapping. These sites included some or all of the following: 1) inward curvature “entrance”, 2) isthmus “common channel”, 3) outward curvature “exit”, and 4) remote RV and LV sites. The number of pacing sites during VT was dependent on the hemodynamic tolerance of the arrhythmia. Pacing was performed from the mini-basket electrodes at a cycle length 10-25ms faster than the TCL. A pacing site demonstrating concealed fusion, PPI-TCL ≤ 30ms, and S-QRS ≤70% TCL was considered within the reentrant circuit.

Dimensions of the isthmus (common channel) were calculated separately from the activation and entrainment maps. From the activation map, the length of the isthmus was measured as the shortest distance between the proximal curvature “entrance” to the distal curvature “exit” of the common channel, while its width was measured from one apparent non-conductive lateral barrier to the opposing parallel non-conductive barrier. Dimensions of the common channel using entrainment were based on the zone that includes sites with concealed QRS fusion, PPI-TCL≤ 30ms, and S-QRS of 0-70% of the TCL. Assessment of conduction velocity in the reentrant circuit was calculated using the “single vector method” from the high-density endocardial mapping. In brief, recording sites were selected on a line that was longitudinal and perpendicular to the isochronal lines. The longitudinal and transverse conduction velocities were calculated from the difference in timing and the known distance between the recording points. Conduction velocity was then calculated for the mean vector of propagation.

Major Findings

1. This study demonstrates the feasibility to map reentrant VTs using Rhythmia^{TM} high-resolution mapping technology. It allows detailed activation mapping of the reentrant circuit, including its protected isthmus.
2. The zone(s) of slow conduction within the reentrant circuit are the inward (entrance) and outward (exit) curvatures, while conduction velocity in the common channel is nearly normal.
3. The common channel is protected by laterally opposing lines of functional block. These allow a transverse conduction that is sufficiently slow to protect the common channel, allowing parallel propagation of the orthodromic wavefront.
4. Conduction velocities within the reentrant circuit are dynamic and are influenced by the vector of wavefront propagation, such that the zone of slow conduction is not geometrically fixed, but influenced by properties of anisotropic conduction.
5. Entrainment mapping overestimates the dimensions of the isthmus. Specifically, exit sites based on entrainment criteria may be well past the true exit as determined by activation.

Study Limitations

This study was performed in swine and it utilized an established human-like model of subendocardial infarction and VT. However, it requires further validation in humans, particularly in patients with non-anterior wall infarction. Nonetheless, our initial clinical experience thus far has been consistent with these findings, particularly in patients with chronic anterior wall infarction. Conduction velocities were calculated using the "single vector" method with the assumption that the tissue is homogeneously anisotropic and two-dimensional (full thickness activation times were not measured). While this may skew the velocity measurements, since the VT substrate in this model is subendocardial, the two-dimensional endocardial results may still allow good representation of the overall conduction velocities within the tissue. Accurate velocity measurements will require mapping with full thickness plunge electrodes.

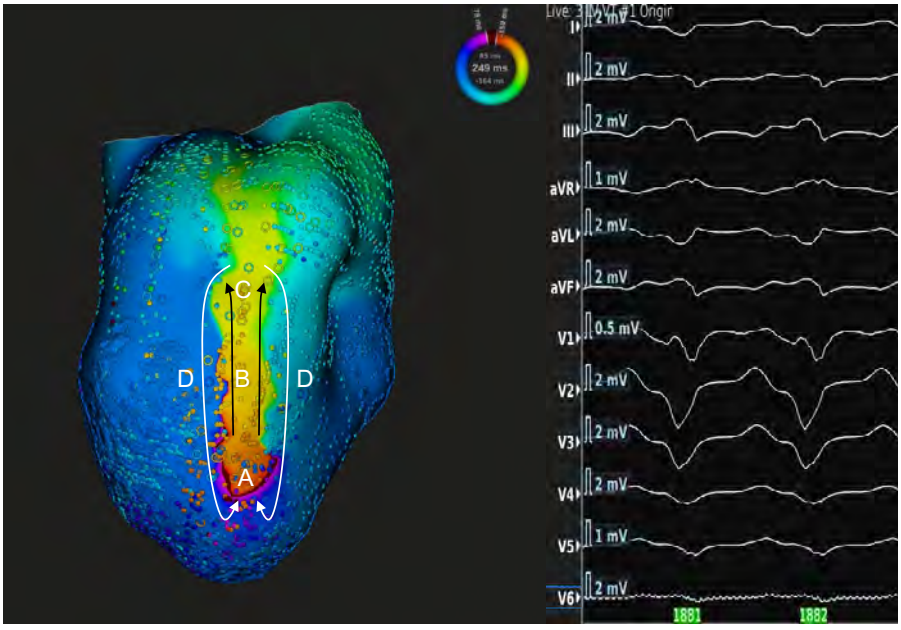

Figure 5.12: High Resolution Activation Map of Reentrant Ventricular Tachycardia

Entire reentrant circuit defined with high resolution activation map acquired in less than 9 minutes with a total of 8430 annotated mapping electrograms. A: Entrance; B: Mid Isthmus; C: Exit; D: Remote.

Clinical Implications

Activation maps of post-infarction reentrant VTs demonstrated distinct electrophysiological elements of reentry, including: 1) entrance of the orthodromic wavefront into a protected channel; 2) protected channel "isthmus" bounded by two laterally opposing line (functional) blocks, allowing orthogonal conduction of the orthodromic wavefront in the isthmus; 3) exit of the orthodromic wavefront into the remainder of the ventricle; 4) outer loops(s) consisting of a wavefront propagating along the outer margin of the isthmus; 5) remote ventricular sites that are not part of the reentrant circuit.

In this model of chronic anterior wall infarction, the predominant circuit configuration was a double loop (figure-of-eight) reentry, as originally described by El Sherif.[77] The axis of the isthmus was uniformly parallel to the long axis of the ventricle and bounded by two parallel lines of block (Figure 5.12). This observation is consistent with post-infarction VT in the canine model. Wit and colleagues mapped the epicardium of subacute canine LAD infarcts, using an array of 192 bipolar electrodes during sustained VT.[78] They found that lines of block during tachycardia were similarly oriented parallel to the long axis of the LV, from base to apex. This appears to be consistent with the human phenotype of patients with LAD infarction mapped with high-resolution mapping technologies (unpublished data). However, this may not be the case for all infarct-related VT, particularly in patients with chronic infarction and ventricular aneurysms.

Furthermore, standard entrainment criteria overestimate the true size of the isthmus, particularly at its exit site, such that concealed QRS fusion combined with PPI-TCL ≤ 30ms can occur beyond the distal curvature. We termed these sites “pseudo-exit” sites to distinguish them from true exit sites at the distal curvature. Pacing at pseudo-exit sites resulted in concealed QRS fusion, which was likely due to similar orthodromic activation wavefront with concealed antidromic fusion. This may be particularly true in double loop reentry, as pacing distal to an exit site results in a point source activation pattern with propagation in multiple directions. However, in contrast to true exit sites, pacing from pseudo-exit sites resulted in a longer PPI. The authors speculate that this may be due to increased curvature gradient (resistance) and activation of partially depolarized tissue, resulting in slower conduction velocity. However, this requires additional investigation into resetting curves at different zones of the circuits. Nonetheless, from a clinical standpoint, this may explain why ablation at exit sites determined by entrainment can fail to terminate the VT and often results in a change of the tachycardia or the inducibility of multiple similar morphologies with minor variations in the exit site. High resolution activation mapping may better guide ablation therapy for this reason.

5.5 Conclusions

Catheter ablation of scar-related ventricular tachycardia (VT) has evolved in recent years. However, clinical outcomes remain suboptimal. A major limitation is an insufficient understanding of scar-related reentrant VT circuit physiology. These studies utilized high-resolution mapping technology to study post-infarction scars and the electrophysiological properties of post-infarction reentrant VT. Consistent with initial and early clinical experiences, multielectrode catheter mapping using smaller electrodes with closer interelectrode space improves mapping resolution in areas of scarring. Regions of “normal” bipolar voltage that

were identified with high resolution catheters are consistent with preserved subendocardial tissue on CMR and histopathology. High-resolution activation mapping of reentrant VT circuits is of particular interest, and initial unpublished investigations may increase the current understanding of circuit physiology and allow better correlation between circuit and substrate.

Chapter 6

Conclusions

Adverse structural and electrical remodeling following myocardial infarction or during variable processes of different non-ischemic cardiomyopathies can promote the manifestation of reentrant monomorphic ventricular tachycardia. Intracardiac mapping can be used to detect and characterize regions of abnormal ventricular substrate critical to the reentrant VT circuit. The work that is discussed in this thesis demonstrates the clinical utility, while recognizing the limitations, of electroanatomic mapping to identify and target these regions of interest in patients with scar-related VT in the setting of variable disease substrates.

While the manifestation of fibrosis remains an inherent part of the adverse remodeling process, there are multiple other factors that also contribute to the development of reentrant VT. In fact, bipolar voltage amplitude alone is the least specific variable to consider, as it is influenced by many factors as discussed in Chapter 4 and Chapter 5. For this reason, voltage alone should not be a primary measure to define barrier formation or slow conduction. A characterization of the electrophysiologic features of tissue regions that are “destined” to form barriers is needed. The studies that are discussed in this thesis and the development of variable mapping technologies demonstrate a broader critical misconception in the field of cardiac electrophysiology: clinicians and investigators often discount the fundamental difference between fibrosis/scar and voltage amplitude. These concepts should not be used interchangeably and voltage amplitude is not a direct measure of myocardial tissue fibrosis quantification. While voltage mapping can provide some idea of the presence of scars that are adjacent to the tissue layer mapped with contact, the “gold standard” continues to be histopathologic analysis.

Understanding of the underlying substrate can be enhanced using small electrode catheters with closer interelectrode distance, a standard wave of activation such as during right ventricular pacing, and with adequate tissue contact force. It is hoped that careful study designs using new, higher-resolution mapping systems, will better identify areas that might form conduction barriers. Moreover, these technologies may also allow rapid mapping VTs to better correlate substrate and function and ultimately improve outcomes.

References

1. Pedersen CT, Kay GN, Kalman J, Borggrefe M, Della-Bella P, Dickfeld T, Dorian P, Huikuri H, Kim Y-H, Knight B, Marchlinski F, Ross D, Sacher F, Sapp J, Shivkumar K, Soejima K, Tada H, Alexander ME, Triedman JK, Yamada T, Kirchhof P, Lip GYH, Kuck KH, Mont L, Haines D, Indik J, Dimarco J, Exner D, Iesaka Y, Savelieva I. EHRA/HRS/APHRS expert consensus on ventricular arrhythmias. *Heart Rhythm*. 2014;11:e166–96.
2. Hsia HH, Callans DJ, Marchlinski FE. Characterization of endocardial electrophysiological substrate in patients with nonischemic cardiomyopathy and monomorphic ventricular tachycardia. *Circulation*. 2003;108:704–710.
3. Cano O, Hutchinson M, Lin D, Garcia F, Zado E, Bala R, Riley M, Cooper J, Dixit S, Gerstenfeld E, Callans D, Marchlinski FE. Electroanatomic substrate and ablation outcome for suspected epicardial ventricular tachycardia in left ventricular nonischemic cardiomyopathy. *J Am Coll Cardiol*. 2009;54:799–808.
4. Josephson ME. Recurrent Ventricular Tachycardia. In: Clinical Cardiac Electrphysiology: Techniques and Interpretations. Lippincott Williams & Wilkins; 2008. p. 446–642.
5. Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Siscovick D, Stevenson WG, Zipes DP, American Heart A, American College of Cardiology F, Heart Rhythm S. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the America. *Circulation*. 2008;118:1497–1518.
6. Russo AM, Stainback RF, Bailey SR, Epstein AE, Heidenreich PA, Jessup M, Kapa S, Kremers MS, Lindsay BD, Stevenson LW. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation appropriate use criteria task force, Heart Rhyt. *Heart Rhythm*. 2013;10:e11–58.
7. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. *N Engl J Med*. 1997;337:1576–1583.
8. Kuck KH, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest : the Cardiac Arrest Study Hamburg (CASH). *Circulation*. 2000;102:748–54.
9. Bokhari F, Newman D, Greene M, Korley V, Mangat I, Dorian P. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). *Circulation*. 2004;110:112–6.
10. Pacifico A, Hohnloser SH, Williams JH, Tao B, Saksena S, Henry PD, Prystowsky EN. Prevention of implantable-defibrillator shocks by treatment with sotalol. d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. *N Engl J Med*. 1999;340:1855–62.
11. Connolly SJ, Dorian P, Roberts RS, Gent M, Bailin S, Fain ES, Thorpe K, Champagne J, Talajic M, Coutu B, Gronefeld GC, Hohnloser SH. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC Study: a randomized trial. *JAMA*. 2006;295:165–71.
12. Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, Kralovec S, Sediva L, Ruskin JN, Josephson ME. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med*. 2007;357:2657–2665.
13. Stevenson WG, Wilber DJ, Natale A, Jackman WM, Marchlinski FE, Talbert T, Gonzalez MD, Worley SJ, Daoud EG, Hwang C, Schuger C, Bump TE, Jazayeri M,

Tomassoni GF, Kopelman HA, Soejima K, Nakagawa H, Multicenter Thermocool VTATI. Irrigated radiofrequency catheter ablation guided by electroanatomic mapping for recurrent ventricular tachycardia after myocardial infarction: the multicenter thermocool ventricular tachycardia ablation trial. *Circulation*. 2008;118:2773–2782.

14. Tung R, Vaseghi M, Frankel DS, Vergara P, Di Biase L, Nagashima K, Yu R, Vangala S, Tseng C-H, Choi E-K, Khurshid S, Patel M, Mathuria N, Nakahara S, Tzou WS, Sauer WH, Vakil K, Tedrow U, Burkhardt JD, Tholakanahalli VN, Saliaris A, Dickfeld T, Weiss JP, Bunch TJ, Reddy M, Kanmanthareddy A, Callans DJ, Lakkireddy D, Natale A, Marchlinski F, Stevenson WG, Della Bella P, Shivkumar K. Freedom from recurrent ventricular tachycardia after catheter ablation is associated with improved survival in patients with structural heart disease: An International VT Ablation Center Collaborative Group study. *Heart Rhythm*. 2015;12:1997–2007.
15. Wit AL, Allessie JJ, Fenoglio Jr. JJ, Bonke FIM, Lammers WJE., Smeets J. Significance of the endocardial and epicardial border zones in the genesis of myocardial infarction arrhythmias. In: Harrison DC, Hall GK, editors. Cardiac Arrhythmias: A Decade of Progress. Medical Publishers; 1981. p. 39–68.
16. Gardner PI, Ursell PC, Fenoglio JJ, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarcts. *Circulation*. 1985;72:596–611.
17. Gardner PI, Ursell PC, Pham TD, Fenoglio Jr. JJ, Wit AL. Experimental chronic ventricular tachycardia: Anatomic and electrophysiologic substrates. In: Josephson ME, Wellens H, editors. Tachycardias: Mechanisms, Diagnosis, Treatment. Lea & Febiger; 1984. p. 29–60.
18. Dillon SM, Allessie MA, Ursell PC, Wit AL. Influences of anisotropic tissue structure on reentrant circuits in the epicardial border zone of subacute canine infarcts. *Circ Res*. 1988;63:182–206.
19. de Bakker JM, van Capelle FJ, Janse MJ, Tasseron S, Vermeulen JT, de Jonge N, Lahpor JR. Slow conduction in the infarcted human heart. “Zigzag” course of activation. *Circulation*. 1993;88:915–26.
20. de Bakker JM, van Capelle FJ, Janse MJ, Wilde AA, Coronel R, Becker AE, Dingemans KP, van Hemel NM, Hauer RN. Reentry as a cause of ventricular tachycardia in patients with chronic ischemic heart disease: electrophysiologic and anatomic correlation. *Circulation*. 1988;77:589–606.
21. de Bakker JM, Coronel R, Tasseron S, Wilde AA, Opthof T, Janse MJ, van Capelle FJ, Becker AE, Jambroes G. Ventricular tachycardia in the infarcted, Langendorff-perfused human heart: role of the arrangement of surviving cardiac fibers. *J Am Coll Cardiol*. 1990;15:1594–1607.
22. Roy D, Marchand E, Théroux P, Waters DD, Pelletier GB, Cartier R, Bourassa MG. Long-term reproducibility and significance of provokable ventricular arrhythmias after myocardial infarction. *J Am Coll Cardiol*. 1986;8:32–9.
23. Kieken F, Mutsaers N, Dolmatova E, Virgil K, Wit AL, Kellezi A, Hirst-Jensen BJ, Duffy HS, Sorgen PL. Structural and molecular mechanisms of gap junction remodeling in epicardial border zone myocytes following myocardial infarction. *Circ Res*. 2009;104:1103–1112.
24. Almendral JM, Rosenthal ME, Stamato NJ, Marchlinski FE, Buxton AE, Frame LH, Miller JM, Josephson ME. Analysis of the resetting phenomenon in sustained uniform ventricular tachycardia: incidence and relation to termination. *J Am Coll Cardiol*. 1986;8:294–300.
25. Kumar S, Stevenson WG, John RM. Arrhythmias in dilated cardiomyopathy. *Card Electrophysiol Clin*. 2015;7:221–33.
26. Cassidy DM, Vassallo JA, Marchlinski FE, Buxton AE, Untereker WJ, Josephson ME. Endocardial mapping in humans in sinus rhythm with normal left ventricles: activation patterns and characteristics of electrograms. *Circulation*. 1984;70:37–42.
27. Josephson ME, Horowitz LN, Farshidi A. Continuous local electrical activity. A mechanism of recurrent ventricular tachycardia. *Circulation*. 1978;57:659–665.

28. Horowitz LN, Josephson ME, Harken AH. Epicardial and endocardial activation during sustained ventricular tachycardia in man. *Circulation*. 1980;61:1227–1238.
29. Josephson ME, Harken AH, Horowitz LN. Long-term results of endocardial resection for sustained ventricular tachycardia in coronary disease patients. *Am Heart J*. 1982;104:51–7.
30. Almendral JM, Stamato NJ, Rosenthal ME, Marchlinski FE, Miller JM, Josephson ME. Resetting response patterns during sustained ventricular tachycardia: relationship to the excitable gap. *Circulation*. 1986;74:722–730.
31. Kindwall KE, Brown JP, Josephson ME. Predictive accuracy of criteria for chronic myocardial infarction in pacing-induced left bundle branch block. *Am J Cardiol*. 1986;57:1255–1260.
32. Ben-Haim SA, Osadchy D, Schuster I, Gepstein L, Hayam G, Josephson ME. Nonfluoroscopic, in vivo navigation and mapping technology. *Nat Med*. 1996;2:1393–5.
33. Marchlinski FE, Callans DJ, Gottlieb CD, Zado E. Linear ablation lesions for control of unmappable ventricular tachycardia in patients with ischemic and nonischemic cardiomyopathy. *Circulation*. 2000;101:1288–96.
34. Callans DJ, Ren JF, Michele J, Marchlinski FE, Dillon SM. Electroanatomic left ventricular mapping in the porcine model of healed anterior myocardial infarction. Correlation with intracardiac echocardiography and pathological analysis. *Circulation*. 1999;100:1744–50.
35. Hutchinson MD, Gerstenfeld EP, Desjardins B, Bala R, Riley MP, Garcia FC, Dixit S, Lin D, Tzou WS, Cooper JM, Verdino RJ, Callans DJ, Marchlinski FE. Endocardial unipolar voltage mapping to detect epicardial ventricular tachycardia substrate in patients with nonischemic left ventricular cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2011;4:49–55.
36. Sapp JL, Beeckler C, Pike R, Parkash R, Gray CJ, Zeppenfeld K, Kuriachan V, Stevenson WG. Initial human feasibility of infusion needle catheter ablation for refractory ventricular tachycardia. *Circulation*. 2013;128:2289–95.
37. Koruth JS, Dukkipati S, Miller MA, Neuzil P, d'Avila A, Reddy VY. Bipolar irrigated radiofrequency ablation: a therapeutic option for refractory intramural atrial and ventricular tachycardia circuits. *Heart Rhythm*. 2012;9:1932–41.
38. Kwon DH, Halley CM, Carrigan TP, Zysek V, Popovic ZB, Setser R, Schoenhagen P, Starling RC, Flamm SD, Desai MY. Extent of left ventricular scar predicts outcomes in ischemic cardiomyopathy patients with significantly reduced systolic function: a delayed hyperenhancement cardiac magnetic resonance study. *JACC Cardiovasc Imaging*. 2009;2:34–44.
39. Liuba I, Frankel DS, Riley MP, Hutchinson MD, Lin D, Garcia FC, Callans DJ, Supple GE, Dixit S, Bala R, Squara F, Zado ES, Marchlinski FE. Scar progression in patients with nonischemic cardiomyopathy and ventricular arrhythmias. *Heart Rhythm*. 2014;11:755–62.
40. Hussein A, Jimenez A, Ahmad G, Mesubi O, Klein T, Gurm G, Beck H, Shams O, See V, Saliaris A, Shorofsky S, Dickfeld T. Assessment of ventricular tachycardia scar substrate by intracardiac echocardiography. *Pacing Clin Electrophysiol*. 2014;37:412–21.
41. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretskiy V V, DeFreitas G, Carabello B, Brandon LI, Godsel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res*. 2006;99:646–55.
42. Saffitz JE. Arrhythmogenic cardiomyopathy and abnormalities of cell-to-cell coupling. *Heart Rhythm*. 2009;6:S62–5.
43. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? *Circulation*. 1996;94:983–91.

44. Corrado D, Basso C, Thiene G, McKenna WJ, Davies MJ, Fontaliran F, Nava A, Silvestri F, Blomstrom-Lundqvist C, Wlodarska EK, Fontaine G, Camerini F. Spectrum of clinicopathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. *J Am Coll Cardiol*. 1997;30:1512–20.
45. Marchlinski FE, Zado E, Dixit S, Gerstenfeld E, Callans DJ, Hsia H, Lin D, Nayak H, Russo A, Pulliam W. Electroanatomic substrate and outcome of catheter ablative therapy for ventricular tachycardia in setting of right ventricular cardiomyopathy. *Circulation*. 2004;110:2293–8.
46. Garcia FC, Bazan V, Zado ES, Ren J-F, Marchlinski FE. Epicardial substrate and outcome with epicardial ablation of ventricular tachycardia in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Circulation*. 2009;120:366–75.
47. Santangeli P, Pieroni M, Dello Russo A, Casella M, Pelargonio G, Di Biase L, Macchione A, Burkhardt JD, Bellocci F, Santarelli P, Tondo C, Natale A. Correlation between signal-averaged ECG and the histologic evaluation of the myocardial substrate in right ventricular outflow tract arrhythmias. *Circ Arrhythm Electrophysiol*. 2012;5:475–83.
48. Polin GM, Haqqani H, Tzou W, Hutchinson MD, Garcia FC, Callans DJ, Zado ES, Marchlinski FE. Endocardial unipolar voltage mapping to identify epicardial substrate in arrhythmogenic right ventricular cardiomyopathy/dysplasia. *Hear Rhythm*. 2011;8:76–83.
49. Haqqani HM, Tschabrunn CM, Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered activation of epicardial scar in arrhythmogenic right ventricular dysplasia: possible substrate for confined epicardial circuits. *Circ Arrhythm Electrophysiol*. 2012;5:796–803.
50. Wyndham CR, Meeran MK, Smith T, Saxena A, Engelman RM, Levitsky S, Rosen KM. Epicardial activation of the intact human heart without conduction defect. *Circulation*. 1979;59:161–8.
51. Sosa E, Scanavacca M, d'Avila A, Pilleggi F. A new technique to perform epicardial mapping in the electrophysiology laboratory. *J Cardiovasc Electrophysiol*. 1996;7:531–6.
52. Brugada J, Berruezo A, Cuesta A, Osca J, Chueca E, Fosch X, Wayar L, Mont L. Nonsurgical transthoracic epicardial radiofrequency ablation: an alternative in incessant ventricular tachycardia. *J Am Coll Cardiol*. 2003;41:2036–43.
53. Roberts-Thomson KC, Seiler J, Steven D, Inada K, Michaud GF, John RM, Koplan BA, Epstein LM, Stevenson WG, Tedrow UB. Percutaneous access of the epicardial space for mapping ventricular and supraventricular arrhythmias in patients with and without prior cardiac surgery. *J Cardiovasc Electrophysiol*. 2010;21:406–11.
54. d'Avila A, Neuzil P, Thiagalingam A, Gutierrez P, Aleong R, Ruskin JN, Reddy VY. Experimental efficacy of pericardial instillation of anti-inflammatory agents during percutaneous epicardial catheter ablation to prevent postprocedure pericarditis. *J Cardiovasc Electrophysiol*. 2007;18:1178–1183.
55. Sosa E, Scanavacca M, D'Avila A, Antônio J, Ramires F. Nonsurgical transthoracic epicardial approach in patients with ventricular tachycardia and previous cardiac surgery. *J Interv Card Electrophysiol*. 2004;10:281–8.
56. Soejima K, Couper G, Cooper JM, Sapp JL, Epstein LM, Stevenson WG. Subxiphoid surgical approach for epicardial catheter-based mapping and ablation in patients with prior cardiac surgery or difficult pericardial access. *Circulation*. 2004;110:1197–201.
57. Schaefer H, Trautwein W. Further experiments on the nature of the excitation wave in the myocardium of the dog. *Pflügers Arch Eur J Physiol*. 1951;253:152–64.
58. Durrer D, Van Der Tweel L. Excitation of the left ventricular wall of the dog and goat. *Ann N Y Acad Sci*. 1957;65:779–803.
59. Stinnett-Donnelly JM, Thompson N, Habel N, Petrov-Kondratov V, Correa de Sa DD, Bates JHT, Spector PS. Effects of electrode size and spacing on the resolution of intracardiac electrograms. *Coron Artery Dis*. 2012;23:126–32.
60. Otomo K, Uno K, Fujiwara H, Isobe M, Iesaka Y. Local unipolar and bipolar electrogram

criteria for evaluating the transmurality of atrial ablation lesions at different catheter orientations relative to the endocardial surface. *Heart Rhythm*. 2010;7:1291–300.
61. Rajappan K, Kistler PM, Earley MJ, Thomas G, Izquierdo M, Sporton SC, Schilling RJ. Acute and chronic pulmonary vein reconnection after atrial fibrillation ablation: a prospective characterization of anatomical sites. *Pacing Clin Electrophysiol*. 2008;31:1598–605.
62. Calkins H, Kuck KH, Cappato R, Brugada J, Camm AJ, Chen SA, Crijns HJ, Damiano Jr. RJ, Davies DW, DiMarco J, Edgerton J, Ellenbogen K, Ezekowitz MD, Haines DE, Haissaguerre M, Hindricks G, Iesaka Y, Jackman W, Jalife J, Jais P, Kalman J, Keane D, Kim YH, Kirchhof P, Klein G, Kottkamp H, Kumagai K, Lindsay BD, Mansour M, Marchlinski FE, McCarthy PM, Mont JL, Morady F, Nademanee K, Nakagawa H, Natale A, Nattel S, Packer DL, Pappone C, Prystowsky E, Raviele A, Reddy V, Ruskin JN, Shemin RJ, Tsao HM, Wilber D. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design. *Europace*. 2012;14:528–606.
63. Hunter RJ, McCready J, Diab I, Page SP, Finlay M, Richmond L, French A, Earley MJ, Sporton S, Jones M, Joseph JP, Bashir Y, Betts TR, Thomas G, Staniforth A, Lee G, Kistler P, Rajappan K, Chow A, Schilling RJ. Maintenance of sinus rhythm with an ablation strategy in patients with atrial fibrillation is associated with a lower risk of stroke and death. *Heart*. 2012;98:48–53.
64. Wynn GJ, Das M, Bonnett LJ, Panikker S, Wong T, Gupta D. Efficacy of catheter ablation for persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized and nonrandomized controlled trials. *Circ Arrhythm Electrophysiol*. 2014;7:841–52.
65. Rajappan K, Ginks M. Catheter ablation of persistent atrial fibrillation. *Future Cardiol*. 2014;10:553–62.
66. Wynn GJ, Panikker S, Morgan M, Hall M, Waktare J, Markides V, Hussain W, Salukhe T, Modi S, Jarman J, Jones DG, Snowdon R, Todd D, Wong T, Gupta D. Biatrial linear ablation in sustained nonpermanent AF: Results of the substrate modification with ablation and antiarrhythmic drugs in nonpermanent atrial fibrillation (SMAN-PAF) trial. *Heart Rhythm*. 2016;13:399–406.
67. Wong KCK, Paisey JR, Sopher M, Balasubramaniam R, Jones M, Qureshi N, Hayes CR, Ginks MR, Rajappan K, Bashir Y, Betts TR. No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol*. 2015;8:1316–24.
68. Kapa S, Desjardins B, Callans DJ, Marchlinski FE, Dixit S. Contact electroanatomic mapping derived voltage criteria for characterizing left atrial scar in patients undergoing ablation for atrial fibrillation. *J Cardiovasc Electrophysiol*. 2014;25:1044–52.
69. Anter E, Tschabrunn CM, Buxton AE JM. Characteristics of Reentrant Ventricular Tachycardia in Healed Myocardial Infarction. *Heart Rhythm*. 2015;12.
70. Euler DE, Prood CE, Spear JF, Moore EN. The interruption of collateral blood flow to the ischemic canine myocardium by embolization of a coronary artery with latex: effects on conduction delay and ventricular arrhythmias. *Circ Res*. 1981;49:97–108.
71. Wit AL, Rosen MR. Afterdepolarizations and triggered activity. In: Brugada P, Wellens H, editors. The Heart and Cardiovascular System. Raven Press; 1986. p. 1449–1490.
72. Wit AL, Allessie MA, Bonke FI, Lammers W, Smeets J, Fenoglio Jr. JJ. Electrophysiologic mapping to determine the mechanism of experimental ventricular tachycardia initiated by premature impulses. Experimental approach and initial results demonstrating reentrant excitation. *Am J Cardiol*. 1982;49:166–185.
73. Sasano T, McDonald AD, Kikuchi K, Donahue JK. Molecular ablation of ventricular tachycardia after myocardial infarction. *Nat Med*. 2006;12:1256–1258.
74. Ashikaga H, Sasano T, Dong J, Zviman MM, Evers R, Hopenfeld B, Castro V, Helm RH, Dickfeld T, Nazarian S, Donahue JK, Berger RD, Calkins H, Abraham MR, Marban

E, Lardo AC, McVeigh ER, Halperin HR. Magnetic resonance-based anatomical analysis of scar-related ventricular tachycardia: implications for catheter ablation. *Circ Res*. 2007;101:939–947.
75. Tung R, Nakahara S, Ramirez R, Lai C, Fishbein MC, Shivkumar K. Distinguishing epicardial fat from scar: analysis of electrograms using high-density electroanatomic mapping in a novel porcine infarct model. *Hear Rhythm*. 2010;7:389–395.
76. Berte B, Relan J, Sacher F, Pillois X, Appetiti A, Yamashita S, Mahida S, Casassus F, Hooks D, Sellal J-M, Amraoui S, Denis A, Derval N, Cochet H, Hocini M, Haïssaguerre M, Weerasooriya R, Jaïs P. Impact of electrode type on mapping of scar-related VT. *J Cardiovasc Electrophysiol*. 2015;Jul 22 [Ep.
77. El-Sherif N, Scherlag BJ, Lazzara R, Hope RR. Re-entrant ventricular arrhythmias in the late myocardial infarction period. 1. Conduction characteristics in the infarction zone. *Circulation*. 1977;55:686–702.
78. Ursell PC, Gardner PI, Albala A, Fenoglio Jr. JJ, Wit AL. Structural and electrophysiological changes in the epicardial border zone of canine myocardial infarcts during infarct healing. *Circ Res*. 1985;56:436–451.

Appendix A

Overview of Manuscript Contributions and Corresponding Author Attestation

I attest to having provided substantial scientific contributions to each of the manuscripts included in this thesis. This includes direct and overt involvement and participation in the study design, data collection, data analysis, interpretation of results, and/or preparation of the manuscript. My involvement is detailed further for each of the included manuscripts in the below table. The included letters from the senior/corresponding authors further confirm my contributions to these works. In addition, I confirm that the selected manuscripts have not been submitted as evidence for which a degree or any other qualification has already been awarded.

Number / Chapter	Manuscript Abbreviated Citation	List of Contributions
1 Chapter 2	Haqqani HM, **Tschabrunn CM,** Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Heart Rhythm. 2011 Aug8(8);1169-76.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
2 Chapter 2	Frankel DS, **Tschabrunn CM**, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Heart Rhythm. 2013 May;10(5): 621-6.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
3 Chapter 2	Bala R. Ren JF, Hutchinson MD, Desjardins B, **Tschabrunn CM**, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):667-73.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
4 Chapter 3	Haqqani HM, **Tschabrunn CM,** Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
5 Chapter 3	Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, **Tschabrunn CM**, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Circ Arrhythm Electrophysiol. 2015 Dec 8;89(6):1413-21.	Data Collection; Data Analysis
6 Chapter 3	**Tschabrunn CM**, Haqqani HM, Zado ES, Marchlinski FE. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
7 Chapter 3	**Tschabrunn CM**, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Heart Rhythm. 2013 Feb;10(2):165-9.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
8 Chapter 4	Anter E, **Tschabrunn CM**, Josephson ME. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
9 Chapter 4	Anter E, Li J, **Tschabrunn CM**, Nezafat R, Josephson ME. Heart Rhythm Case Rep. 2015 Nov 1;1(6):472-6.	Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
10 Chapter 5	**Tschabrunn CM**, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Heart Rhythm. 2016 Jan;13(1):262-73.	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation
11 Chapter 5	**Tschabrunn CM**, Roujol S, Dorman NC, Nezafat R, Josephson ME, Anter E. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).	Study Design; Data Collection; Data Analysis; Interpretation of Results; Manuscript Preparation

Penn Medicine

Hospital *of the* University *of* Pennsylvania

Penn Heart and Vascular Center

Cardiac Electrophysiology

Francis E. Marchlinski, MD
Richard T. and Angela Clark
President's Distinguished Professor
Director of EP Laboratory
Hospital of the University of Pennsylvania
Director of Electrophysiology
University of Pennsylvania Health System

July 20, 2016

Mark Haddad, PhD
School of Health Sciences
City University of London
Northampton Square
London EC1V 0HB, United Kingdom

RE: Attestation of Author Contributions – Cory M. Tschabrunn

Dear Dr. Haddad,

As the senior and corresponding author of the following publications, I confirm that Cory Tschabrunn provided significant scientific contributions in the study design, data collection, interpretation of results, and/or manuscript preparation to each of the publications detailed below. In addition, I certify that to the best of my knowledge, none of these manuscripts have been submitted as supportive evidence for which any other qualification has already been awarded.

1. Haqqani HM, Tschabrunn CM, Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson, MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Isolated Septal Substrate for Ventricular Tachycardia in Nonischemic Dilated Cardiomyopathy: Incidence, Characterization and Implications. Heart Rhythm. 2011 Aug8(8);1169-76.

2. Frankel DS, Tschabrunn CM, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical Ventricular Tachycardia Morphology in Left Ventricular Non-Ischemic Cardiomyopathy Predicts Poor Transplant Free Survival. Heart Rhythm. 2013 May;10(5): 621-6.

3. Bala R. Ren JF, Hutchinson MD, Desjardins B, Tschabrunn CM, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):667-73.

4. Haqqani HM, Tschabrunn CM, Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

5. Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, Tschabrunn CM, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Long-term Outcome with Catheter Ablation of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2015 Dec 8;89(6):1413-21.

6. Tschabrunn CM, Haqqani HM, Zado ES, Marchlinski FE. Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

7. Tschabrunn CM, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Percutaneous Epicardial Ventricular Tachycardia Ablation After Non-Coronary Cardiac Surgery or Pericarditis. Heart Rhythm. 2013 Feb;10(2):165-9.

Sincerely,

[redacted]

Francis E. Marchlinski, MD
Richard T. and Angela Clark President's
Distinguished Professor
Director, Cardiac Electrophysiology
UPHS

Ruth *and* Raymond Perelman Center *for* Advanced Medicine
East Pavilion, Second Floor | 3400 Civic Center Boulevard | Philadelphia, PA 19104

Address for Correspondence:
Hospital of the University of Pennsylvania | 9 Founders Pavilion | 3400 Spruce Street | Philadelphia, PA, 19104 | 215.662.6005 | Fax: 215.662.2879

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Elad Anter, MD

Director
Translational Electrophysiology

Associate Director
Clinical Electrophysiology

Assistant Professor of Medicine
Harvard Medical School

Harvard-Thorndike
Electrophysiology Institute

185 Pilgrim Road
Baker 4
Boston, MA 02215

(617) 632-9209 **Phone**

(617) 632-7620 **Fax**

eanter@bidmc.harvard.edu

July 1, 2016

Mark Haddad, PhD
School of Health Sciences
City University of London
Northampton Square
London EC1V 0HB, United Kingdom

RE: ATTESTATION OF AUTHOR CONTRIBUTIONS – CORY M. TSCHABRUNN

Dear Dr. Haddad,

As the senior and corresponding author of the following publications, I confirm that Cory Tschabrunn provided significant scientific contributions in the study design, data collection, interpretation of results, and/or manuscript preparation to each of the publications detailed below. In addition, I certify that to the best of my knowledge, none of these manuscripts have been submitted as supportive evidence for which any other qualification has already been awarded.

1. Anter E, Tschabrunn CM, Contreras-Valdes FM, Li J, Josephson ME. Pulmonary Vein Isolation Using the Rhythmia Mapping System: Verification of Intracardiac Signals Using the Orion Mini-basket Catheter. Heart Rhythm. 2015 Sep;12(9):1927-34.

2. Anter E, Tschabrunn CM, Josephson ME. High-resolution Mapping of Scar-related Atrial Arrhythmias Using Smaller Electrodes with Closer Interelectrode Spacing. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

3. Anter E, Li J, Tschabrunn CM, Nezafat R, Josephson ME. Mapping of a Post-infarction Left Ventricular Aneurysm-Dependent Macroreentrant Ventricular Tachycardia. Heart Rhythm Case Rep. 2015 Nov 1;1(6):472-6.

4. Tschabrunn CM, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Swine Model of Infarct-related Reentrant Ventricular Tachycardia: Electroanatomic, Magnetic Resonance, and Histopathologic Characterization. Heart Rhythm. 2016 Jan;13(1):262-73.

5. Tschabrunn CM, Roujol S, Dorman NC, Nezafat R, Josephson ME, Anter E. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016 Jun;9(6) [Epub ahead of print].

Sincerely,

[redacted]

Elad Anter, MD

Appendix B

Chapter 2 Full Text Manuscripts

Chapter 2 – Electrophysiologic Substrate in Patients with Dilated Non-Ischemic Cardiomyopathy and Ventricular Tachycardia

Haqqani HM, **Tschabrunn CM,** Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Isolated Septal Substrate for Ventricular Tachycardia in Nonischemic Dilated Cardiomyopathy: Incidence, Characterization and Implications. Heart Rhythm. 2011 Aug8(8);1169-76.

Frankel DS, **Tschabrunn CM**, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical Ventricular Tachycardia Morphology in Left Ventricular Non-Ischemic Cardiomyopathy Predicts Poor Transplant Free Survival. Heart Rhythm. 2013 May;10(5): 621-6.

Bala R. Ren JF, Hutchinson MD, Desjardins B, **Tschabrunn CM**, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation. Circ Arrhythm Electrophysiol. 2011 Oct;4(5):667-73.

Isolated septal substrate for ventricular tachycardia in nonischemic dilated cardiomyopathy: Incidence, characterization, and implications

Haris M. Haqqani, MBBS, PhD, Cory M. Tschabrunn, CEPS, Wendy S. Tzou, MD, Sanjay Dixit, MD, FHRS, Joshua M. Cooper, MD, Michael P. Riley, MD, PhD, David Lin, MD, Mathew D. Hutchinson, MD, FHRS, Fermin C. Garcia, MD, Rupa Bala, MD, Ralph J. Verdino, MD, David J. Callans, MD, FHRS, Edward P. Gerstenfeld, MD, Erica S. Zado, PA-C, FHRS, Francis E. Marchlinski, MD, FHRS

From the Section of Cardiac Electrophysiology, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

BACKGROUND The substrate for ventricular tachycardia (VT) in nonischemic cardiomyopathy (NICM) has a predilection for the basolateral left ventricle with right bundle branch block VT morphology.

OBJECTIVE The purpose of this study was to describe a unique group of NICM patients with septal VT substrate.

METHODS Between 1999 and 2010, 31 (11.6%) of 266 patients with NICM undergoing VT ablation had septal substrate and no lateral involvement. Mean age was 59 ± 12 years, and ejection fraction was 30% ± 14%. Eight patients had heart block.

RESULTS Cardiac magnetic resonance showed septal delayed enhancement in 8 of 9 patients. Electroanatomic mapping demonstrated bipolar low voltage (<1.5 mV) extending from the basal septum in 22 of 31 patients. The remaining 9 patients had normal endocardial bipolar voltage but abnormal unipolar septal voltage (<8.3 mV) consistent with intramural abnormalities. Epicardial mapping in 14 patients showed no scar in 9 and patchy basal left ventricular summit scar in 5. VTs were mapped to the septal substrate, with 62% having right bundle branch block morphology and V_2 precordial transition pattern break in 17% suggesting periseptal exit. After substrate and targeted VT ablation, no VT was inducible in 66% and no "clinical targeted" VT in 86%. Over a mean follow-up of 20 ± 28 months, VT recurred in 10 (32%) patients.

CONCLUSION Isolated septal VT substrate is uncommon in NICM. Biventricular low-voltage zones extending from the basal septum are characteristic, but septal scarring can be entirely intramural as evidenced by unipolar/bipolar electrograms and imaging. Multiple unmappable morphologies are the rule, often requiring several procedures aggressively targeting the septal substrate to achieve moderate long-term VT control.

KEYWORDS Cardiomyopathy; Catheter ablation; Electroanatomic mapping; Heart failure; Ventricular tachycardia

ABBREVIATIONS CMR = cardiac magnetic resonance; DGE = delayed gadolinium enhancement; **EAM** = electroanatomic mapping; **ICD** = implantable cardioverter-defibrillator; **ICE** = intracardiac echocardiography; **LBBB** = left bundle branch block; **LV** = left ventricle; **NICM** = nonischemic cardiomyopathy; **RBBB** = right bundle branch block; **RV** = right ventricle; **VT** = ventricular tachycardia

(Heart Rhythm 2011;8:1169–1176)

Introduction

Monomorphic ventricular tachycardia (VT) in the context of nonischemic cardiomyopathy (NICM) can present significant management challenges, and catheter ablation has emerged as an important therapy.[1–4] Unmappable VT accounts for the majority of VT morphologies induced at these procedures,[5] and the development of substrate-based ablation strategies has allowed for the targeting and ablation of these arrhythmias during sinus rhythm.[1] We previously showed that the substrate for VT in NICM characteristically affects the basal periannular region of the left ventricle (LV), on both the endocardium and epicardium.[6–8] Although the majority of these patients appear to have isolated basolateral substrate or both basolateral and basal septal involvement,[7] this is not invariable. The purpose of this study was to characterize the electrophysiologic and electroanatomic characteristics of NICM patients with isolated septal substrate for VT.

Dr. Haqqani is the recipient of an Overseas Training Fellowship (544309) from the National Health and Medical Research Council of Australia and the Bayer Fellowship from the Royal Australasian College of Physicians. Dr. Marchlinski has received honoraria and research funding from Biosense Webster unrelated to this study. **Address reprint requests and correspondence:** Dr. Francis E. Marchlinski, Cardiovascular Division, Hospital of the University of Pennsylvania, 3400 Spruce Street, Founders 9, Philadelphia, Pennsylvania 19104. E-mail address: francis.marchlinski@uphs.upenn.edu. (Received January 4, 2011; accepted March, 2, 2011.)

1547-5271/$ -see front matter doi:10.1016/j.hrthm.2011.03.008

Apical ventricular tachycardia morphology in left ventricular nonischemic cardiomyopathy predicts poor transplant-free survival

David S. Frankel, MD, Cory M. Tschabrunn, CEPS, Joshua M. Cooper, MD, Sanjay Dixit, MD, FHRS, Edward P. Gerstenfeld, MD, FHRS, Michael P. Riley, MD, PhD, David J. Callans, MD, FHRS, Francis E. Marchlinski, MD, FHRS

From the Electrophysiology Section, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

BACKGROUND The scar of patients with left ventricular (LV) nonischemic cardiomyopathy (NICM) and ventricular tachycardia (VT) typically originates at or near the mitral annulus and extends a variable distance toward the apex.

OBJECTIVE To determine whether electrocardiograms of VT with LV apical exit sites would identify patients with larger scars extending a greater distance from the base toward the apex and decreased heart transplant/left ventricular assist device (LVAD)-free survival.

METHODS Consecutive patients with LV NICM undergoing VT ablation between May 2008 and April 2011 were studied. All electrocardiograms of spontaneous and induced VT were analyzed. Apical VT was defined as left bundle branch morphology with precordial transition $\geq V_5$ or right bundle branch morphology with precordial transition $\leq V_3$. Scar percentage was defined as the area of low voltage divided by the total surface area.

RESULTS Thirty-two of 76 patients had 1 or more apical VTs. Those with apical VTs had larger percentage of endocardial and epicardial bipolar scars (14.9% vs 8.1%, $P = .01$, and 15.5% vs 5.5%, $P = .03$, respectively), scar that, although originating from the periannular region (94.7% of the patients), was more likely to extend apically beyond the basal half (48.3% vs 24.4%, $P = .05$ endocardial, and 85.7% vs 25.9%, $P = .07$ epicardial), and worse transplant/LVAD-free survival during a mean follow-up of 332 days ($P = .006$).

CONCLUSIONS Patients with NICM and apical VTs have larger voltage abnormality extending as contiguous or patchy "scar" from the base further toward the apex and worse transplant/LVAD-free survival. Particular attention should be paid to optimal heart failure management in these patients, with more guarded prognosis.

KEYWORDS Nonischemic cardiomyopathy; Ventricular tachycardia; Electroanatomic mapping; Heart failure; Left ventricular assist device; Transplant-free survival

ABBREVIATIONS ECG = electrocardiogram; **LVAD** = left ventricular assist device; **LVEF** = left ventricular ejection fraction; **NICM** = nonischemic cardiomyopathy; **VT** = ventricular tachycardia

(Heart Rhythm 2013;10:621–626)

Introduction

The area of low-voltage, abnormal bipolar electrograms consistent with "scar" in patients with left ventricular nonischemic cardiomyopathy (NICM) and ventricular tachycardia (VT) typically originates at or near the mitral annular region and extends a variable distance toward the apex.[1] While patients with VT and NICM as a whole have better survival than those with VT and ischemic cardiomyopathy,[2] there remains substantial variability in survival among those with NICM. We hypothesized that patients with NICM and VT morphologies suggesting an apical left ventricular exit site would have larger scars extending a greater distance from the base toward the apex and, consequently, worse transplant- and left ventricular assist device (LVAD)-free survival following ablation.

Methods

Study population

We studied consecutive patients with left ventricular NICM and sustained VT, who were referred to the Hospital of the University of Pennsylvania for ablation between May 2008 and April 2011. Patients with idiopathic VT, right ventricular cardiomyopathy, or ischemic cardiomyopathy, as defined by history of myocardial infarction or obstructive coronary artery disease on angiography, were excluded. Patients undergoing multiple ablation procedures during this time

This study was supported in part by the F. Harlan Batrus Research Fund and the Susan and Murray Bloom Fund. **Address reprint requests and correspondence:** Dr David S. Frankel, Electrophysiology Section, Cardiovascular Division, Hospital of the University of Pennsylvania, 9 Founders Pavilion, 3400 Spruce St, Philadelphia, PA 19104. E-mail address: david.frankel@uphs.upenn.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2012.12.029

Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation

Rupa Bala, MD; Jian-Fang Ren, MD; Mathew D. Hutchinson, MD; Benoit Desjardins, MD; Cory Tschabrunn, CEPS; Edward P. Gerstenfeld, MD; Rajat Deo, MD; Sanjay Dixit, MD; Fermin C. Garcia, MD; Joshua Cooper, MD; David Lin, MD; Michael P. Riley, MD; Wendy S. Tzou, MD; Ralph Verdino, MD; Andrew E. Epstein, MD; David J. Callans, MD; Francis E. Marchlinski, MD

Background—Intracardiac echocardiography (ICE) has played a limited role in defining the substrate for ventricular tachycardia (VT). The purpose of this study was to assess whether ICE could identify abnormal epicardial substrate in patients with nonischemic cardiomyopathy (NICM) and VT.

Methods and Results—We studied 18 patients with NICM and recurrent VT who had abnormal echogenicity identified on ICE imaging. Detailed left ventricular (LV) endocardial and epicardial electroanatomic mapping was performed in all patients. Low-voltage areas (<1.0 mV) in the epicardium were analyzed. ICE imaging in the NICM group was compared to a control group of 30 patients with structurally normal hearts who underwent ICE imaging for other ablation procedures. In 18 patients (age, 53±13 years; 17 men) with NICM (ejection fraction, 37±13%), increased echogenicity was identified in the lateral LV by ICE imaging. LV endocardial electroanatomic mapping identified normal voltage in 9 patients and at least 1 confluent low-voltage area (6.6 cm^2; minimum-maximum, 2.1–31.7 cm^2) in 9 patients (5 posterolateral LV, 4 perivalvular LV). Detailed epicardial mapping revealed areas of low voltage (39 cm^2; minimum-maximum, 18.5–96.3 cm^2) and abnormal, fractionated electrograms in all 18 patients (15 posterolateral LV, 3 lateral LV). In all patients, the epicardial scar identified by electroanatomic mapping correlated with the echogenic area identified on ICE imaging. ICE imaging identified no areas of increased echogenicity in the control group.

Conclusions—ICE imaging identified increased echogenicity in the lateral wall of the LV that correlated to abnormal epicardial substrate. These findings suggest that ICE imaging may be useful to identify epicardial substrate in NICM. **(*Circ Arrhythm Electrophysiol*. 2011;4:667-673.)**

Key Words: catheter ablation ■ imaging ■ echocardiography ■ tachycardia ventricular ■ epicardial mapping

Intracardiac echocardiography (ICE) is routinely used during catheter ablation for atrial fibrillation to facilitate transseptal catheterization, assess cardiac anatomy, monitor pulmonary vein flows, provide real-time imaging of catheter tip position and lesion formation, and monitor for complications. Despite its widespread use in ablation for atrial fibrillation, ICE imaging has not been routinely used during catheter ablation for ventricular tachycardia (VT).[1] Several studies have highlighted the use of ICE in VT ablation to guide catheter placement on specific anatomic targets, such as the papillary muscles; to facilitate mapping and ablation of aortic cusp VT; and to monitor lesion development.[1–4] There is limited information on the ability of ICE to assess for abnormal substrate during VT ablation.[5–7]

Clinical Perspective on p 673

We present a unique series of patients with nonischemic cardiomyopathy (NICM) and recurrent VT in whom ICE imaging identified abnormal echogenicity in the lateral wall of the left ventricle (LV). We characterized this substrate by detailed endocardial and epicardial mapping; analysis of electrograms in low-voltage areas; and correlation with other imaging modalities, including MRI and CT angiography.

Methods

Study Population

The study population comprised 18 patients with NICM and recurrent VT who underwent radiofrequency ablation at our institution. These 18 patients had increased echogenicity in the lateral wall of the LV as identified by ICE imaging. We compared the ICE imaging in

Received March 15, 2011; accepted August 5, 2011.

From the Electrophysiology Section, Cardiovascular Division, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA.

Correspondence to Rupa Bala, MD, Department of Cardiology, Division of Electrophysiology, Hospital of the University of Pennsylvania, 3400 Spruce St, 9 Founders Pavilion, Philadelphia, PA 19104. E-mail balar@uphs.upenn.edu

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.111.963553**

Appendix C

Chapter 3 Full Text Manuscripts

Chapter 3 – Electrophysiologic Substrate in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy and Ventricular Tachycardia

Haqqani HM, **Tschabrunn CM,** Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, **Tschabrunn CM**, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Long-term Outcome with Catheter Ablation of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy. Circ Arrhythm Electrophysiol. 2015 Dec 8;89(6):1413-21.

Tschabrunn CM, Haqqani HM, Zado ES, Marchlinski FE. Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

Tschabrunn CM, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Percutaneous Epicardial Ventricular Tachycardia Ablation After Non-Coronary Cardiac Surgery or Pericarditis. Heart Rhythm. 2013 Feb;10(2):165-9.

Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia

Possible Substrate for Confined Epicardial Circuits

Haris M. Haqqani, MBBS, PhD; Cory M. Tschabrunn, CEPS; Brian P. Betensky, MD; Nimrod Lavi, MD; Wendy S. Tzou, MD; Erica S. Zado, PA-C; Francis E. Marchlinski, MD

Background—Ventricular tachycardia ablation in arrhythmogenic right ventricular dysplasia (ARVD) is more successful when including epicardial ablation. Scarring may cause independent, layered epicardial activation and promote epicardially confined ventricular tachycardia circuits. We aimed to characterize transmural right ventricular activation in ARVD patients and to compare this with reference patients without structural heart disease.

Methods and Results—Eighteen ARVD patients underwent detailed endocardial and epicardial sinus rhythm electroanatomic mapping. Bipolar activation was annotated at the sharpest intrinsic deflection including late potentials and compared with 6 patients with normal hearts. Total scar area was larger on the epicardium (97±78 cm^2) than the endocardium (57±44 cm^2; P=0.04), with significantly more isolated potentials. Total epicardial activation time was longer than endocardial (172±54 versus 99±27 ms; P<0.01), and both were longer than in reference patients. Earliest endocardial site was the right ventricular anteroseptum in 17 of 18 ARVD patients versus 5 of 6 controls (P=0.446), and latest endocardial site was in the outflow tract in 13 of 18 ARVD patients versus 4 of 6 controls and tricuspid annulus in 5 of 18 ARVD patients versus 2 of 6 controls (P=1.00). In reference patients, epicardial activation directly opposite endocardial sites occurred in 5.2±1.9 ms, suggesting direct transmural activation. In contrast, ARVD patients had major activation delay to the epicardium with laminar central scar activation from the scar border, not by direct transmural spread from the endocardium.

Conclusions—Transmural right ventricular activation is modified by ARVD scarring with a delayed epicardial activation sequence suggestive of independent rather than direct transmural activation. This may predispose ventricular tachycardia circuits contained entirely within the epicardium in ARVD and explains observations on the need for direct epicardial ablation to eliminate ventricular tachycardia. **(*Circ Arrhythm Electrophysiol*. 2012;5:796-803.)**

Key Words: ablation ■ cardiomyopathy ■ catheter ablation ■ electrophysiology ■ tachycardia

Arrhythmogenic right ventricular dysplasia (ARVD) is a genetically determined cardiomyopathy characterized by cardiomyocyte loss with replacement of the myocardium by fibrofatty tissue.[1] The altered myocardial architecture resulting from this process causes delayed and disordered electric propagation and predisposes to the development of reentrant ventricular tachycardia (VT). Although the left ventricle (LV) can be involved,[2] the disease process predominantly affects the right ventricle (RV), and both pathological and electroanatomic studies show a disproportionate burden of disease on the epicardium compared with the endocardium.[3,4] This is likely to have implications on the nature and location of the reentrant VT circuits seen in ARVD. In particular, confluent epicardial or intramural scarring may prevent transmural endocardial-to-epicardial activation during VT, precluding endocardial involvement, and establish the potential for all or major components of VT circuits to be confined entirely to the epicardium. We postulated that the compartmentalized activation of the epicardium induced by such confluent scarring would also alter the sinus rhythm right ventricular endocardial-to-epicardial activation sequence.

The purpose of this study was to define the pattern of activation of the RV endocardium and epicardium in patients without structural heart disease and to compare this with patients with anticipated extensive RV scarring caused by ARVD.

Clinical Perspective on p 803

Methods

The study population (group 1) consisted of 18 consecutive patients with ARVD (13 men; mean age, 43±15 years) who had detailed endocardial and epicardial electroanatomic mapping (EAM) performed. Patients were studied between 2007 and 2010 and met the Revised Task Force Criteria for ARVD as listed in Table 1. They had recurrent VT and multiple implantable cardioverter-defibrillator (ICD) therapies, despite antiarrhythmic drugs, and were undergoing catheter ablation. Thirteen of the 18 patients (72%) had undergone a prior ablation procedure. Patients had recurrent monomorphic VT documented either by 12-lead electrocardiograph or by stored ICD electrograms. The reference group

Received August 22, 2011; accepted May 18, 2012.

From the Section of Cardiac Electrophysiology, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia, PA.

Correspondence to Francis E. Marchlinski, MD, FACC, Hospital of the University of Pennsylvania, 3400 Spruce Street, Founders 9, Philadelphia, PA 19104. E-mail francis.marchlinski@uphs.upenn.edu

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.111.967935**

Original Article

Long-Term Outcome With Catheter Ablation of Ventricular Tachycardia in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy

Pasquale Santangeli, MD; Erica S. Zado, PA-C; Gregory E. Supple, MD; Haris M. Haqqani, MBBS, PhD; Fermin C. Garcia, MD; Cory M. Tschabrunn, CEPS; David J. Callans, MD; David Lin, MD; Sanjay Dixit, MD; Mathew D. Hutchinson, MD; Michael P. Riley, MD, PhD; Francis E. Marchlinski, MD

Background—Catheter ablation of ventricular tachycardia (VT) in arrhythmogenic right ventricular cardiomyopathy improves short-term VT-free survival. We sought to determine the long-term outcomes of VT control and need for antiarrhythmic drug therapy after endocardial (ENDO) and adjuvant epicardial (EPI) substrate modification in patients with arrhythmogenic right ventricular cardiomyopathy.

Methods and Results—We examined 62 consecutive patients with Task Force criteria for arrhythmogenic right ventricular cardiomyopathy referred for VT ablation with a minimum follow-up of 1 year. Catheter ablation was guided by activation/entrainment mapping for tolerated VT and pacemapping/targeting of abnormal substrate for unmappable VT. Adjuvant EPI ablation was performed when recurrent VT or persistent inducibility after ENDO-only ablation. Endocardial plus adjuvant EPI ablation was performed in 39 (63%) patients, including 13 who crossed over to ENDO–EPI after VT recurrence during follow-up, after ENDO-only ablation. Before ablation, 54 of 62 patients failed a mean of 2.4 antiarrhythmic drugs, including amiodarone in 29 (47%) patients. During follow-up of 56±44 months after the last ablation, VT-free survival was 71% with only a single VT episode in additional 9 patients (15%). At last follow-up, 39 (64%) patients were only on β-blockers or no treatment, 21 were on class 1 or 3 antiarrhythmic drugs (11 for atrial arrhythmias), and 2 were on amiodarone as a bridge to heart transplantation.

Conclusions—The long-term outcome after ENDO and adjuvant EPI substrate ablation of VT in arrhythmogenic right ventricular cardiomyopathy is good. Most patients have complete VT control without amiodarone therapy and limited need for antiarrhythmic drugs. **(*Circ Arrhythm Electrophysiol*. 2015;8:1413-1421. DOI: 10.1161/CIRCEP.115.003562.)**

Key Words: ablation techniques ■ antiarrhythmic drugs ■ arrhythmogenic right ventricular dysplasia ■ catheter ablation ■ tachycardia, ventricular

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is characterized by diffuse or segmental loss of RV myocytes with replacement by fibrous and fatty tissue, which characteristically involves more extensively the epicardium (EPI) than the endocardium (ENDO).[1,2] This peculiar pathological process leads to islets of residual myocytes interspersed among adipocytes and fibrous tissue, providing an ideal milieu for reentrant ventricular tachycardia (VT).[3] The management of recurrent VT in ARVC is challenging with antiarrhythmic drug (AAD) therapy having limited efficacy.[4] Initial experiences with catheter ablation using an ENDO-only approach led to disappointing results.[5–7] Given the more extensive epicardial pathological substrate,[8,9] catheter ablation approaches using a combination of ENDO–EPI ablation have been recently shown to significantly improve VT-free survival at the short to the mid-term follow-up.[9–12] Few data are available on the long-term outcome associated after ENDO–EPI ablative therapy in patients with ARVC and recurrent VT. In this study, we report our institutional experience on catheter ablation of VT in ARVC and document the long-term outcomes associated with extensive ENDO or ENDO–EPI VT ablation and substrate modification in these patients as it relates to VT recurrence and requirement for continued AAD therapy.

Methods

Study Population

Sixty-two consecutive patients with ARVC and recurrent VT referred to the Hospital of the University of Pennsylvania for radiofrequency catheter ablation between 1998 and 2013 were included in the study. During the same study period, a total of 2716 VT ablation procedures were performed at our institution, of which 325 (12%) were epicardial; secular trends in the number of VT ablation procedures and epicardial procedures are shown in Figure I in the Data Supplement. All patients met the International Task Force criteria

Received July 31, 2015; accepted November 2, 2015.

From the Department of Medicine, Cardiovascular Division, Hospital of the University of Pennsylvania, Philadelphia.

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.115.003562/-/DC1.

Correspondence to Francis E. Marchlinski, MD, Cardiovascular Division, Hospital of the University of Pennsylvania, 9 Founders Pavilion, 3400 Spruce St, Philadelphia, PA 19104. E-mail francis.marchlinski@uphs.upenn.edu

Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome

CORY M. TSCHABRUNN, C.E.P.S., HARIS M. HAQQANI, M.B.B.S., PH.D., ERICA S. ZADO, P.A.-C., and FRANCIS E. MARCHLINSKI, M.D.

From the Cardiac Electrophysiology Program, Cardiovascular Medicine Division, Hospital of the University of Pennsylvania, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA

Safety and Efficacy of Repeat Epicardial Access. ***Introduction:*** **Epicardial mapping and ablation of ventricular tachycardia (VT) has been increasingly performed. Occasionally additional ablation is necessary, requiring repeat percutaneous access to the pericardial space.**

Methods and Results: **We studied 30 consecutive patients who required a repeat epicardial procedure. We specifically examined the success and safety of repeat percutaneous pericardial access as well as the ability to map and ablate epicardial VT targets. Percutaneous pericardial access at a median of 110 days after the last procedure was successful in all 30 patients. Significant adhesions interfering with catheter mapping were encountered in 7 patients (23%); 6 had received intrapericardial triamcinolone acetate (IPTA) with prior procedures. Using blunt dissection with a deflected ablation catheter and a steerable sheath, adhesions were divided allowing for complete catheter mapping in 5 patients with areas of dense adherence compartmentalizing the pericardium in 1 patient and precluding ablation over previously targeted ablation site in the second. Targeted VT noninducibility was achieved in 27 (90%) patients including 7 patients with adhesions. No direct complications related to pericardial access or adhesions disruption occurred. One periprocedural death occurred from refractory cardiogenic shock in patient with LV ejection fraction of 10%. Another patient developed asymptomatic positive *Haemophilus influenzae* pericardial fluid cultures identified at second procedure, which was successfully treated.**

Conclusions: **Repeat access can be obtained after prior epicardial ablation. Adhesions from prior procedures may limit mapping, but can usually be disrupted mechanically and allow for ablation of recurrent VT. IPTA may not completely prevent adhesions.** *(J Cardiovasc Electrophysiol, Vol. 23, pp. 744-749, July 2012)*

adhesions, catheter ablation, epicardial access, mapping, pericardium, ventricular tachycardia

Introduction

Catheter ablation is increasingly employed for both idiopathic and scar-related ventricular tachycardia (VT).[1] Typically, VT ablation targets for both focal and reentrant forms of VT are accessible from the right or left ventricular endocardium or the aortic sinuses of Valsalva.[2-4] However, for certain disease substrates, VT ablation targets are located on the epicardial surface of the ventricles, and accessing these targets requires a percutaneous, transpericardial approach. Epicardial VT mapping and ablation is increasingly utilized since it was first described by Sosa and colleagues in 1996.[5-11] The risks, benefits, and safety of *de novo* epicardial procedures for the treatment of different VT substrates have been described.[12,13] In some cases, repeat epicardial mapping and ablation may be needed, thus requiring a repeated percutaneous access to the pericardium in the same patient. The ability to safely obtain repeat access to the pericardial space, and the presence and clinical impact of pericardial adhesions noted at repeat epicardial procedures has not been previously described. The purpose of this study was to evaluate the safety and efficacy of repeat percutaneous pericardial access and mapping/ablation of recurrent epicardial VT.

Methods

Study Population

We examined consecutive patients undergoing epicardial VT mapping and ablation at the Hospital of the University of Pennsylvania from June 2002 to April 2011. All procedures were performed according to the institutional guidelines of the University of Pennsylvania Health System and all patients provided written informed consent. Patients requiring 2 or more percutaneous pericardial punctures for mapping and ablation of VT were included. Patients who had previous cardiac surgery were excluded from this analysis. The decision to move forward with an epicardial approach was based on (1) the VT morphology on the surface 12-lead ECG;[14,15] (2) the presence of epicardial substrate on imaging studies (computed tomography [CT], cardiovascular magnetic resonance [CMR], intracardiac echocardiography);[16] and/or (3)

Funding sources: Harlan Batrus Research Fund. Dr. Haqqani is the recipient of an Overseas Training Fellowship (544309) from the National Health and Medical Research Council of Australia and the Bayer Fellowship from the Royal Australasian College of Physicians.

Dr. Marchlinski has received research funding from Biosense Webster unrelated to this study. Other authors: No disclosures.

Address for correspondence: Francis E. Marchlinski, M.D., Cardiac Electrophysiology, Hospital of the University of Pennsylvania, 3400 Spruce Street, Founders 9, Philadelphia, PA 19104, USA. Fax: 215-662-2879; E-mail: francis.marchlinski@uphs.upenn.edu

Manuscript received 7 November 2011; Revised manuscript received 23 December 2011; Accepted for publication 5 January 2012.

doi: 10.1111/j.1540-8167.2011.02286.x

Percutaneous epicardial ventricular tachycardia ablation after noncoronary cardiac surgery or pericarditis

Cory M. Tschabrunn, CEPS, Haris M. Haqqani, MBBS, PhD, Joshua M. Cooper, MD, Sanjay Dixit, MD, FHRS, Fermin C. Garcia, MD, Edward P. Gerstenfeld, MD, FHRS, David J. Callans, MD, FHRS, Erica S. Zado, PA-C, FHRS, Francis E. Marchlinski, MD, FHRS

From the Cardiac Electrophysiology Program, Cardiovascular Medicine Division, Hospital of the University of Pennsylvania, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

BACKGROUND Patients with previous noncoronary cardiac surgery or pericarditis may require epicardial access to facilitate successful ventricular tachycardia (VT) ablation. Percutaneous pericardial access is known to be difficult in these patients owing to the presence of pericardial adhesions.

OBJECTIVE To examine the success and safety of percutaneous pericardial access as well as the ability to map and ablate epicardial VT targets.

METHODS We studied 10 consecutive patients with prior noncoronary cardiac surgery (8 patients) or prior pericarditis (2 patients) who required epicardial access for VT ablation.

RESULTS Percutaneous pericardial access was achieved by experienced operators, and dense adhesions interfering with catheter mapping were encountered in all patients. Using blunt dissection with a deflected ablation catheter, adhesions were divided over the course of 19–125 minutes (mean 57 ± 38 minutes; median 47 minutes). This dissection allowed for sufficient epicardial mapping in 9 of 10 (90%) patients. The clinical targeted VTs were rendered noninducible in 8 (80%) patients. One patient had 70 cm^3 of bleeding with the initial puncture. No other complications occurred. During a long-term follow-up of 24 ± 27 months (median 13 months), 5 patients have remained VT-free.

CONCLUSIONS Percutaneous pericardial access for epicardial VT ablation in patients with previous noncoronary cardiac surgery or pericarditis can usually be obtained. However, dense pericardial adhesions are often encountered and may limit the ability to map the entire epicardial space. Typically, appropriate targets can be reached and ablated by disrupting the adhesions with the ablation catheter and/or deflectable sheath, facilitating excellent long-term clinical outcome in half of the patients with no major complications.

KEYWORDS Epicardial access; Pericardium; Ventricular tachycardia; Adhesions; Mapping; Ablation; Pericarditis; Cardiac surgery

ABBREVIATIONS **AVR** = aortic valve replacement; **CHF** = congestive heart failure; **ECG** = electrocardiography; **LV** = left ventricle; **RV** = right ventricle; **VT** = ventricular tachycardia; **OHT** = orthotopic heart transplant

(Heart Rhythm 2013;10:165–169)

Introduction

Catheter ablation is increasingly employed as a treatment for both idiopathic and scar-related ventricular tachycardia (VT).[1] Typically, VT ablation targets for both focal and reentrant forms of VT are accessible from the right or left ventricular endocardium or the aortic sinuses of Valsalva.[2–4] In some instances however, VT ablation targets are located on the epicardial aspect of the ventricles and accessing these targets requires a percutaneous transpericardial approach. Epicardial VT mapping and ablation are increasingly utilized since Sosa and colleagues[5–9] first described it in 1996. The risks, benefits, and safety of de novo and repeat epicardial procedures for the treatment of different VT substrates have been described.[10–12] Patients with VT who have had prior cardiac surgery or pericarditis may require percutaneous epicardial mapping and ablation to successfully eliminate their arrhythmia. The ability to safely obtain access to the pericardial space and the presence and clinical impact of pericardial adhesions have not been previously described in these patients. The purpose of this study was to evaluate the safety and efficacy of percutaneous pericardial access and mapping/ablation in patients with prior noncoronary cardiac surgery or pericarditis.

This study was supported in part by F. Harlan Batrus Research Fund, Murray and Susan Bloom Research Fund, and the Mark Marchlinski Research Fund. Dr Haqqani is the recipient of an Overseas Training Fellowship (544309) from the National Health and Medical Research Council of Australia and the Bayer Fellowship from the Royal Australasian College of Physicians. Dr Marchlinski, Dr Haqqani, Dr Gerstenfeld, and Dr Dixit have received research funding from Biosense Webster unrelated to this study. **Address reprint requests and correspondence:** Francis E. Marchlinski, MD, Cardiac Electrophysiology Program, Hospital of the University of Pennsylvania, 3400 Spruce St, Founders 9, Philadelphia, PA 19104. E-mail address: francis.marchlinski@uphs.upenn.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2012.10.012

Appendix D

Chapter 4 Full Text Manuscripts

Chapter 4 – High Resolution Catheter and Mapping Technologies: Insight from Clinical Laboratory Investigations

Anter E, **Tschabrunn CM**, Josephson ME. High-resolution Mapping of Scar-related Atrial Arrhythmias Using Smaller Electrodes with Closer Interelectrode Spacing. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

Anter E, Li J, **Tschabrunn CM**, Nezafat R, Josephson ME. Mapping of a Post-infarction Left Ventricular Aneurysm-Dependent Macroreentrant Ventricular Tachycardia. Heart Rhythm Case Rep. 2015 Nov 1;1(6):472-6.

Original Article

High-Resolution Mapping of Scar-Related Atrial Arrhythmias Using Smaller Electrodes With Closer Interelectrode Spacing

Elad Anter, MD; Cory M. Tschabrunn, CEPS; Mark E. Josephson, MD

Background—The resolution of mapping is influenced by electrode size and interelectrode spacing. Smaller electrodes with closer interelectrode spacing may improve mapping resolution, particularly in scar. The aims of this study were to establish normal electrogram criteria in the atria for both 3.5-mm electrode tip linear catheters (Thermocool) and 1-mm multielectrode-mapping catheters (Pentaray) and to compare their mapping resolution in scar-related atrial arrhythmias.

Methods and Results—Normal voltage amplitude cutoffs for both catheters were validated in 10 patients with structurally normal atria. In 20 additional patients with scar-related atrial arrhythmias, similar sequential mapping with both catheters was performed. Normal bipolar voltage amplitude was similar between 3.5- and 1-mm electrode catheters with a fifth percentile of 0.48 and 0.52 mV, respectively (P=0.65). In patients with scar-related atrial arrhythmias, the total area of bipolar voltage <0.5 mV measured using 1-mm electrode catheters was smaller than that measured using 3.5-mm catheter (14.7 versus 20.4 cm2; P=0.02). The mean bipolar voltage amplitude in this area of low voltage was significantly higher with 1-mm electrode catheters (0.28 and 0.17 mV; P=0.01). Importantly, 54.4% of all low voltage data points recorded with 1-mm electrode catheter had distinct electrograms that allowed annotation of local activation time compared with only 21.4% with 3.5-mm electrode tip catheters (P=0.01). Overdrive pacing with capture of the tachycardia from within the area of low voltage was more frequent with 1-mm electrode catheters (66.7 versus 33.4; P=0.01).

Conclusions—Mapping with small closely spaced electrode catheters can improve mapping resolution within areas of low voltage. **(*Circ Arrhythm Electrophysiol*. 2015;8:537-545. DOI: 10.1161/CIRCEP.114.002737.)**

Key Words: arrhythmias, cardiac ■ catheter ablation ■ electrophysiology

Atrial fibrillation (AF) ablation is an acceptable therapeutic option for patients with symptomatic AF refractory to medications.[1] Pulmonary vein isolation is the cornerstone of the procedure and is associated with a reasonable clinical outcome in patients with paroxysmal AF. However, in patients with persistent AF, pulmonary vein isolation is less effective and additional substrate ablation is frequently performed.[2,3] This approach often results in the development of postablation, scar-related, organized atrial tachyarrhythmias (AT).[4–6]

The mechanism of these arrhythmias is usually re-entry involving pre-existing or iatrogenic ablation–related scar tissue.[7,8] These circuits are typically challenging to map because of significant scar coupled with fractionated and multicomponent electrograms, limiting local time annotation. In addition, entrainment and postpacing interval mapping techniques may be difficult to perform and interpret because of high output pacing and lack of capture in these areas of low voltage.

The standard catheter for mapping these arrhythmias is a linear catheter with a 3.5-mm distal electrode separated by 2 mm from a proximal 2-mm electrode, resulting in a center-to-center interelectrode spacing of 4.75 mm. As such, each bipolar electrogram represents an underlying tissue diameter ranging from 3.5 to 7.5 mm, depending on the angle of incidence (from perpendicular to parallel to the tissue, respectively). Catheters with 1-mm electrodes, 2-mm interelectrode spacing, and 3-mm center-to-center interelectrode spacing record electrograms from a significantly smaller underlying tissue diameter, ranging from 1 to 4.0 mm (also dependent on catheter orientation relative to the surface). These catheters may have advantages for mapping scar-related arrhythmias, including (1) higher mapping resolution that can identify heterogeneity within the area of low voltage, localizing channels of surviving bundles; (2) smaller electrodes with closer interelectrode spacing are subjected to less signal averaging and cancellation effects, and may thus record higher bipolar voltage amplitude with shorter electrogram duration, allowing more accurate time annotation; (3) pacing with capture at lower output because of increased electric density.

The aims of this study were to (1) establish normal voltage amplitude cutoffs in the atria for both 3.5-mm electrode tip catheters and 1-mm multielectrode-mapping catheters;

Received November 19, 2014; accepted March 2, 2015.

From the Cardiovascular Division, Department of Medicine, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA.

Correspondence to Elad Anter, MD, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Baker 4, Boston, MA 02215. E-mail eanter@bidmc.harvard.edu

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.114.002737**

Mapping of a postinfarction left ventricular aneurysm–dependent macroreentrant ventricular tachycardia

Elad Anter, MD,[*†] Jianqing Li, MD,[*†] Cory M. Tschabrunn, CEPS,[*†] Reza Nezafat, PhD,[†] Mark E. Josephson, MD[*†]

From the [*]Harvard-Thorndike Electrophysiology Institute, and [†]Cardiovascular Division, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

Introduction

Activation mapping of ventricular tachycardia (VT) is rarely accomplished owing to limited temporal and spatial resolution, unacceptably long mapping time, and hemodynamic instability.[1] Entrainment mapping is a reasonable approach to identify targets for ablation in patients with tolerated postinfarction reentrant VTs; however, it often does not allow delineation of the entire VT circuit.[2,3] Introduction of newer mapping technologies capable of rapid and high-resolution electroanatomic mapping may allow detailed activation mapping of macroreentrant VTs, enhancing our understanding of macroreentrant circuit geometry and electrophysiology to facilitate ablation.[4]

Case report

We present the case of a 77-year-old man transferred to our institution for the management of recurrent monomorphic VT. The patient has a history of hypertension, hypercholesterolemia, diabetes, and multivessel coronary artery disease with prior inferior myocardial infarction. The baseline sinus 12-lead electrocardiogram (ECG) is shown in Figure 1A. Six weeks earlier, he underwent coronary artery bypass graft surgery. At the time of surgery, a thin-walled large aneurysm at the base of the inferior wall was identified and a pericardial patch was placed over it. The aneurysm contained thin fibrous, noncontractile material that was associated with dyskinetic wall motion abnormality, consistent with a contained ruptured wall from his old transmural myocardial infarction. A cardiac magnetic resonance of the left ventricle (LV) including the basal inferior aneurysm is depicted in Supplemental Figure 1 (available online).

The patient recovered well from surgery with only mild congestive heart failure symptoms (New York Heart Association class I–II) and a left ventricular ejection fraction of 35%–40%, as was shown on transthoracic echocardiography 1 month after surgery. However, he developed frequent and recurrent episodes of sustained monomorphic VT requiring external shocks due to hemodynamic instability. He failed therapy with antiarrhythmic drugs including amiodarone, quinidine, and mexiletine. The 12-lead ECG of the clinical VT is shown in Figure 1B. The VT cycle length was 360 milliseconds and it had a left bundle branch block pattern with left superior axis, suggestive of a basal inferior wall exit.

In an attempt to obtain detailed mapping of the VT circuit with as short as possible mapping duration, we elected to use the Rhythmia mapping system with its proprietary Orion mini-basket catheter (Boston Scientific, Cambridge, MA).[4] The mini-basket consists of 8 splines, each containing 8 very small electrodes of 0.4 mm^2 that are separated by 2.5 mm from center to center, and with an overall extended basket diameter of 18 mm.[5] Activation mapping is automated and is determined based on the combination of the bipolar and unipolar electrograms and timed at the maximal (−) dV/dt of the local unipolar electrogram.

A pentapolar catheter was placed in the right ventricular apex (RVA) with its proximal electrode in the inferior vena cava serving as an indifferent unipolar electrode. An intracardiac ultrasound catheter was placed at the base of the right ventricle in order to visualize the LV and confirm tissue contact of the mini-basket catheter. Heparin was administered to maintain an activated clotting time of 300–350 seconds for the duration of the procedure. The 8F mini-basket bidirectional catheter was introduced into the LV using a retrograde transaortic approach. The mini-basket catheter was placed in the aneurysm and the clinical VT was induced with single extrastimuli from the RVA. Pacing from the RVA during VT showed ECG fusion, consistent with a reentrant mechanism. The entire reentrant circuit was

KEYWORDS Myocardial infarction; Ventricular aneurysm; Ventricular tachycardia; Mapping; Radiofrequency ablation

ABBREVIATIONS **ECG** = electrocardiogram; **LV** = left ventricle; **RVA** = right ventricular apex; **VT** = ventricular tachycardia

(Heart Rhythm Case Reports 2015;1:472–476)

Elad Anter receives research grants from Biosense Webster and Boston Scientific. Mark Josephson receives research grants and speaking honoraria from Medtronic. **Address reprint requests and correspondence:** Elad Anter, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Baker 4, Boston, MA 02215. E-mail address: eanter@bidmc.harvard.edu.

http://dx.doi.org/10.1016/j.hrcr.2015.07.011

Appendix E

Chapter 5 Full Text Manuscripts

Chapter 5 – High Resolution Mapping of Ventricular Scar: Insight from Experimental Laboratory Investigations

Tschabrunn CM, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Swine Model of Infarct-related Reentrant Ventricular Tachycardia: Electroanatomic, Magnetic Resonance, and Histopathologic Characterization. Heart Rhythm. 2016 Jan;13(1):262-73.

Tschabrunn CM, Roujol S, Dorman NC, Nezafat R, Josephson ME, Anter E. High-Resolution Mapping of Ventricular Scar: Comparison Between Single and Multielectrode Catheters. Circ Arrhythm Electrophysiol. 2016 Jun;9(6).

A swine model of infarct-related reentrant ventricular tachycardia: Electroanatomic, magnetic resonance, and histopathological characterization

Cory M. Tschabrunn, CEPS,[*] Sébastien Roujol, PhD,[†] Reza Nezafat, PhD,[†] Beverly Faulkner-Jones, MD, PhD,[‡] Alfred E. Buxton, MD,[*] Mark E. Josephson, MD,[*] Elad Anter, MD[*]

From the [*]Harvard-Thorndike Electrophysiology Institute, Cardiovascular Division, Department of Medicine, [†]Cardiovascular Division, Department of Medicine, and [‡]Surgical Pathology Division, Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts.

BACKGROUND Human ventricular tachycardia (VT) after myocardial infarction usually occurs because of subendocardial reentrant circuits originating in scar tissue that borders surviving myocardial bundles. Several preclinical large animal models have been used to further study postinfarct reentrant VT, but with varied experimental methodologies and limited evaluation of the underlying substrate or induced arrhythmia mechanism.

OBJECTIVE We aimed to develop and characterize a swine model of scar-related reentrant VT.

METHODS Thirty-five Yorkshire swine underwent 180-minute occlusion of the left anterior descending coronary artery. Thirty-one animals (89%) survived the 6–8-week survival period. These animals underwent cardiac magnetic resonance imaging followed by electrophysiology study, detailed electroanatomic mapping, and histopathological analysis.

RESULTS Left ventricular (LV) ejection fraction measured using CMR imaging was 36% ± 6.6% with anteroseptal wall motion abnormality and late gadolinium enhancement across 12.5% ± 4.1% of the LV surface area. Low voltage measured using endocardial electroanatomic mapping encompassed 11.1% ± 3.5% of the LV surface area (bipolar voltage ≤1.5 mV) with anterior, anteroseptal, and anterolateral involvement. Reentrant circuits mapped were largely determined by functional rather than fix anatomical barriers, consistent with "pseudo-block" due to anisotropic conduction. Sustained monomorphic VT was induced in 28 of 31 swine (90%) (67 VTs; 2.4 ± 1.1; range 1–4) and characterized as reentry. VT circuits were subendocardial, with an arrhythmogenic substrate characterized by transmural anterior scar with varying degrees of fibrosis and myocardial fiber disarray on the septal and lateral borders.

CONCLUSION This is a well-characterized swine model of scar-related subendocardial reentrant VT. This model can serve as the basis for further investigation in the physiology and therapeutics of humanlike postinfarction reentrant VT.

KEYWORDS Myocardial infarction; Mapping; Ventricular tachycardia; Ablation

ABBREVIATIONS **CMR** = cardiac magnetic resonance; **EAM** = electroanatomic mapping; **ECG** = electrocardiogram/electrocardiographic; **EGM** = electrogram; **ILP** = isolated late potential; **LAD** = left anterior descending; **LV** = left ventricle/ventricular; **MI** = myocardial infarction; **MTS** = Masson trichrome stain; **RV** = right ventricle/ventricular; **TCL** = tachycardia cycle length; **VT** = ventricular tachycardia

(Heart Rhythm 2016;13:262–273)

Introduction

The pathophysiology of infarct-related ventricular tachycardia (VT) includes structural remodeling that occurs after myocardial cell death, resulting in inhomogeneous scarring with varying degrees of survived myocardial tissue contiguous with dense fibrosis, forming the so-called arrhythmogenic substrate.[1]

This arrhythmogenic substrate is characterized by zones of slow conduction due to nonuniform anisotropy resulting in fixed and/or functional regions of conduction block. This facilitates reentry as it generates enough time for tissue in the circuit to recover its excitability to allow the excitation

Biosense Webster and Boston Scientific provided partial funding for this study in the form of an investigator-initiated study. This study was also partially funded by the National Institutes of Health (grant no. 1R21HL127650-01). Dr Anter receives research grants and speaking honoraria from Biosense Webster and Boston Scientific. Dr Buxton receives research grants from Biosense Webster and Medtronic. Dr Josephson receives speaking honoraria from Medtronic. Mr Tschabrunn receives research grants from Biosense Webster. **Address reprint requests and correspondence:** Dr Elad Anter, Cardiovascular Division, Department of Medicine, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Baker 4, Boston, MA 02215. E-mail address: eanter@bidmc.harvard.edu.

1547-5271/$-see front matter http://dx.doi.org/10.1016/j.hrthm.2015.07.030

Original Article

High-Resolution Mapping of Ventricular Scar
Comparison Between Single and Multielectrode Catheters

Cory M. Tschabrunn, CEPS; Sebastien Roujol, PhD; Nicole C. Dorman, BSc; Reza Nezafat, PhD; Mark E. Josephson, MD; Elad Anter, MD

Background—Mapping resolution is influenced by electrode size and interelectrode spacing. The aims of this study were to establish normal electrogram criteria for 1-mm multielectrode-mapping catheters (Pentaray) in the ventricle and to compare its mapping resolution within scar to standard 3.5-mm catheters (Smart-Touch Thermocool).

Methods and Results—Three healthy swine and 11 swine with healed myocardial infarction underwent sequential mapping of the left ventricle with both catheters. Bipolar voltage amplitude in healthy tissue was similar between 3.5- and 1-mm multielectrode catheters with a 5th percentile of 1.61 and 1.48 mV, respectively. In swine with healed infarction, the total area of low bipolar voltage amplitude (defined as <1.5 mV) was 22.5% smaller using 1-mm multielectrode catheters (21.7 versus 28.0 cm2; *P*=0.003). This was more evident in the area of dense scar (bipolar amplitude <0.5 mV) with a 47% smaller very low–voltage area identified using 1-mm electrode catheters (7.1 versus 15.2 cm^2; *P*=0.003). In this region, 1-mm multielectrode catheters recorded higher voltage amplitude (0.72±0.81 mV versus 0.30±0.12 mV; *P*<0.001). Importantly, 27% of these dense scar electrograms showed distinct triphasic electrograms when mapped using a 1-mm multielectrode catheter compared with fractionated multicomponent electrogram recorded with the 3.5-mm electrode catheter. In 8 mapped reentrant ventricular tachycardias, the circuits included regions of preserved myocardial tissue channels identified with 1-mm multielectrode catheters but not 3.5-mm electrode catheters. Pacing threshold within the area of low voltage was lower with 1-mm electrode catheters (0.9±1.3 mV versus 3.8±3.7 mV; *P*=0.001).

Conclusions—Mapping with small closely spaced electrode catheters can improve mapping resolution within areas of low voltage. **(*Circ Arrhythm Electrophysiol*. 2016;9:e003841. DOI: 10.1161/CIRCEP.115.003841.)**

Key Words: electrodes ■ heart ■ myocardial infarction ■ swine ■ ventricular tachycardia

The pathophysiology of infarct-related reentrant ventricular tachycardia (VT) includes myocardial cell death and ventricular remodeling, resulting in inhomogeneous scarring with variable degrees and configurations of surviving myocardial bundles within the areas of fibrosis. This provides the necessary electrophysiological substrate for formation of reentrant VTs that are predominantly located in the subendocardium.[1,2]

See Editorial by Tung and Ellenbogen

Standard mapping catheters have several limitations for mapping scar-related VTs. These catheters have a 3.5-mm distal tip electrode that is separated by 1 mm from a proximal 1-mm electrode, resulting in a center-to-center interelectrode spacing of 3.25 mm. As such, each bipolar electrogram represents recording from an underlying tissue diameter ranging from 3.5 to 5.5 mm, depending on the angle of the catheter (from perpendicular to parallel to the tissue, respectively). This mapping resolution may not be adequate to identify surviving myocardial bundles (including isthmuses) within the area of low voltage because there may be cancellation effects of bipolar electrograms recorded within these areas.[3] In addition, electrograms recorded using these relatively large electrode catheters often record long, fractionated, and multicomponent signals because of the underlying pattern of activation. The presence of such fractioned electrograms limits accurate annotation of local activation time during activation mapping and interpretation of entrainment mapping.

Catheters with 1-mm electrodes, 2-mm interelectrode spacing, and an overall 3-mm center-to-center interelectrode spacing record electrograms from a significantly smaller underlying tissue area, ranging from 1 to 4 mm. This design offers several advantages for mapping scar-related arrhythmias, including (1) higher mapping resolution that may identify heterogeneity within the area of low voltage during sinus rhythm mapping allowing localizing channels of surviving myocardial bundles; (2) smaller electrodes with closer

Received December 11, 2015; accepted April 20, 2016.

From the Harvard-Thorndike Electrophysiology Institute (C.M.T., M.E.J., E.A.) and Cardiovascular Division, Department of Medicine (C.M.T., S.R., R.N., M.E.J., E.A.), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; and Biosense Webster, Johnson & Johnson, Diamond Bar, CA (N.C.D.).

The Data Supplement is available at http://circep.ahajournals.org/lookup/suppl/doi:10.1161/CIRCEP.115.003841/-/DC1.

Correspondence to Elad Anter, MD, Harvard-Thorndike Electrophysiology Institute, Beth Israel Deaconess Medical Center, 185 Pilgrim Rd, Baker 4, Boston, MA 02215. E-mail eanter@bidmc.harvard.edu

Appendix F

Abbreviated Curriculum Vitae

Current Hospital/Academic Appointment

9/2012 – Present	Technical Director, Experimental Electrophysiology Harvard-Thorndike Electrophysiology Institute Beth Israel Deaconess Medical Center Harvard Medical School – Boston, Massachusetts

Prior Hospital/Academic Appointments

6/2002 – 10/2006	Research Assistant, Cardiovascular Medicine Southside Hospital – North Shore LIJ Health System Bay Shore, New York
10/2006 – 8/2009	Senior Research Analyst, Cardiac Electrophysiology Stony Brook University Medical Center Stony Brook, New York
8/2009 – 9/2012	Research Assistant, Clinical Electrophysiology Hospital of the University of Pennsylvania Philadelphia, Pennsylvania

Report of Scholarship

Peer Reviewed Manuscripts

1. Stephenson K, **Tschabrunn CM**, Vasu S, Rashba EJ. When, How, and Why Should Sinus Rhythm Be Restored in Patients with Persistent Atrial Fibrillation. Current Treatment Options in Cardiovascular Medicine 2007, 9: 372-378.

2. Van Herendael H, Garcia F, Lin D, Riley M, Bala R, Cooper J, Tzou W, Hutchinson MD, Verdino R, Gerstenfeld EP, Dixit S, Callans DJ, **Tschabrunn CM**, Zado ES, Marchlinski FE. Idiopathic Right Ventricular Arrhythmias not Arising from the Outflow Tract: Prevalence, Electrocardiographic Characteristics and Outcome of Catheter Ablation. Heart Rhythm. 2011 Apr8(4):511-8.

3. Haqqani HM, **Tschabrunn CM,** Tzou WS, Dixit S, Cooper JM, Riley MP, Lin D, Hutchinson MD, Garcia FC, Bala R, Verdino RJ, Callans DJ, Gerstenfeld EP, Zado ES, Marchlinski FE. Isolated Septal Substrate for Ventricular Tachycardia in Nonischemic Dilated Cardiomyopathy: Incidence, Characterization and Implications. Heart Rhythm. 2011 Aug8(8);1169-76.

4. Bala R. Ren JF, Hutchinson MD, Desjardins B, **Tschabrunn CM**, Gerstenfeld EP, Deo R, Dixit S, Garcia FC, Cooper J, Lin D, Riley MP, Tzou WS, Verdino R, Epstein A, Callans DJ, Marchlinski FE. Assessing Epicardial Substrate Using Intracardiac Echocardiography During VT Ablation. Circ Arrhythm Electrophysiol.. 2011 Oct;4(5):667-73.

5. **Tschabrunn CM,** Rosenbach M, Lavi N, Cooper JM. Allergic Reaction to Suture Material after an ICD Procedure: Device Infection Mimicry. J Cardiovasc Electrophysiol. 2012 Mar;23(3):330-2.

6. Park RE, Saghy L, Zado E, **Tschabrunn CM,** Marchlinski FE. Influence of Left Ventricular Hypertrophy on Scar Identification During Bipolar Voltage Mapping. J Interv Card Electrophysiol. 2012 Jun;34(1):45-50.

7. Elkassabany N, Garcia F, **Tschabrunn CM**, Raiten J, Gao W, Chaichana K, Dixit S, Speck RM, Zado E, Marchlinski F, Mandel J. Anesthic Management of Patients Undergoing Pulmonary Vein Isolation for Treatment of Atrial Fibrillation Using High Frequent Jet Ventilation. J Cardiothorac Vasc Anesth. 2012 Junl26(3):433-8.

8. Abularach ME, Campos B, Park KM, **Tschabrunn CM**, Frankel DS, Park RE, Gerstenfeld EP, Mountantonakis S, Garcia FC, Dixit S, Tzou WS, Hutchinson MD, Lin D, Riley MP, Cooper JM, Bala R, Callans DJ, Marchlinski FE. Ablation of Ventricular Arrhythmias Arising Near the Anterior Epicardial Veins from the Left Sinus of Valsalva Region: ECG Features, Anatomic Distance and Outcome. Heart Rhythm. 2012 Jun;9(6):865-73.

9. Betensky BP, **Tschabrunn CM**, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC, Cooper JM. Long Term Follow-up of patients with cardiac sarcoidosis and implantable cardiverter-defibrillators. Heart Rhythm. 2012 Jun;9(6): 884-91.

10. **Tschabrunn CM**, Haqqani HM, Zado ES, Marchlinski FE. Repeat Percutaneous Epicardial Mapping and Ablation of Ventricular Tachycardia: Safety and Outcome. J Cardiovasc Electrophysiol. 2012 Jul;23(7): 744-9.

11. Haqqani HM, **Tschabrunn CM,** Betensky BP, Lavi N, Tzou WS, Zado ES, Marchlinski FE. Layered Activation of Epicardial Scar in Arrhythmogenic Right Ventricular Dysplasia: Possible Substrate for Confined Epicardial Circuits. Circ Arrhythm Electrophysiol. 2012 Aug 1;5(4):796-803.

12. **Tschabrunn CM**, Haqqani HH, Cooper JM, Dixit S, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Percutaneous Epicardial Ventricular Tachycardia Ablation After Non-Coronary Cardiac Surgery or Pericarditis. Heart Rhythm. 2013 Feb;10(2):165-9.

13. **Tschabrunn CM**, Anter E, Marchlinski FE. Identifying Non-inducible Ventricular Tachycardia Origin Utilizing Defibrillator Electrograms. J Interv Card Electrophysiol. 2013 Apr;36(3):243-6.

14. Frankel DS, **Tschabrunn CM**, Cooper JM, Dixit S, Gerstenfeld EP, Riley MP, Callans DJ, Marchlinski FE. Apical Ventricular Tachycardia Morphology in Left Ventricular Non-Ischemic Cardiomyopathy Predicts Poor Transplant Free Survival. Heart Rhythm. 2013 May;10(5): 621-6.

15. Mountantonakis SE, **Tschabrunn CM,** Deyell MW, Cooper JM. Same-day contralateral implantation of a permanent device after lead extraction for isolated pocket infection. Europace. 2014 Feb;16(2):252-7.

16. Anter E, Contreras-Valdes FM, Shvilkin A, **Tschabrunn CM**, Josephson ME. Acute pulmonary vein reconnection is a predictor of atrial fibrillation recurrence following pulmonary vein isolation. J Interv Card Electrophysiol. 2014 Apr;39(3):225-32.

17. Anter E, **Tschabrunn CM,** Contreras-Valdes FM, Buxton AE, Josephson ME. Radiofrequency Ablation Annotation Algorithm Reduces the Incidence of Linear Gaps and Reconnection Following Pulmonary Vein Isolation: Ablation annotation algorithm to improve electrical contiguity during PVI. Heart Rhythm. 2014 May;11(5):783-90.

18. Van Herendael H, Zado ES, Haqqani H, **Tschabrunn CM**, Callans DJ, Frankel DS, Lin D, Garcia F, Hutchinson MD, Riley M, Bala R, Dixit S, Yadava M, Marchlinski FE. Catheter ablation of ventricular fibrillation: importance of left ventricular outflow tract and papillary muscle triggers. Heart Rhythm. 2014 Apr;11(4):566-73.

19. Anter E, Silverstein J, **Tschabrunn CM**, Shvilkin A, Haffajee CI, Zimetbaum PJ, Buxton AE, Josephson ME, Gelfand E, Manning WJ. Comparison of intracardiac echocardiography and transesophageal echocardiography for imaging of the right and left atrial appendages. Heart Rhythm. 2014 Nov;11(11):1890-7.

20. **Tschabrunn CM,** Marchlinski FE. Ventricular tachycardia mapping and ablation in arrhythmogenic right ventricular cardiomyopathy/dysplasia: lessons learned. World J Cardiology. 2014 Sept 26;6(9):959-67.

21. Weingärtner S, Akçakaya M, Roujol S, Basha T, **Tschabrunn C**, Berg S, Anter E, Nezafat R. Free-breathing combined three-dimensional phase sensitive late gadolinium enhancement and T1 mapping for myocardial tissue characterization. Magn Reson Med. 2015 Oct;74(4):1032-41.

22. Mountantonakis SE, Frankel DS, **Tschabrunn CM**, Hutchinson MD, Riley MP, Lin D, Bala R, Garcia FC, Dixit S, Callans DJ, Zado ES, Marchlinski FE. Ventricular arrhythmias from the coronary venous system: prevalence, mapping, and ablation. Heart Rhythm. 2015 Jun;12(6):1145-53.

23. **Tschabrunn CM**, Silverstein J, Berzin T, Ellis E, Buxton AE, Josephson ME, Anter E. Comparison between single and multi-sensor esophageal temperature probes during atrial fibrillation ablation: thermodynamic characteristics. Europace. 2015 Jun;17(6):891-7.

24. Anter E, **Tschabrunn CM**, Josephson ME. High-resolution mapping of scar-related atrial arrhythmia using smaller electrodes with closer interelectrode spacing. Circ Arrhythm Electrophysiol. 2015 Jun;8(3):537-45.

25. Anter E, **Tschabrunn CM**, Contreras-Valdes FM, Li J, Josephson ME. Pulmonary vein isolation using the Rhythmia mapping system: verification of intracardiac signals using the Orion mini-basket catheter. Heart Rhythm. 2015 Sep;12(9):1927-34.

26. **Tschabrunn CM**, Roujol S, Nezafat R, Faulkner-Jones B, Buxton AE, Josephson ME, Anter E. Swine model of infarct-related reentrant ventricular tachycardia: electroanatomic, magnetic resonance, and histopathologic characterization. Heart Rhythm. 2016 Jan;13(1):262-73.

27. Hsu BB, Conway W, **Tschabrunn CM**, Mehta M, Perez-Cuevas M, Zhang S, Hammond PT. Clotting mimicry from robust hemostatic bandages based on self-assembling peptides. ACS Nano. 2015 Sep 22;9(9):9394-406.

28. Anter E, Li J, **Tschabrunn CM**, Nezafat R, Josephson ME. Mapping of a post-infarction left ventricular aneurysm-dependent macroreentrant ventricular tachycardia. Heart Rhythm Case Rep. 2015 Nov1;1(6):472-6.

29. Santangeli P, Zado ES, Supple G, Haqqani HM, Garcia FC, **Tschabrunn C**, Callans DJ, Lin D, Dixit S, Hutchinson MD, Riley M, Marchlinski FE. Long-term outcome with catheter ablation of ventricular tachycardia in patients with arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythm Electrophysiol. 2015. Dec;8(6):1413-21.

30. Wolbrom DH, Rahman A, **Tschabrunn CM**. Mechanisms and Clinical Management of Ventricular Arrhythmias Following Blunt Chest Trauma. Cardiol Res Pract. 2016 16:7270247.

31. Loschak PM, Degirmenci A, Tenzer Y, **Tschabrunn CM**, Anter E, Howe RD. A 4-DOF Robot for Positioning Ultrasound Imaging Catheters. Journal of Mechanisms and Robotics. 2016Oct;8(5):0510161-510169.

32. **Tschabrunn CM**, Roujol S, Dorman N, Nezafat R, Josephson ME, Anter E. High-Resolution Mapping of Ventricular Scar: Comparison Between 3.5mm and 1mm Electrode Catheters. Circ Arrhythm Electrophysiol. 2016 Jun;9(6). [Epub – Ahead of Print].

33. Anter E, **Tschabrunn CM**, Buxton A, Josephson ME. High-Resolution Mapping of Post-Infarction Reentrant Ventricular Tachycardia: Electrophysiological Characterization of the Circuit. Circulation. 2016 [Accepted – In Press].

Manuscripts Under Review/Revision

1. **Tschabrunn CM**, Haqqani HM, Santangeli P, Zado ES, Marchlinski FE. 12 Lead ECG to Localize Region of Abnormal Electroanatomic Substrate in Arrhythmogenic Right Ventricular Cardiomyopathy. [Submitted – In Review – J Am Coll Cardiol.]

2. Basha T, Tang M, Tsao C, **Tschabrunn CM**, Anter E, Manning W, Nezafat R. Dark Blood Late Gadolinium Enhancement (DB-LGE) Using a Joint T2 Magnetization Preparation and Inversion Protocol. [Submitted – In Review – Radiology.]

Book Chapters

1. Almasry I, **Tschabrunn CM**. Antiarrhythmic Electrophysiology and Pharmacotherapry. Cardiac Intensive Care Second Edition. Saunders Elsevier, Philadelphia PA. 2010 Mar;2(40):488-503 ISBN: 9781416037736.

2. **Tschabrunn CM,** Haqqani HM, Marchlinski FE. Ablation of Ventricular Tachycardia in Patients with Arrhythmogenic Right Ventricular Dysplasia. Ventricular Tachycardia Ablation: A Practical Guide. Cardiotext Publishing, Minneapolis MN. 2014;1(38):425-38 ISBN 9781935395751.

3. **Tschabrunn CM,** Josephson ME. Myocardial Infarction in the Presence of Left Bundle Branch Block and Right Ventricular Pacing. ECG Handbook of Contemporary Challenges. Cardiotext Publishing, Minneapolis MN. 2015;1(13):171-8 ISBN 9781935395881.

Published Abstracts (Prior 5 Years)

1. Haqqani HM, **Tschabrunn CM**, Zado E, Marchlinski FM. Nonischemic Cardiomyopathy Patients With Predominant Septal Substrate: Incidence, Characterization and Implications. Heart Rhythm Society 2010 Poster.

2. Haqqani HM, **Tschabrunn CM**, Zado E, Marchlinski FM. Ventricular Tachycardia Aarising From Nonischemic Septal Scar: Comparison with Septal Right Ventricular Outflow Tract VT. Heart Rhythm Society 2010

3. Elkassabany N, Gao W, Speck RM, **Tschabrunn CM**, Marchlinski FE, Mandell JE. Use of High-Frequency Jet Ventilation in Radiofrequency Ablation Treatment of Patients with Atrial Fibrillation. American Society of Anesthesiology 2010.

4. Campos B, Jauregui ME, Gerstenfeld EP, Park Kyoung-Min, Dallaglio P, Dixit S, Bala R, Hutchinson MD, Lin D, Epstein AE, Callans DJ, Cooper JM, Riley MP, **Tschabrunn CM**, Marchlinski FE, Garcia FC. Electrocardiographic Features of PVC Ablation From the Right Coronary Cusp. Heart Rhythm Society 2011 Poster.

5. Garcia FC, Zado ES, Elkassabany N, Callans D, Anastasio N, Gerstenfeld EP, Lin D, Dixit S, Hutchinson M, Tzou W, Bala R, Haqqani HM, Rile M, Cooper JM, **Tschabrunn CM**, Mandel J, Marchlinski FE. Techniques for Improving Catheter Stability during Atrial Fibrillation Ablation: the Importance of JET Ventilation. Heart Rhythm Society 2011 Poster.

6. Garcia FC, Zado ES, Elkassabany N, Callans D, Anastasio N, Gerstenfeld EP, Lin D, Dixit S, Hutchinson M, Tzou W, Bala R, Haqqani HM, Rile M, Cooper JM, **Tschabrunn CM**, Mandel J, Marchlinski FE. Improving Catheter Stability during Atrial Fibrillation Ablation: the Importance of JET Ventilation on Clinical Outcome and Chronic PV Reconnection. Heart Rhythm Society 2011 Poster.

7. Mountantonakis SE, **Tschabrunn CM,** Jauregui ME, Hutchinson MD, Riley MP, Lin D, Garcia FC, Gerstenfeld EP, Callans DJ, Zado ES, Marchlinski FE. Ventricular Premature Depolarizations Arising from the Epicardial Venous Anatomy: Prevalence, Mapping and Ablation. Heart Rhythm Society 2011 Poster.

8. Betensky BP, **Tschabrunn CM,** Zado ES, Goldberg LR, Marchlinski FE, Cooper JM. Long-Term Follow-Up of Patients with Cardiac Sarcoidosis and Implantable Cardioverter-Defibrillators. Heart Rhythm Society 2011 Poster.

9. Haqqani HM, **Tschabrunn CM,** Zado ES, Marchlinski FE. Endocardial and Epicardial Scar Pattern Predicts Electrocardigraphic Changes in Arrhythmogenic Right Ventriular Dysplasia. Heart Rhythm Society 2011 Poster.

10. Haqqani HM, **Tschabrunn CM**, Zado ES, Marchlinski FE. Lack of Direct Transmural Activation to Epicardial Scar in ARVD: Substrate for Confined Epicardial Circuit? Heart Rhythm Society 2011 Oral Presentation.

11. **Tschabrunn CM,** Rosenbach M, Lavi N, Cooper JM. Allergy to Suture Material Can Mimic an ICD Wound Infection. Heart Rhythm Society 2011 Poster.

12. Cooper JM, **Tschabrunn C,** Deyell M, Mountantonakis S. Same-Day Contralateral Implantation of a Permanent Device after Extraction for Local Infection. Dead Sea Symposium 2012.

13. Cooper JM, **Tschabrunn C,** Anter E. Salvage of Focally Infected ICD System by In-Situ Hardware Sterilization. Dead Sea Symposium 2012.

14. **Tschabrunn CM**, Haqqani HM, Mountantonakis S, Anter E, Zado ES, Marchlinski FE. Utility of High Frequency JET Ventilation During WPW Ablation. Heart Rhythm Society 2011 Oral Presentation.

15. Rivera J, **Tschabrunn CM**, Zado ES, Marchlinski FE. Incidental Findings Found During Routine Pre-procedure Imaging Requiring Cancellation of AF Ablation Procedure. Heart Rhythm Society 2012 Poster Abstract.

16. **Tschabrunn CM**, Anter E, Marchlinski FE. Utilizing ICD Electrocardiograms to Narrow 12 lead ECG Pacemap Target and Ablate Non-inducible VT. Heart Rhythm Society 2012 Oral Presentation.

17. **Tschabrunn CM**, Haqqani HM, Lorine AM, Cooper JM, Garcia FC, Dixit S, Zado ES, Callans DJ, Marchlinski FE. Percutaneous Pericardial Access in Patients with Prior Cardiac Surgery or Pericarditis. Heart Rhythm Society 2012 Oral Presentation.

18. **Tschabrunn CM**, Deyell MW, Callans DJ. A Unique Origin of VT in a Patient with Tetralogy of Fallot Repair. Heart Rhythm Society 2012 Oral Presentation.

19. Park KM, **Tschabrunn CM**, Marchlinski FE. Novel Pacing Method to Predict Idiopathic VPD-Induced Cardiomyopathy. Heart Rhythm Society 2012 Featured Poster.

20. Park KM, **Tschabrunn CM**, Marchlinski FE. ECG Characteristics Magnify the Presence of Occult Myocardial Disease in Patients with VPD-Induced Cardiomyopathy. Heart Rhythm Society 2012 Featured Poster.

21. Park KM, **Tschabrunn CM**, Marchlinski FE. Useful ECG Parameters that Predict Right Coronary Cusp Sites of Origin. Heart Rhythm Society 2012 Poster.

22. Jauregui Abularach ME, Camps B, Park KM, **Tschabrunn C**, Zado ES, Park R, Frankel DS, Mountantonakis S, Tzou W, Dixit S, Cooper J, Garcia FC, Hutchinson MD, Gerstenfeld MD, Marchlinski F. New electrocardiographic criteria for identifying paraseptal epicardial ventricular tachycarding: Pacing protocol. Heart Rhythm Society 2012 Poster.

23. Frankel DS, **Tschabrunn CM**, Marchlinski FE. Apical Ventricular Tachycardia in Non-Ischemic Cardiomyopathy Convey a Poor Prognosis. Heart Rhythm Society 2012 Featured Poster.

24. Zado ES, **Tschabrunn CM**, Haqqani HM, Frankel DS, Dahu MD, Dixit S, Callans D, Marchlinski FE. Parahisian Atrial Tachycardia Ablated From the Non-coronary Cusp of the Aortic Valve. Heart Rhythm Society 2012 Oral Presentation.

25. **Tschabrunn CM**, Barbera S, Almasry I, Fan R, Rashba EJ. Novel Protocol for Deep Sedation with Etomidate by Electrophysiologists. Heart Rhythm Society 2013 Poster.

26. Zado ES, Garcia FG, Mountantonakis S, **Tschabrunn CM**, Marchlinski FE. Ventricular Tachycardia due to Left Ventricular Assist Device: A Unique Case. Heart Rhythm Society 2013 Poster.

27. Brattain LJ, Loschak PM, **Tschabrunn CM**, Anter E, Howe RD. Robotic Steering of Cardiac Ultrasound Catheters. Proceedings of the 6th Hamlyn Symposium on Medical Robotics 2013 Conference Paper.

28. Santangeli P, Liuba I, **Tschabrunn CM**, Rile M, Garcia F, Bala R, Hutchinson M, Supple G, Lin D, Frankel D, Schaller R, Callans D, Zado E, Marchlinski F. Disease Progression in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy and Ventricular Tachycardia: A Longitudinal Study with Unipolar Voltage Mapping. 2014 America Heart Association Scientific Sessions Abstract.

29. Brattain LJ, Loschak PM, **Tschabrunn CM**, Anter E, Howe RD. Instrument Tracking and Visualization for Ultrasound Catheter Guided Procedures. MICCAI Workshop on Augmented Environments for Computer Assisted Interventions 2014 Conference Paper.

30. Roujol S, Basha TA, **Tschabrunn CM**, Kissinger KV, Josephson ME, Manning WJ, Anter E, Nezafat R. Imaging surrogate of the ventricular arrhythmia substrate in a swine model of ventricular tachycardia: high resolution LGE vs. high resolution electroanatomical mapping. SCMR 2015 Poster. J Card Magn Resonance. 2015 17(Suppl 1):Q133.

31. Anter E, **Tschabrunn CM**, Zilberman I, Govari A, Josephson ME. Small Electrode Catheters Improve Mapping Resolution of Post-Infraction LV Scar. Heart Rhythm Society 2015 Poster.

32. Anter E, **Tschabrunn CM**, Buxton AE, Josephson ME. In-vivo High-Resolution Mapping of Post-Infraction Reentrant Ventricular Tachycardias. Heart Rhythm Society 2015 Poster.

33. Anter E, **Tschabrunn CM**, Buxton AE, Josephson ME. Isthmus Characteristics of Reentrant Ventricular Tachycardia in Healed Myocardial Infarction. Heart Rhythm Society 2015 Poster.

34. Anter E, Josephson ME, Buxton AE, **Tschabrunn CM**, McElderry TH, Awad KA, Gunter A, Mounsey P, Kumar P, Nakagawa H. Rhythmia Mapping System: Feasibility, Safety and Short-Term Efficacy in Left Atrial Procedures: The Initial Multicenter Experience in the U.S. Heart Rhythm Society 2015 Poster.

35. **Tschabrunn CM,** Roujol S, Basha T, Nezafat R, Faulkner-Jones B, Josephson ME, Anter E. A Swine Model of Infarct-Related Reentrant Ventricular Tachycardia: Electroanatomic, Magnetic Resonance, and Histopathologic Characterization. Heart Rhythm Society 2015 Poster.

36. **Tschabrunn CM,** Roujol S, Basha T, Nezafat R, Faulkner-Jones B, Josephson ME, Anter E. High Resolution Mapping of Ventricular Scar: Comparison Between Linear and Multielectrode Catheters for Identification of Reentrant VT Channels. Heart Rhythm Society 2015 Oral Abstract.

37. Melman YF, Anter E, **Tschabrunn CM,** Josephson ME, Shvilkin A. Electromechnical Mapping of Left Ventricular Healthy Myocardium and Scar Using Contract Force Catheter. Heart Rhythm Society 2015 Poster.

38. Roujol S, **Tschabrunn C**, Basha TA, Kissinger KV, Manning WJ, Josephson ME, Anter E, Nezafat R. A novel framework for unified analysis of in-vivo and ex-vivo cardiac data using an in-vivo MRI-derived 3D printed model: application to cardiac MRI. ISMRM 2015 Poster 2580.

Miscellaneous Contributions and Acknowledgments

1. Rashba EJ, Lamas GA, Couderc JP, Hollist SM, Dzavik V, Ruzyllo W, Fridrich V, Buller CE, Forman SA, Kufera JA, Carvalho AC, Hochman JS for the OAT-EP Investigators. Electrophysiological Effects of Late Percutaneous Coronary Intervention for Infarct-Related Coronary Artery Occlusion. Circulation. 2009 Feb;119(6):779-87.

Appendix G

Figure and Manuscript Reproduction and Adaptation Publisher Permissions