High Density Mapping Of Ventricular Scar- Insights Into Mechanisms Of Ventricular Tachycardia

By

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To my wife Pallavi

& Parents

Urmila and Raj Kumar Dham

ABSTRACT

Ventricular tachyarrhythmias related to structural heart disease are the most common cause of sudden cardiac death. Many of these occur in patients with ventricular scarring, related predominantly to coronary artery disease or dilated cardiomyopathies. These regions of scarring remodel over time with ongoing collagen turnover and do not stay stable, such that patients are often subject to repeated episodes of the arrhythmia.

Ventricular scars are composed of variable regions of dense interstitial fibrosis that create conduction block, interspersed with viable myocyte channels with diminished coupling which produce substrate for circuitous slow conduction pathways that promote reentry. During sinus rhythm, these channels can be identified by the presence of late potentials and long stimulus to QRS intervals during pacing in the channel. A high density of sampling in the left ventricle allows recording of small amplitude electrograms that are of fundamental emphasis in ventricular substrate mapping. Several studies have characterized channels in patients with ventricular scar and ventricular tachycardia (VT). However, there has been no assessment on the functional characteristics of these channels and whether channels that are critical to the VT circuit differ from non-VT channels.

Chapter 1 reviews literature on arrhythmic burden and epidemiology of scar related VT, its cellular mechanisms, substrate characterization, techniques of VT mapping and gaps in the current knowledge. Chapter 2 presents the high density characterization of substrate in ischemic cardiomyopathy (ICM) patients with VT and compares the features of VT supporting channels with channels that do not support VT. This study showed that compared to non-VT channels, VT channels are more often located in the dense scar, longer in length, have long stimulus to QRS latencies and slower conduction velocity. Chapter 3 describes the electrogram properties in

regions of VT channels, and development of a stepwise model from multiple electrogram properties to ensemble regions supporting VT(s) during sinus rhythm. It also discusses the application of Shannon entropy, a fundamental measure of information content in signals, to map VT channels in sinus rhythm. This system of ablation along with high density mapping will significantly advance VT mapping and help individualize substrate based ablation. Chapter 4 presents data on high density characterization of substrate in ICM patients with VT and compares with those who do not have spontaneous VT. It showed that patients without spontaneous VT have fewer channels with shorter lengths and faster conduction, compared to VT patients. These observations partly explain the relative higher predilection of few selected surviving myocyte channels in the post infarct ventricles to sustain VT.

Structural heterogeneity in the scar produces spatial and temporal disturbances in ventricular repolarization over multiple time scales. Chapter 5 evaluates the role of acute autonomic modulation on beat-to-beat QT variability in patients with heart failure with and without VT, and contrasts it with patients without structural heart disease. It showed that acute pacing and humoral modulation including beta-blockade fail to bring down high repolarization instability in heart failure patients and VT.

Catheter ablation is the mainstay for treatment of recurrent ventricular arrhythmias in patients with structural heart disease. Chapter 6 analyses published literature on ventricular arrhythmia storm ablation in a systematic review and meta-analysis. It showed that the interventions are safe and patients often need multiple procedures including non-radiofrequency ablation measures. Although patients who had successful ablation had good long-term outcomes, a failed procedure portended an early and high rate of mortality compared with medically managed historic controls. It raised a pertinent concern of possible harmful effects of catheter ablation in a high risk patient population.

In summary, this thesis has developed innovative insights into the surviving myocyte channels in patients with ischemic cardiomyopathy. It describes a novel tool for

ventricular substrate mapping that is readily applicable in the clinical laboratory. The repolarization instability is elevated in these patients and is resistant to modulation by acute beta-blocker treatment. Finally, catheter ablation is safe and should be advised in most patients with ventricular arrhythmia storm.

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I certify that no part of this work will, in the future, be used in a submission for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

The work was performed at Centre for Heart Rhythm Disorders, University of Adelaide and Royal Adelaide Hospital, Adelaide, Australia.

I certify that the writing of this thesis, the results, interpretation, opinions and suggestions are entirely my own work. This thesis does not exceed the length of 80,000 words exclusive of tables, figures and bibliography.

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(Sachin Nayyar)

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TABLE OF CONTENTS

PUBLICATIONS AND COMMUNICATIONS TO LEARNED SOCIETIES

Chapter 2

- **Manuscript** accepted for publication in Circulation Arrhythmia Electrophysiology
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- **Presented** as an oral at Annual Heart Rhythm Society meeting, 2012 & 2013, USA, and **published** in abstract form (*Heart Rhythm*.2012;9:S329-S356) (*Heart Rhythm*.2013;10:S85)
-
- **Best Clinical paper award** at Annual Asia Pacific Heart Rhythm Society meeting, 2012, Taiwan.

- **Best Poster Award** at Annual Cardiac Society of Australia and New Zealand meeting, 2012, and published in abstract form (Heart, Lung and Circulation, 2012;21:S1-S330)

- Ralph Reader Young Investigator Award, Clinical, Finalist at Annual Cardiac Society of Australia and New Zealand meeting, 2013

Chapter 3

- **Presented** as an moderated and innovation posters at Annual Heart Rhythm Society meeting, 2013, USA, and **published** in abstract form (*Heart Rhythm*.2013;10:S482)

- **NIMMO First Prize**, 2013 for Full Time Research, Royal Adelaide Hospital

- Best Poster award, Catheter ablation at Annual Asia Pacific Heart Rhythm Society meeting, 2013, Hong Kong

- **Manuscript** organized for publication

Chapter 4

- **Manuscript** organized for publication

Chapter 5

- **Presented** as a poster at Annual Heart Rhythm Society meeting, 2013, USA, and **published** in abstract form (*Heart Rhythm*.2013;10:S388-S433)
- **Manuscript** published as Original Research article in American Journal of Physiology- Heart and Circulatory Physiology:. *Autonomic modulation of repolarization instability in patients with heart failure prone to ventricular tachycardia.* Nayyar S, Roberts-Thomson KC, Hasan MA, et al. Am J Physiol Heart Circ Physiol. doi:10.1152/ajpheart.00448.2013

Chapter 6

- **Manuscript published** as Clinical Update & Reviews in European Heart Journal: *Venturing into ventricular arrhythmia storm: a systematic review and meta-analysis.* Nayyar S, Ganesan AN, Brooks AG, et al. European Heart Journal 2013; 34: 560-569

- **Presented** as a poster at Annual Heart Rhythm Society meeting, 2012, Boston, and **published** in abstract form, Heart Rhythm.2012;9:S357–S388

- **Presented** as a poster at Annual Asia Pacific Heart Rhythm Society meeting, 2012, Taiwan.

ABBREVIATIONS

AP: Action potential

ECG: Electrocardiogram

EF: Ejection fraction

ICD: Implantable cardioverter defibrillator

ICM: Ischemic cardiomyopathy

DCM: Dilated cardiomyopathy

LV: Left ventricle

QTV: QT variability

RV: Right ventricle

ShEn: Shannon entropy

S-QRS: Stimulus-QRS

VA: Ventricular arrhythmia

VF: Ventricular fibrillation

VT: Ventricular tachycardia