

Novel mapping and ablation approaches within myocardial scar

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by

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DECLARATION OF ORIGINALITY

I confirm that the work presented in this thesis is my own and was carried out under the supervision of Professor Prapa Kanagaratnam, Dr Nicholas Linton and Professor Nicholas S. Peters at Imperial College Healthcare NHS Trust and Imperial College London. Any contributions from others are clearly stated below.

Dr Vishal Luther

18/07/2017

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Abstract

The arrhythmogenic substrate within myocardial scar contains regions of slow conduction that support reentry, characterized by low amplitude and fractionated electrograms (EGMs). Ablation therapy to prevent arrhythmias associated with such scar needs both accurate identification and interpretation of these EGMs and effective delivery of radiofrequency energy. This thesis explored new clinical approaches to the mapping and ablation of these EGMs within scar based arrhythmia.

Previous studies from our institution have shown how robotically controlled catheters offer increased stability to achieve deeper lesions. At the start of this thesis, we demonstrated the feasibility of using the Hansen Robotic System within ventricular scar during post-infarct Ventricular Tachycardia (VT) ablation to reduce future implantable cardiac defibrillator (ICD) therapies. This included patients with advanced substrates having already incurred multiple previous ICD therapies. Having proven the possibility of robotic VT ablation, we investigated, as a randomised study, whether earlier substrate ablation after the first ICD therapy may improve outcomes. Earlier ablation delayed the time to VT recurrence compared to a non-ablative approach, though this did not reach statistical significance. In patients with LV ejection fraction >30%, ablation did significantly delay time to recurrence.

In these studies, the substrate was broadly characterized by EGMs with bipolar voltage <1.5mV. Inaccurate delineation of the arrhythmogenic substrate may have been responsible for future VT recurrence. We analysed the effectiveness of increasing EGM resolution within scar using the ultra-high density Rhythmia system. This was preliminarily tested during post-AF ablation Atrial Tachycardia (AT) procedures, a more common and stable reentrant model than VT, but also involving complex circuits between scar and conductive tissue. Improving EGM/mapping resolution using the Rhythmia system was not entirely useful, as we were mis-lead by small rotational activations observed on most of the maps, the majority of which were pseudo-reentrant, often related to mis-annotation of EGM local activation time (LAT) and inaccurate interpolation of activation within regions of low voltage.

An alternative means of displaying activation within scar without the need to reduce EGMs to a single LAT was required. Ripple Mapping (RM) was previously developed in our institution to provide this alternative means, and displays an EGM in its entirety as a moving bar on the map. We prospectively tested the feasibility of Ripple mapping within scar; we first developed a method of using RM to

differentiate regions of ablation related scar from low voltage but functional tissue in iatrogenic ATs, and observed very high ablation success. This was reproducible during multi-centre studies. Within post-infarct ventricular scar, mapping in sinus rhythm/controlled pacing, RM helped us to differentiate local from far-field activation, especially with small tip and narrowly spaced electrodes, and visualise channels of delayed conduction through scar that collocated with the diastolic pathway mapped in VT, ablation of which reduced future VT recurrence.

However, ablation within these ventricular channels did not eliminate future VT recurrence. We considered whether the lines of block bordering these channels may be functional by comparing the scar locations under different cycle lengths and activation directions. Remapping post ablation atrial scars under different cycle lengths and activation directions using RM demonstrated a generally fixed scar distribution. Within ventricular scars, where the diastolic pathway could be mapped in VT, in certain areas, it was formed of functional block during tachycardia with preserved EGMs in sinus rhythm; further studies within ventricular scar under different pacing rates and activation directions may better our understanding of the ventricular substrate.

In conclusion, this thesis proposes that RM be considered the gold standard approach to mapping EGMs to determine the arrhythmogenic substrate in post ablation ATs. In post-infarct VT, undertaking ablation using robotic navigation after the first ICD therapy, specifically in patients with EF >30%, and using RM based approach to define this arrhythmogenic substrate can help to improve outcomes.

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Chapter 3:

Luther V, Jamil-Copley S, Shun-Shin M, Koa-Wing M, Wright I, Hayat S, Linton N, Lim PB, Lefroy D, Whinnett Z, Davies DW, Peters NS, Kanagaratnam P. Non-randomised comparison of acute and long term outcomes of robotic versus manual ventricular tachycardia ablation in a single center ischemic cohort. *J Interv Card Electrophysiol*. 2015 Aug;43(2):175-85

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Chapter 3:

P Kanagaratnam, **V Luther**, S Jamil Copley, M Koa-Wing, A Copley, M Castro, D Webster, I Wright, N Linton, PB Lim, Z Whinnett, C Kirkby, R Schilling, N Gall, D Lefroy, NS Peters, DW Davies, AT Prevost, N Poulter, K Rajappan. A Prospective Randomised Study of Early Robotic Ablation by Substrate Elimination of Ventricular Tachycardia

JP Howard, **V Luther**, DP Francis, P Kanagaratnam. Early catheter ablation for ventricular tachycardia in patients with ischaemic heart disease: a meta-analysis

Chapter 7:

V Luther, N Qureshi, M Koa-Wing, S Jamil-Copley, PB Lim, Z Whinnett, DW Davies, NS Peters, P Kanagaratnam, N Linton. Isthmus sites identified by Ripple Mapping are usually anatomically stable: A novel method to guide atrial substrate ablation?

First author abstracts

Chapter 3

Oral: V. Luther, S. Jamil-Copley, M. Shun-Shin, M. Koa-Wing, I. Wright, S. Hayat, N. Linton, P.B. Lim, D. Lefroy, Z. Whinnett, D.W. Davies, N.S. Peters, P. Kanagaratnam. Acute and long-term outcomes for patients undergoing radiofrequency catheter ablation of scar-related ventricular tachycardia by robotic catheter navigation. *Europace* (2014) 16 (Suppl 3): iii10

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Poster: Luther V, Sikkell M, Bennett N, Guerrero F, Leong K, Qureshi N, Ng FS, Hayat SA, Sohaib SM, Malcolm-Lawes L, Lim E, Wright I, Koa-Wing M, Lefroy DC, Linton NW, Whinnett Z, Kanagaratnam P, Davies DW, Peters NS, Lim PB. Visualizing Localised Reentry With Ultra-High Density Mapping in Iatrogenic Atrial Tachycardia: Beware Pseudo-Reentry. *Heart Rhythm* 2017;14(5):S444

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Abbreviations

AAD – Anti-arrhythmic Drug

AF – Atrial Fibrillation

AP – Antero-posterior

AT – Atrial Tachycardia

ATP – Anti-tachycardia pacing

BMI - Body mass Index

CABG – Coronary artery bypass grafting

CFAE – Complex Fractionated Atrial EGM

DM - Diabetes Mellitus

ECG – Electrocardiogram

EF – Ejection Fraction

EGM – Electrogram

FAM- Fast Anatomical Mapping

HTN – Hypertension

HRA – High right atrium

ICD – Implantable Cardiac Defibrillator

Inf – Inferior

LA – Left atrium

LAA – left atrial appendage

LAO – Left anterior oblique

LAT – Local activation time

LR – Localised Reentry

LV – Left Ventricle

PA – Postero-anterior

PV – Pulmonary veins

PVI – Pulmonary Vein Isolation

RAO – Right anterior oblique

RCM – Remote catheter manipulator

RA – Right Atrium

RF – Radiofrequency

RM – Ripple Mapping

RV – Right Ventricle

RVOT – RV Outflow Tract

Sup – Superior

TCL – Tachycardia Cycle length

VT – Ventricular Tachycardia

WOI – Window of Interest

WPW – Wolf Parkinson White

Chapter 1

1 Introduction

1.1 Historical perspectives of catheter ablation

The first human description of an electrocardiogram occurred in 1887 by Augustus D. Waller at St Mary's Hospital Medical School. This was achieved by photographing the movement of a column of mercury on a travelling plate, connected to the body by a pair of electrodes strapped to the front and back of the chest. This mercury column was contained within a Lippmann's capillary electrometer, and was seen to "pulsate" in response to a light beam with each heartbeat, as seen in figure 1-1.¹

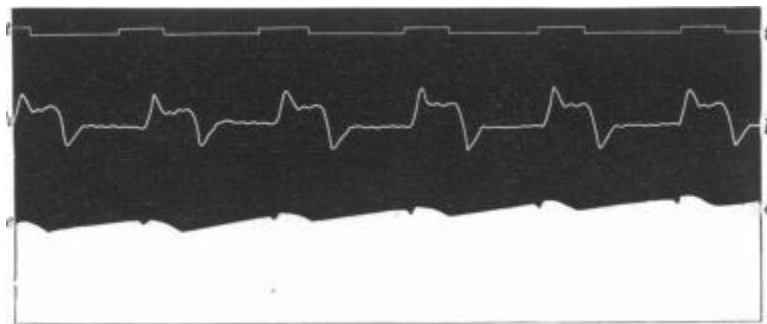


Figure 1-1: First recording of an electrocardiogram in man

Recording taken from a pair of electrodes strapped to the front and back of the chest moving a mercury electrometer with each heartbeat. Line "h" (see right of figure for annotation) indicates the heart's movement. Line "e" reflects the level of the mercury in response to a light beam in the capillary.¹

The field of cardiac electrophysiology has advanced significantly since then, particularly within the last 50 years. In the late 1960's, an increased understanding into the mechanisms of human arrhythmogenesis arose following the development of programmed electrical stimulation techniques using intra-cardiac catheter recordings, specifically patients with Wolff-Parkinson-White syndrome (WPW) and Ventricular Tachycardia (VT).^{2, 3} This knowledge inspired curative surgical therapies, including transection of the atrio-ventricular connection responsible for WPW, or excision of the area of abnormal impulse formation in VT.^{4, 5} Catheter ablation as a therapeutic approach to treat cardiac arrhythmias was introduced in the early 1980s, following the ability to localise the site of origin/pathway of a tachycardia using percutaneous catheter techniques, and eliminate them with high energy shocks, obviating the need for open-heart surgery.⁶ With the introduction of radiofrequency (RF) energy, catheter ablation became a safe and effective curative approach for many common arrhythmias.⁷⁻⁹

In the late 1990's, the observation that ectopic impulse formation from the pulmonary veins (PVs) could initiate Atrial Fibrillation (AF) drove a tremendous growth in catheter ablation technologies to isolate the PVs.^{10, 11} Between 2003-2006, there were at least 21,000 ablation procedures performed worldwide for the treatment of AF.¹² The development of electro-anatomical mapping enabled non-fluoroscopic navigation within a reconstructed geometry of the heart, allowing precise localisation of ablation lesions.¹³ As a result of these improvements, for many ablation procedures, including typical atrial flutter, nodal reentry tachycardia and focal VT, patients can now experience first time curative success of at least 90%.¹⁴

However, some of the more complex arrhythmias still remain challenging. These complex arrhythmias are often seen within or around scar tissue, commonly following ablation therapy or previous infarction. These arrhythmias are often difficult to interpret and ablate.

This thesis explores new clinical approaches to the mapping and ablation of scar based arrhythmias, with a particular emphasis on post-ablation Atrial Tachycardia (AT) and post-infarct Ventricular Tachycardia (VT). In this chapter, the literature relevant to the mechanisms, mapping and ablation of arrhythmia in general is first reviewed, and then focus is given to the mechanisms of scar based arrhythmias, as this understanding underpins the interpretation of the electrograms (EGMs) recorded. The current limitations in the mapping and ablation within scar will be discussed, and the novel approaches to overcome these limitations that are used within the thesis will be introduced.

1.2 Mechanisms of arrhythmia

Cardiac arrhythmias can arise from abnormalities in impulse formation, impulse conduction, or a combination of both. There are two subsequent patterns of arrhythmia activation: focal and reentrant.¹⁵

Focal arrhythmias are characterized by activation originating within a small area from where it spreads out centrifugally towards the rest of the cardiac chamber. These are considered to occur secondary to either enhanced cellular automaticity above that of the natural pacemaker within the sinus node, or triggered activity following premature tissue activation by after-depolarisations.¹⁶ At the site of latest activity, activation collides with itself or with anatomical barriers such that propagation is terminated. The next activation wave arises from the next focal impulse. Ablation of the earliest site of activation can achieve curative treatment for these arrhythmias.¹⁷

Reentry occurs when an activation wave fails to extinguish itself and reactivates a region that has recovered from refractoriness, allowing self-perpetuation of the arrhythmia.^{16, 18} The first demonstration of reentry was recognized by Mayer in 1906, involving the sub-umbrella tissue of a jellyfish. The application of a stimulus to the jellyfish tissue induced a sustained circular rhythm that was visible to the naked eye due to the movement of the tissue (*Rhythmical pulsation in scyphomedusae: Part II. Papers Tortugas Lab Carnegie Institution of Washington 1:115-131, 1908*). In 1913, Mines applied these findings to cardiac activation, and discovered the association between arrhythmia and reentry using the tortoise heart.¹⁹ This gave rise to the prototypical example of reentry as a ring model around an anatomic obstacle (figure 1-2), in which Mines illustrated how reentry required both regions of conduction slowing and shortened refractoriness within the circuit for excitability to recover and activation to sustain.

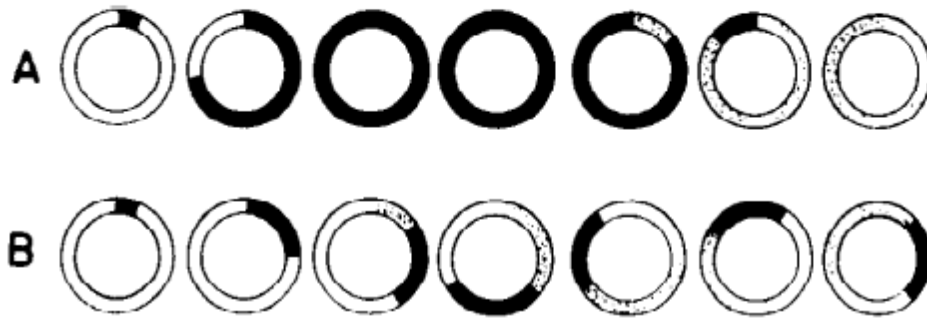


Figure 1-2: The ring model of reentry

The rings are a schematic, using shading to represent activation: black - depolarised (i.e. refractory); stippled - partially recovered; white - excitable. Both rows A and B show excitatory events around the ring in one direction owing to unidirectional block next to an initial stimulus. In A, the excitatory wave travels too quickly around the ring, and returns to its point of initiation prior to the recovery of tissue excitability. Thus the impulse cannot sustain. In B, the ring is composed of slowly conducting tissue with shortened refractoriness. An excitatory wave conducts slowly around the ring and returns to its point of initiation once it has recovered excitability, allowing reentry.¹⁹

Mines described that reentry required 3 conditions:

- 1) At least two electrically isolated pathways joined at the beginning and end.
- 2) The presence of an area of heterogeneous refractoriness to facilitate the occurrence of unidirectional block in one pathway.
- 3) Slow conduction down the unblocked pathway that allows the activation wave to pass around the circuit in a time long enough to allow the tissue to become repolarized, allowing it to follow the same path again.

Reentry is dependent upon the presence of an obstacle around which rotation can arise. These central obstacles can be fixed, including anatomical structures such as vein orifices or valve annuli; or functional as a result of spatial dispersions in conduction velocity and refractoriness in heterogeneous tissue.²⁰ Unidirectional block can occur if there is anatomical asymmetry of the conduction tissue, or if there is functional asymmetry in excitability. A reentrant circuit subsequently arises if the time it takes for the activation wave to travel around the obstacle is greater than the time it takes for the tissue behind it to recover excitability. The circuit length required will thus depend on the conduction velocity and the refractory period - the slower conduction, the smaller the circuit need be.

Reentry is responsible for some of the most common and treatable forms of arrhythmia. Typical right atrial flutter involves counter-clockwise macro-reentry around the tricuspid annulus. Atrio-ventricular nodal reentrant tachycardia (AVNRT) is caused by reentry within the AV node, using “fast” and “slow” pathways. Arrhythmias in the WPW syndrome are attributable to an additional atrio-ventricular connection leading to atrio-ventricular reentrant tachycardia (AVRT).² Ablation delivered to transect an isthmus between the tricuspid annulus and the inferior vena cava supporting typical flutter, or the slow pathway in AVNRT or the accessory pathways in WPW has become a routine procedure often offered as first line therapy.^{7, 21, 22}

1.3 Mapping techniques

Mapping describes the recording of electrical activity from a roving catheter to characterize the arrhythmia mechanism. A summary of the principles and methods of mapping are described.

1.3.1 Intra-cardiac electrograms

Local electrical activity is recorded in the form of an EGM. EGMs are generated by the potential (voltage) differences when subtracting signals recorded by two electrodes.²³ There are two types – unipolar and bipolar. Unipolar EGMs represent the difference between an electrode placed within the heart and a second electrode placed a large distance away with little or no cardiac signal. The second electrode can be an indifferent electrode in the inferior vena cava or Wilson's central terminal on the body surface. Unipolar EGMs offer a measure of the local activation time immediately underneath the electrode as well as the direction of the activation wavefront. Activation that moves towards the electrode generates a positive deflection, and that which moves away generates a negative deflection. The derivation of a unipolar EGM is illustrated in figure 1-3. The maximum negative slope ($-dV/dt$) of the signal coincides with the arrival of the activation wave directly beneath the electrode.

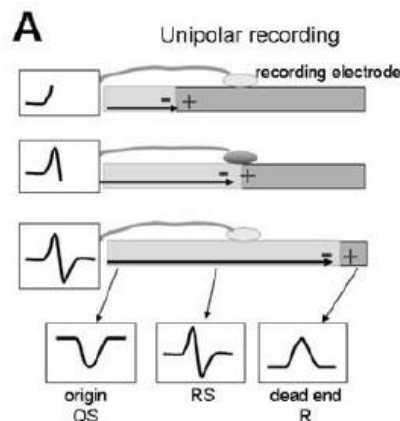


Figure 1-3: Derivation of the Unipolar EGM

An activation wave moves from left to right along a sheet of myocardium, represented by a horizontal bar. Electrodes resting on the tissue are shown as grey circles and theoretical unipolar EGMs from three sites along the sheet are depicted. As the wavefront propagates towards the electrode, a positive deflection is inscribed. As the wavefront propagates past the recording electrode, a negative deflection is inscribed. Recording from the initial site of depolarization produces a QS complex as activation moves away in all directions from the recording electrode, and recording at the right side of the tissue produces a monophasic R wave.²³

Bipolar EGMs represent the difference between two closely spaced electrodes. Unlike unipolar EGMs, the morphology of the bipolar EGM does not indicate activation direction, but is preferred for analysis of activation timing as unipolar EGMs include signal from tissue well away from the recording electrode (far-field signal), which can challenge interpretation. As the far-field signal is similar between two closely spaced electrodes, it is largely subtracted out, displaying only local signal generated beneath the electrode tip.²³

EGMs are subject to noise recording from respiration, catheter movement and variability in tissue catheter contact, manifesting as low-frequency oscillation. These can be removed by applying a high pass filter that attenuates frequencies slower than a specified cut-off. High frequency noise can be avoided with low pass filters that attenuate frequencies above a specified cut-off. An example of the influence of these filters is seen in figure 1-4.

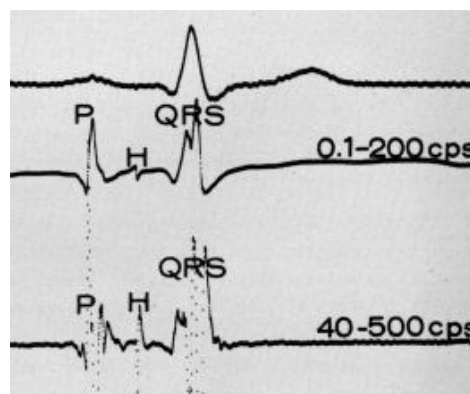


*Figure 1-4: The first intra-cardiac recording of a bipolar His bundle EGM
The bipolar signal becomes more complex and additional peaks are introduced as the high pass filter is raised.²⁴*

In order to emphasize components of the signal that correspond to activation, most recorded signals are band-pass filtered, typically between 30-250Hz.

1.3.2 Pacing manoeuvres

Whilst the study of local EGM morphology and its timing relationship to the ECG provide a putative understanding of the location of the mapping catheter in relation to the arrhythmia, pacing manoeuvres from these locations enable a more detailed understanding of the catheter location, and of the arrhythmia mechanism itself.

1.3.2.1 Entrainment

Entrainment is the continual resetting of a reentrant arrhythmic circuit, performed by pacing at a point of interest faster than the arrhythmic tachycardia cycle length (TCL) in order to enter the circuit and speed it up.²⁵ The first description of entrainment in typical atrial flutter described how different responses to entrainment identified the location of the pacing catheter in relation to the circuit. These responses included the post pacing interval (PPI) and the paced morphology. The PPI represents the time it takes for a paced wavefront to travel towards and around the circuit, then back to the pacing site. Outside the circuit, the PPI is longer than the TCL. Within the circuit, the PPI equals the TCL. Furthermore, when pacing from sites distant to the circuit, the paced wavefront and the tachycardia wavefront will fuse, leading to a different paced morphology as compared to tachycardia. Pacing within the circuit, the paced wavefront will travel in the same direction as the tachycardia, hence the paced morphology is identical to the tachycardia (concealed).

1.3.2.2 Pace-mapping

A pace-map is a comparison of the 12 lead ECG morphology produced during endocardial stimulation with the surface 12 lead ECG of the targeted arrhythmia. Pace-mapping is based on the principle that stimulation at the site of origin will mimic the electrocardiographic pattern of the arrhythmia. A perfect pace-map will replicate the ECG morphology in all 12 surface leads (12/12 match). Pace-mapping is more commonly practiced within the ventricle owing to the size of the QRS when mapping VT, as opposed to the P wave when mapping AT.

1.3.3 3D contact mapping

The mapping techniques described above are considered “classical” forms of catheter mapping. The approaches used X-ray fluoroscopy to navigate intra-cardiac electrodes within the heart. 3D contact mapping systems evolved in the late 1990s with the intention to reduce fluoroscopy time, improve catheter localisation, and document the positions of ablation sites. These systems now use either an electromagnetic or impedance-based catheter localisation method to create 3D anatomic shells of the cardiac chamber. Computer software tracks various positions reached by the catheter, and then applies an algorithm to overlay a shell upon these points.

The most commonly used system is CARTO (Biosense Webster, Inc., Diamond Bar, California). Electromagnetic fields emanating from three separate coils beneath the patient are detected by a

location sensor embedded in the catheter tip. The strength of each coil's magnetic field measured by the location sensor is inversely proportional to the distance between the sensor and coil, and this triangulates the location of the catheter in space.¹³ EnSite NavX system (Endocardial Solutions, St. Jude Medical, Inc., St. Paul, MN, USA) is also widely used, and employs impedance localisation. This involves the passing of a small current through orthogonally placed skin patches which is detected by the intra-cardiac catheters as a voltage and impedance recording and used to triangulate the catheter location in space.²⁶ Using these systems, new approaches to mapping became possible which combined data from each acquired EGM with the reconstruction of the intra-cardiac chamber. This included both local activation time maps, which offered a visual representation of intra-cardiac activation throughout the cardiac chamber, and voltage maps, which offered an understanding of the underlying tissue health and possible regions of scar.^{27, 28}

1.3.3.1 Local Activation Time Mapping

In these maps, the local activation time (LAT) of EGMs sampled from different places within the heart are compared to a stable reference signal, and a measurement of the difference in timing between the 2 signals is calculated (figure 1-5), and plotted according to a colour bar on the reconstructed chamber geometry that the system acquires.²⁹

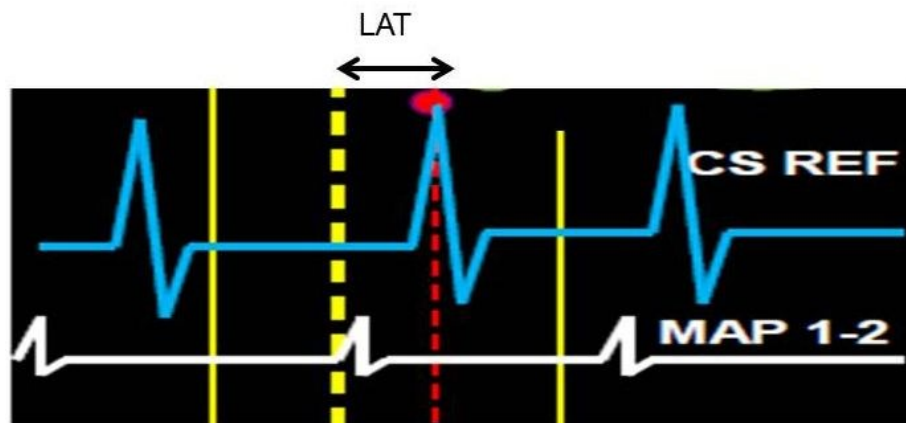


Figure 1-5: Measurement of LAT

Measurement of LAT of a sampled EGM (MAP 1-2) during atrial flutter. A catheter positioned within the coronary sinus (CS REF) provides a stable reference (dashed vertical red line). The timing difference between the reference signal and the local EGM (dashed vertical yellow line) determines the LAT (courtesy of Biosense Webster).

Annotation of LAT requires a timing Window of Interest (WOI) to ensure that EGMs from the same beat are compared. A WOI is defined by specifying a timing interval both before and after the reference point. The position of the reference point in relation to the window is arbitrary, but by convention is

within the middle of the window when mapping a regular arrhythmia. The sum of the WOI is often chosen between 90-100% of the mapped TCL.

A colour is designated to each acquired LAT according to a colour scale that follows the spectrum of the rainbow (figure 1-6). The width of the colour scale spans one complete interval of the tachycardia circuit. Using this colour code, red represents the earliest measurement of LAT in relation to the reference signal, and purple represents the latest.



Figure 1-6: Rainbow colour code of the LAT map

In a focal arrhythmia, as activation spreads away from the focus in all directions, the site of earliest activation, labelled red on the LAT map, is considered the focal source. Figure 1-7 is one of the first examples of a focal arrhythmia correctly depicted on a 3D LAT map.

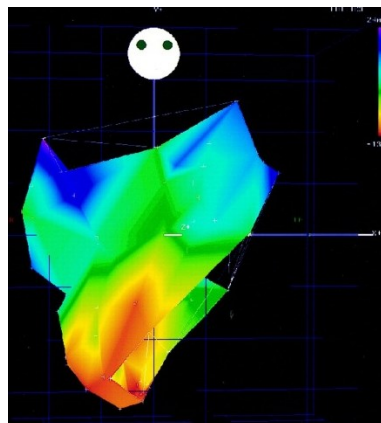


Figure 1-7: Focal activation

One of the first examples of 3D LAT mapping, captured from swine RV during sinus rhythm. Earliest activation appears from the inferior septum, and travels away towards the apex.¹³

In reentrant tachycardia, the concept of “early” and “late” is a misnomer, because any given area of activation will have other sites that are activated before or after that location. If the entire reentrant circuit is completely mapped, the red area of earliest activation will be adjacent to a purple area of latest activation, because the circulating wavefront moves from the purple region back into the red region to complete the circuit. In a reentrant circuit, changing the selected reference time changes the WOI and the subsequent location of the red region, creating colour coded maps that appear quite different, but contain the same propagation pattern. An example is illustrated in figure 1-8.²⁹

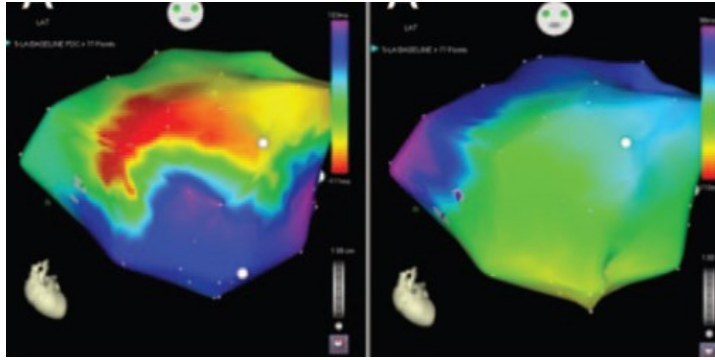


Figure 1-8: Macroreentrant activation

Two LAT maps of the same macro-reentrant circuit were created with 2 different temporal references. In the right image, the map is constructed based on a reference point that is 120ms later than that selected for the left image. “Earliest” activation (red) is seen in the roof in the left image, but has changed location (hidden from view) in the right image.²⁹

Successful LAT mapping requires precise annotation of local activation time at all mapped points. Although the steepest downslope of the unipolar EGM is closely timed with the upslope of the local intracellular action potential, owing to the contribution of far-field signal and the subsequent difficulty assigning LAT, unipolar EGMs in isolation are generally not used to display activation. Whilst bipolar EGMs contain less far-field signal, the link between a bipolar EGM and underlying cellular activity is unknown, thus no consensus exists on how to annotate LAT. In any case, bipolar EGMs are preferred to assign LAT, and 3D mapping systems offer the user a choice – the onset of bipolar activation, the absolute peak, or the maximal negative slope as fiducial markers of LAT.³⁰ Following acquisition of at least 2 LAT points, the system can display the proposed activation pattern as a moving propagation map, where the operator can follow the leading edge of the activation wavefront through the WOI as it moves across the cardiac chamber.

1.3.3.2 Voltage Mapping

The amplitude of an EGM, measured in millivolts, is determined by the volume of tissue surrounding the recording electrode that activates at the same time. In normal tissue, large areas will activate simultaneously, and the amplitude will be relatively large. In diseased myocardium, as myocardial fibres become increasingly separated, only small areas will activate at the same time, and the EGM amplitude will decrease. EGMs are thus used as a surrogate marker of tissue health. Bipolar EGMs are again preferred as they are less affected by far-field signal. 3D mapping systems collect voltage data simultaneous with activation timing, and display this information across the shell by measuring the peak-peak amplitude of each EGM within the WOI and plotting this value according to a colour code

from red to purple. An example is presented in figure 1-9. Normal and healthy myocardium is characterized by large amplitude bipolar EGMs with peak to peak amplitude $>3\text{mV}$.³¹

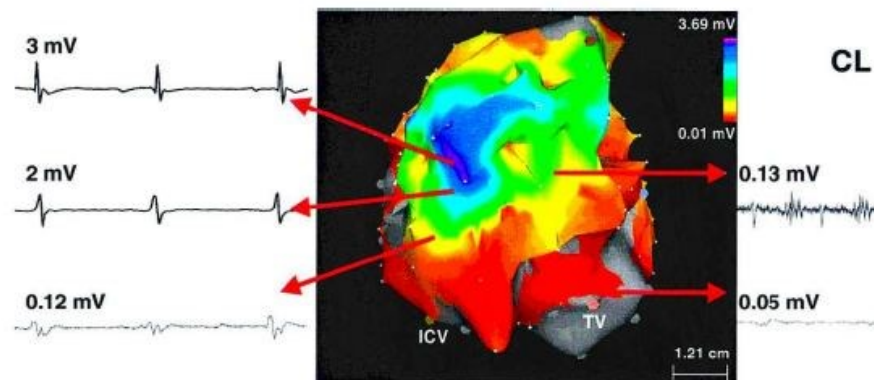


Figure 1-9: Bipolar voltage Map

A right atrial voltage map recorded in a patient with tricuspid atresia who underwent a Fontan procedure. The amplitudes of the recorded bipolar signals are indicated by the colour legend at the top of the map. Low voltage areas are coloured red where as high voltage areas are coloured blue - purple.³²

1.3.4 Non-contact mapping

Whilst contact mapping systems combine local electrophysiological and anatomic information, non-contact systems offer a global visual of all electrophysiological information within a cardiac chamber. This is achieved using a multi-electrode array (Ensite, Endocardial Solutions Inc., St. Paul, MN, USA). The multi-electrode array is an inflatable balloon with 64 electrodes on its surface mesh. When situated mid cavity, it is able to sense and record far-field endocardial activity throughout the chamber from only one single beat. This information is transformed via inverse-solution mathematics into several thousand “near-field” points and is plotted on a “virtual” endocardium to present global activation.³³

1.4 Principles of radiofrequency ablation

RF ablation damages cardiac tissue by heating. High frequency electrical current delivered from the catheter tip generates heat through conduction, creating an irreversible dense central core of necrosis.³⁴ This has enabled percutaneous ablation of focal sources and regions supporting reentrant circuits.

Optimization of the electrode tip–tissue contact is crucial to deliver effective and durable lesions. The size and depth of an ablation lesion is dependent upon the magnitude and duration of power delivery, the contact force of the catheter on the tissue, and the catheter stability.³⁵ Excessive tissue heating can lead to protein denaturation and subsequent char formation, and has been associated with systemic embolisation and stroke. Excessive heating can also lead to tissue boiling and localised perforation, with pooling of blood into the pericardial space and tamponade. To avoid these complications, energy delivery systems limit ablation by a power and/or temperature threshold that is lower than that which allows char to form, monitored by temperature sensors embedded in the electrode tip.³⁶

In order to achieve a more durable lesion, irrigated ablation evolved to allow greater RF energy delivery. Saline flows through a lumen in the catheter towards the electrode tip, cooling the tissue, allowing more power to be applied, with more current to flow through the tissue.³⁷ Multiple studies have demonstrated that the lesions created are larger than those achieved with non-irrigated electrodes. Irrigation during ablation is now conventional practice.^{38, 39}

Until recently, the efficacy of an ablation lesion had been indirectly judged by using a combination of visual observation of catheter tip motion, tactile feedback, local EGM attenuation, and impedance monitoring.⁴⁰ Direct resistive heating is produced by a high density of alternating current, the magnitude of which declines with the inverse square of the distance; therefore a measure of “tissue contact” can better improve effective lesion formation.⁴¹ A measure of contact force is a robust and simple parameter for ablation efficacy, especially during irrigated ablation, where tip temperatures inadequately reflect actual tissue heating. The advent of contact force sensing technology enabled real-time assessment of the applied force at the catheter tissue interface and increased durable lesion delivery.⁴²

1.5 Electro-architecture within scar

Scarred myocardium offers the perfect milieu for reentry – anatomical obstacles and the potential for slow conduction secondary to disruption of fibre orientation (tissue anisotropy).⁴³ This section explores the electro-architecture within scar and proposed models of reentry.

Cardiac myocytes are embedded in a network of fibroblasts and collagen fibres that provide the physical support that maintains myocardial structure. In the healthy heart, this network consists of thin weaves, allowing myocyte cell-to-cell contact. In diseased states, fibroblast collagen synthesis is enhanced, leading to a reduction in electrical myocyte cell-to-cell coupling and impairment of propagation of the electrical impulse.⁴⁴ Microscopy studies have demonstrated different types of fibrosis with varying landscapes of collagen-dense areas, triggered by different aetiologies, and perhaps responsible for different arrhythmias types. “Replacement fibrosis” occurs secondary to tissue injury and cell death – here, collagen is deposited as a result of wound healing to preserve the structural integrity of myocardium after cell death. Replacement fibrosis comprises two types, compact and patchy. Compact fibrosis consists of dense fibrotic regions completely devoid of conductive tissue, resulting in an anatomic barrier to conduction. Patchy fibrosis is characterized by areas where collagen fibres and myocardial bundles intermingle, resulting in slowed conduction through the scar.⁴⁵ Microscopic images of these two types are presented in figure 1-10.

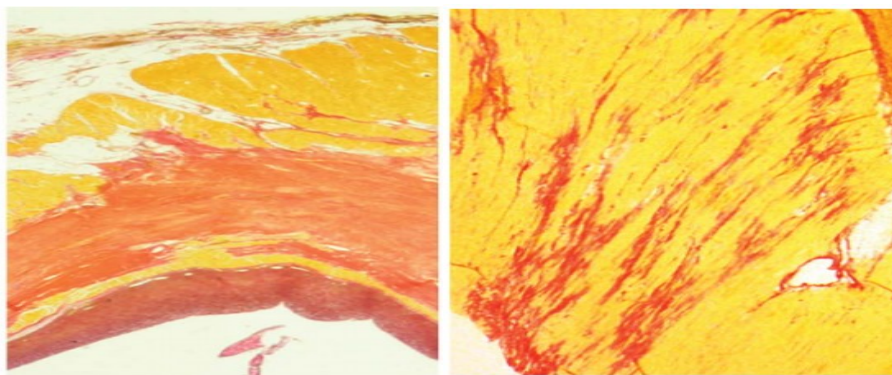


Figure 1-10: Replacement fibrosis

Microscopy images of fibrous myocardial tissue stained with picrosirius red and visualised by light microscopy. Collagen appears in orange-red. Left: Compact fibrosis consists of areas of dense collagen deprived of any myocardial tissue; Right: Patchy fibrosis consists of a mixture of myocardial and collagen bundles.⁴⁴

Much has been learned about the electro-architecture of scar in studies involving ventricular tissue post myocardial infarction. De Bakker and colleagues performed high resolution mapping of the spread of activation within presumed patchy fibrosis of infarcted papillary muscle (figure 1-11). They described a “zigzag” course of activation along bundles of surviving myocytes separated by collagenous septa.^{46, 47, 48}

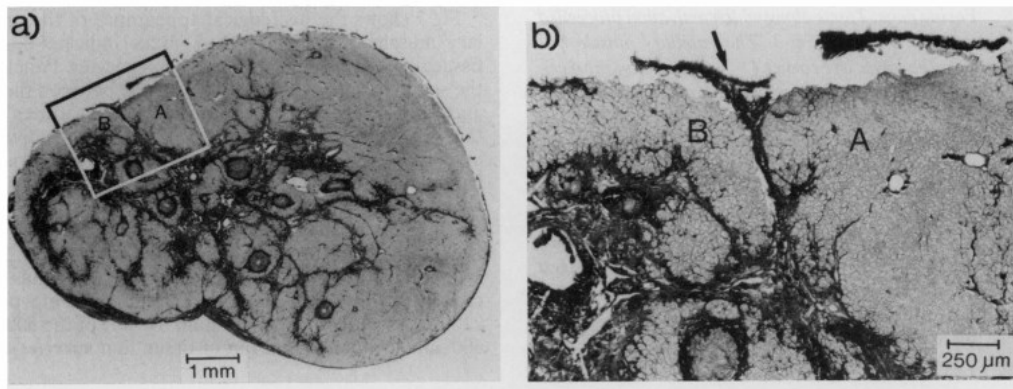


*Figure 1-11: Viable bundles of tissue within infarcted muscle
(a) Perpendicular sections of infarcted papillary muscle that show strands of fibrous tissue (dark areas) that separate viable tissue into bundles. (b) is a magnified view of (a).⁴⁶*

One of the first studies of EGMs within abnormal tissue involved analysis of bipolar EGMs in canine models of ischaemic tissue.⁴⁹ Changes in bipolar EGMs were observed within the ischaemic zone characterized by reduced amplitude, delayed and fragmented activation. Examples of EGMs from within and outside the ischaemic zone are illustrated in figure 1-12.

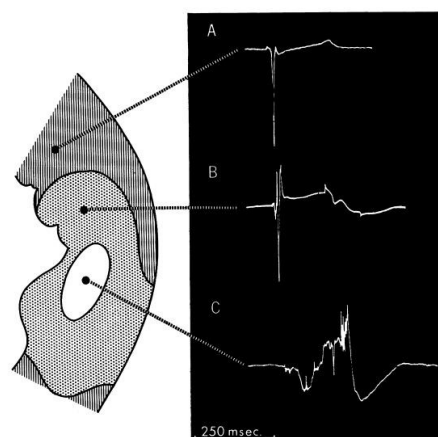


*Figure 1-12: EGMs around regions affected by ischemia
The schematic on the left illustrates tissue characteristics around regions affected by ischaemia. “A” represents a normal bipolar EGM and corresponds with normal tissue. In B, an EGM recorded from a peripheral region of ischaemia is shown containing two late spikes suggestive of a uniformly delayed region of activation. C was recorded from the epicentre of the ischaemic area, and demonstrates fragmentation lasting for almost 250 msec.⁴⁹*

Josephson and colleagues further described EGMs in regions of slow conduction, as observed in both arrhythmia and sinus rhythm within post infarct scar.^{31, 50, 51} This included fractionated EGMs, characterized by low amplitude, high frequency, multicomponent signals of prolonged duration; and late EGMs, as those recorded after the inscription of the latest surface QRS activity (figure 1-13).

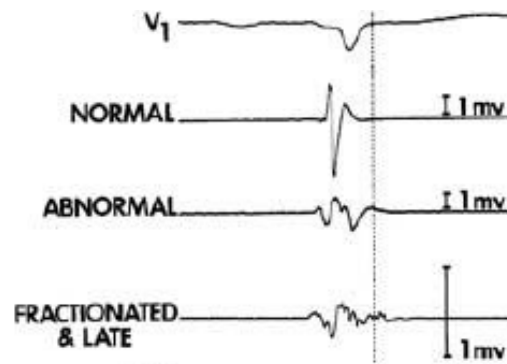


Figure 1-13: EGMs within post infarct scar

Example of normal EGM, and EGMs sampled within regions of scar, including fractionated and late signals.⁵⁰

1.5.1 Channels of slow conduction

From the early 1980's, this understanding of EGM signals within ischaemic scar lead to various models of the scar electro-architecture supporting reentry. This involved islands of unexcitable myocardium and intervening pathways of relatively viable and electrically active but slowly conducting tissue with the potential to support reentry. A proposed model of this electro-architecture is presented in figure 1-14.

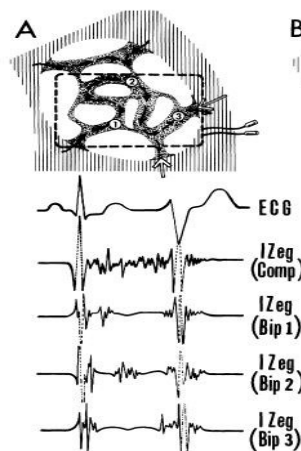


Figure 1-14: The electroarchitecture within infarcted tissue

A schematic of tissue conduction within infarcted tissue that arises between the last initiating and first reentrant beat. Multiple islands of unexcitable myocardium (white areas) and intervening pathways of relatively viable muscle tissue (black zone) are illustrated. Three bipolar electrodes (Bip 1, Bip 2, Bip 3) are located within these pathways, and record local signal along these pathways. An activation wavefront invades the infarcted zone at multiple sites (black arrows) while failing to conduct at other sites (white arrows) creating areas of unidirectional conduction block. The bipolar electrodes depict the local arrival of the activation wavefront as it passes close by (from Bip 1 to Bip 3) which is slow and fractionated, spanning most of the diastolic interval.⁵²

Various responses to entrainment manoeuvres further supported this electro-architectural model of reentry within scar. Stevenson and colleagues described the region of viable tissue, bordered on either side by fixed scar, as a “channel” with an entrance and exit site.⁵³ The channel demonstrated entrainment with concealed fusion with perfect return cycles along its length. This is in contrast to sites outside of the circuit which demonstrated manifest fusion. Figure 1-15 is a landmark illustration from Stevenson of the proposed reentrant pathway through this channel, and remains the foundation of our current understanding of the reentrant circuit within post-infarct scar.

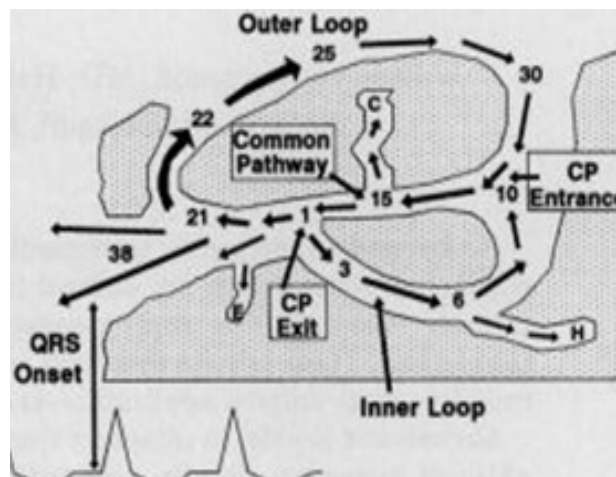


Figure 1-15: Model of reentry within ventricular scar

A reentrant circuit is supported by a channel bordered on either side by unexcitable scar. Grey stippled regions are not excitable during tachycardia. Arrows indicate propagation of excitation wave fronts through the circuit.⁵³

Histological studies, as illustrated in figure 1-16, have mirrored these electro-architectural models.⁵⁴

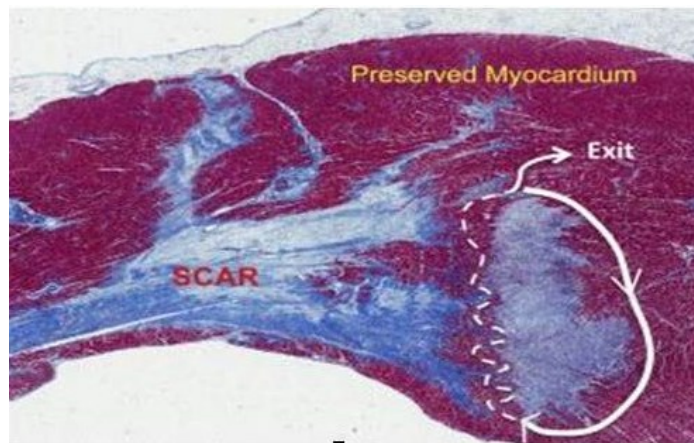


*Figure 1-16: Histological model of reentry
Cross section view of infarcted myocardium with Masson trichrome stain (top right) highlights a “channel” of preserved myocardium (purple) surrounded by scar tissue (blue).⁵⁵*

The scar associated with non-ischaemic cardiomyopathies (NICM) is thought to be distinctly different from post-infarct scar. This has been determined from MRI studies and combined 3D mapping of the epicardial and endocardial substrate.⁵⁶ Whilst post-infarct scars are predominantly sub-endocardial within a given coronary territory, non-ischaemic scars are predominantly epicardial, less confluent, and with less late potentials.⁵⁷ Furthermore, the patchy scar in NICM may have fewer fixed boundaries and regions of slow conduction, with different functional properties that allow for reentrant propagation. Furthermore, epicardial low voltage can arise within fibro-fatty tissue as well as scar, making the interpretation of the epicardial voltage map more challenging. Patients with NICM are not studied in this thesis.

1.5.2 Constraining barriers

Akin to the classical Stevenson illustration of the reentrant circuit within ventricular scar, Kalman and colleagues described a similar electro-architectural model in the atria again using entrainment (figure 1-17). However, this model differed in that the channel did not reside within scar, but around the scar and a nearby anatomical obstacle (suggesting a “compact scar” type).

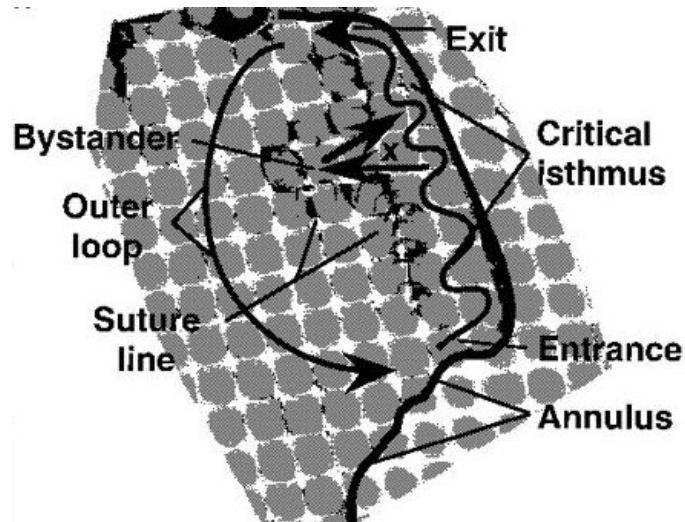


Figure 1-17: Model of reentry within atrial scar
A narrow channel or “isthmus” of conduction exists between a stylized atriotomy and the TA. The entrance and exit sites of the critical isthmus are shown.⁵⁸ The circuit involves a blind loop and a bystander area.

Unlike ventricular scar, the aetiology of atrial scar is most often iatrogenic after surgical incisions or catheter ablation.⁵⁹⁻⁶³ Idiopathic scars do occur, but are relatively rare in comparison, with the mechanism being unknown.^{64, 65} The first recognition of scar based reentry within the atria was macro-reentrant around surgical scars created from prior incisions and suture lines (figure 1-18). These facilitated the formation of nonconductive constraining barriers, creating protected zones or “isthmuses” for maintaining reentrant activation.^{58, 66-68}

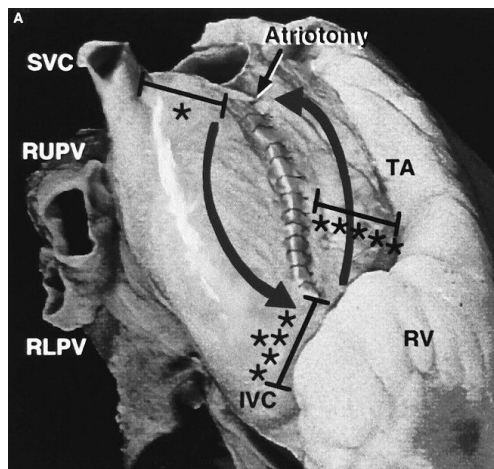


Figure 1-18: Atrialotomy scar
Epicardial aspect of the right atrium demonstrating atriotomy scar, and a potential macro-reentrant circuit around the scar.⁵⁸

Proof of reentry included entrainment around the scar, and that isthmus ablation, which involved extending the nonconductive barrier to a natural atrial boundary, was sufficient to terminate reentry and prevent recurrence.⁶⁶ Unlike the slow conduction zones seen within ventricular scar, some of these studies reported that conduction was relatively uniform, without specific areas of slow conduction.^{66, 68-70} Other studies have alluded to the presence of EGM fractionation within the channels as surrogates for slow conduction.⁵⁸

Post-ablation atrial reentry is a disease of the era of extensive delivery of ablation for persistent AF.^{62, 71} This ablation can include encircling the PVs, linear lesions across the left atrial roof and mitral isthmus, fibrillatory EGM defragmentation, and rotor elimination.^{10, 72-74} An example of a 3D left atrial geometry illustrating the linear lesions and encircling lesions around the PVs is presented in figure 1-19.

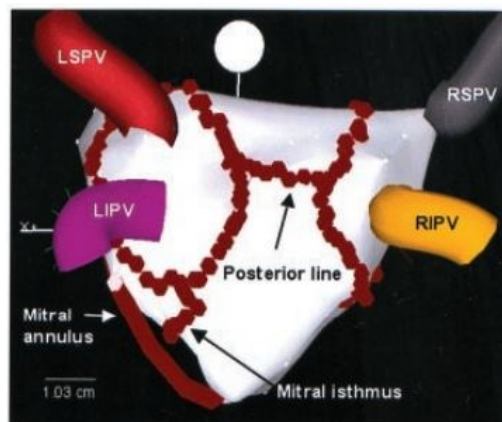


Figure 1-19: Linear lesions

A 3D representation of LA and PVs constructed with an electro-anatomic mapping system during an AF ablation. Red tags represent sites at which RF energy was delivered. Left and right-sided PVs are encircled. Also shown are ablation lines along the mitral isthmus and posterior LA.⁷⁵

Whilst these ablation lesions sets are used to isolate or eliminate the triggers that initiate or maintain AF, these lesions inadvertently create new fixed obstacles that can act as constraining barriers that stabilise propagation, representing ideal substrates for large reentrant circuits. A complete roof and mitral isthmus lesion can act as a constraining barrier, contributing to the development of an anterior wall and lateral wall circuit respectively by altering the left atrial activation patterns, which then promote reentry at another location.⁷⁶ Figure 1-20 illustrates how ablation between the left lower PV and the mitral annulus can constrain activation around the anterior and posterior wall.

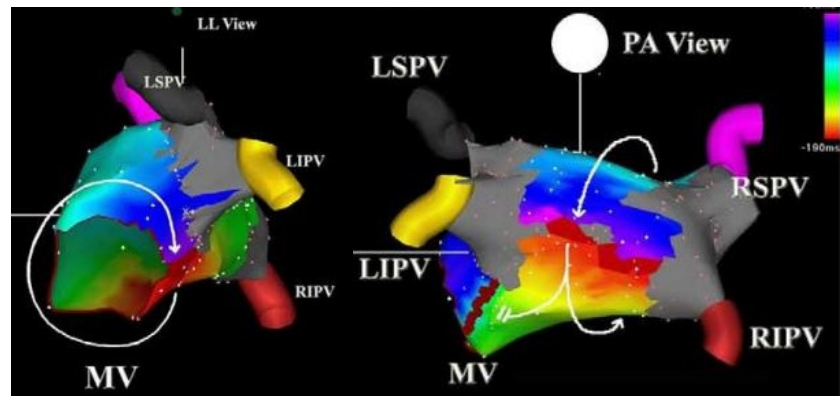


Figure 1-20: Mitral and LA Roof dependent tachycardia
Left: LA activation map in LAO showing macro reentry dependent upon the mitral isthmus.
Right: After ablation and block at the mitral isthmus, a new macro reentrant circuit was induced, dependent upon an isthmus at the roof between two previously ablated areas along the PVs.⁷⁷

Continuous linear ablation lesions can be difficult to achieve. Incomplete lines or recovery of conduction along a previously blocked line can also create “channels of slow conduction” with the potential to support reentry, as has been described within ventricular scar. Several studies have demonstrated that gap-related macro-reentry is the most common mechanism of reentry post AF ablation, as successful sites of ablation were located along previous ablation lines.^{60-63, 77} More recently, where two gaps in close proximity occur along a formerly deployed line, regions of extremely slow conduction have been observed, characterised by fractionated EGMs, that facilitate small localised reentrant circuits to arise without short-circuiting.^{78, 79} Thus these ATs seen post ablation can occur around constraining barriers to conduction with relatively preserved conduction velocity, or from slow conduction through prior ablation lines.

1.6 Limitations of mapping arrhythmia in scarred myocardium

The underlying electro-architecture within scar is complex and poses several challenges to conventional mapping, which are now described.

1.6.1 Interpreting fractionated electrograms

As we have seen, the identification of fractionated EGMs within scar is thought to represent the slow conduction zone supporting reentry.^{80,51,81} Fractionation arises where myocardial bundles and collagen fibres intermingle, especially where the direction of propagation is perpendicular to fibre direction, due to non-uniform anisotropy. Multiple deflections are generated by activation of various myocardial bundles along a tortuous route between the electrical barriers imposed by the collagen fibres.⁸² However, fractionation is not exclusive to slow conduction, and can arise from movement artefact, catheter knocking, mains or electromyographic interference, and when far-field signal is fused with local signal. Furthermore, fractionated EGMs recorded during sinus rhythm can be a normal finding due to wave-front collision, and not necessarily always evidence of the underlying tissue characteristic.⁸³ Figure 1-21 illustrates an example of fractionation secondary to collision of two wavefronts. Therefore, a fractionated EGM cannot be interpreted in isolation, but rather in context of the surrounding activation.

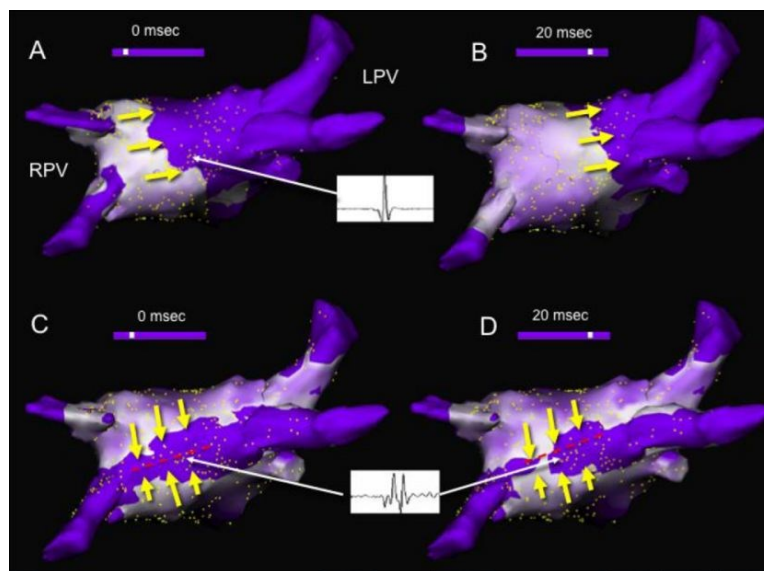


Figure 1-21: Functional fractionation

Left atrial propagation map during sinus rhythm (A & B) and coronary sinus pacing (C & D) created by the NAVX Velocity system (roof view). White colour represents the activation wave. A single and homogeneous activation wave is evident along the roof during sinus rhythm, where a normal EGM is recorded. During coronary sinus pacing, a fractionated EGM is recorded from the same area of the roof, where 2 wavefronts collide (red broken line).⁸³

1.6.2 Annotating low voltage electrograms

Incorrect assignment of LAT for a small number of EGMs can invalidate the entire activation map. In regions of slow conduction, low-amplitude fractionated EGMs of long duration are often seen, and selecting which component of the EGM to annotate activation timing is challenging.⁸⁴ In regions of scar, this often requires manual readjustment of timing annotation of several data points which is both time consuming and subjective.³⁰

This limitation is best illustrated in the mapping of localised reentry as recently described within atrial scar (figure 1-22). Although thought to involve slow conduction and reentry around a small area of scar characterized by long duration and fractionated EGMs around the circuit, owing to the difficulty annotating activation times in areas of slow conduction, localised reentrant circuits can appear as focal.⁸⁵⁻⁸⁸

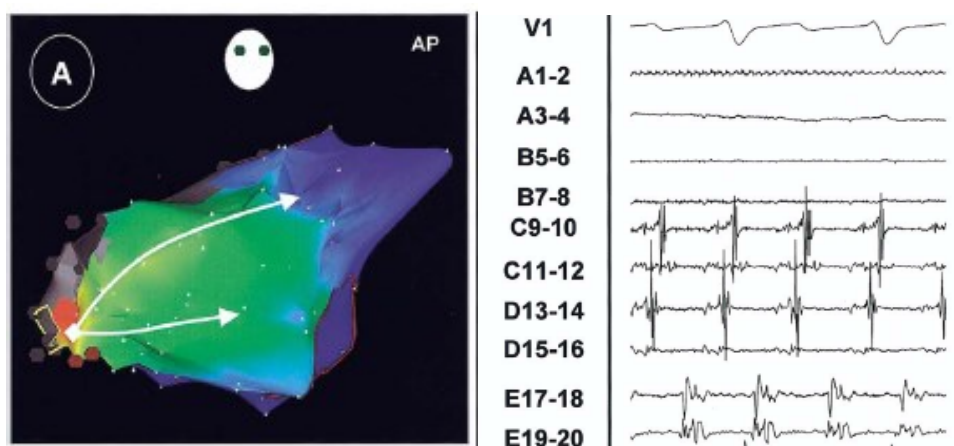


*Figure 1-22: Localised reentry that appears as focal
Long duration and fractionated EGMs adjacent to the LA septum spanning the full TCL can be seen, however, the activation map from the same tachycardia demonstrates focal activation from this site.⁷⁹*

EGMs within ventricular scar are often composed of 2 components: the local signal from within scar, and the larger far-field signal from the thicker surrounding tissue/epicardial surface (figure 1-23).⁸⁹

Differentiating between these 2 components can be challenging and can lead to incorrect assignment of LAT and voltage to the far-field component, misleading interpretation.

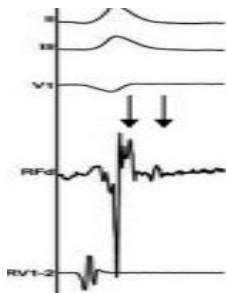


Figure 1-23: Near and far-field components

An EGM collected within ventricular scar composed of far-field (left arrow) and local near field (right arrow). The local signal occurs just after a short iso-electric period. It is considerably smaller in amplitude than the far-field component, thus annotation of LAT and measurement of voltage may be incorrectly measured to the far-field component.⁸⁹

1.6.3 Interpolation

LAT maps employ an interpolation algorithm that assigns the average activation time between mapped points in order to display an interpretable propagation pattern on the assumption that activation is uniform; however, these estimates of timing and voltage within unmapped sites may not be accurate, especially in areas where activation is complex. For example, when adjacent areas are separated by a line of conduction block, the wavefront may reach these adjacent locations from different paths. If the map allows interpolation over a large area, it can create a “pseudo-interval” between the activation times either side of the line of block, creating the false appearance of slow conduction.²⁹

1.6.4 Intra-cardiac activation time exceeds the WOI

Successful LAT mapping is dependent upon careful selection of the WOI. In tissue with excessive low voltage, the duration of the activation wavefront navigating through the chamber of interest can be prolonged, and can even exceed the designated WOI (figure 1-24). More than one site of early activation can subsequently be seen creating a chaotic activation pattern.

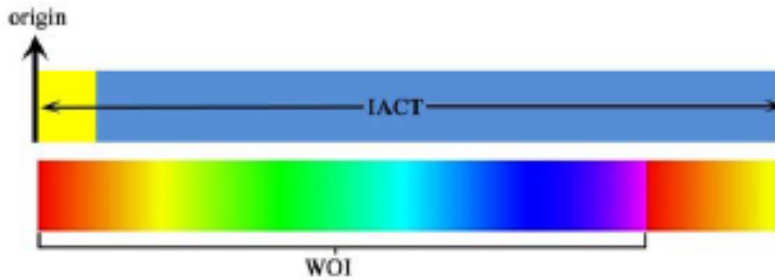


Figure 1-24: Chamber conduction time > WOI

The top row presents the total duration of activation within a chamber from the point of earliest activation to the site of very latest activation. Within scarred atria, this total duration can exceed the duration of the WOI. Whilst the true origin of activation is tagged as the earliest part in the WOI, the later part of the cycle would be annotated as the head of next cycle, creating an “early meets late” appearance.⁹⁰

1.6.5 Non-capture

Entrainment manoeuvres and pace-mapping within and around scar can be difficult to perform, either failing to capture the myocardium or risking termination or change of the clinical arrhythmia.⁹¹ Furthermore, entrainment manoeuvres in areas of slow conduction can lead to post pacing intervals that are not exact.⁹²

1.7 Limitations of mapping the arrhythmic substrate during sinus rhythm

Identifying the region of slow conduction supporting reentry is dependent upon studying activation during the arrhythmia. Patients with paroxysmal arrhythmias planned for ablation may be non-inducible or poorly sustained on the day of their procedure, precluding effective mapping and identification of these critical regions of slow conduction. An understanding of the location of scar and patterns of activation through the scar in sinus rhythm or controlled pacing has been used to predict the location of these underlying regions of slow conduction. Colour coded voltage maps have been used to identify low voltage areas as a surrogate for scar, and multiple approaches to ablation outside of the clinical arrhythmia have been proposed, known as substrate based ablation.⁹³⁻⁹⁷

Within the ventricle, prior studies from Marchlinski and colleagues identified that 95% of all bipolar EGM signals were above 1.5mV, and this value has been used to define normal endocardium.⁹⁵ Bipolar signals <0.5mV are considered to reflect “dense scar.” Signals between 0.5mV and 1.5 mV indicate the border-zone between scar and healthy tissue. These values appear to correlate well with previous macroscopic histological studies of scar (figure 1-25) and cardiac magnetic resonance imaging.⁹⁸⁻¹⁰¹

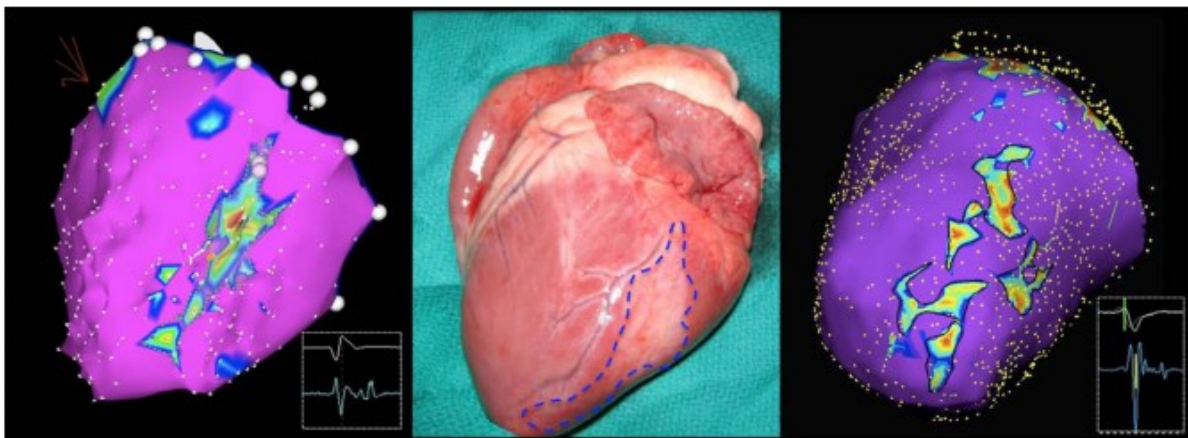


Figure 1-25: Histological validation of bipolar voltage scar threshold
Electro-anatomic bipolar voltage map of porcine endocardial left ventricular scar post circumflex infarct. (A): The gross pathologic specimen of the infarcted areas is outlined by the blue line. Voltage is displayed using a colour range from 0.5 to 1.5mV (purple represents > 1.5mV; red represents <0.5mV. The infarct scar is well depicted on both CARTO (left) and NAVX map (right).¹⁰¹

Extensive ablation within areas $<1.5\text{mV}$ has been performed to “homogenise” the scar. Ablation along the border zone between $0.5\text{--}1.5\text{mV}$ has been applied to disconnect regions of slow conduction from surrounding ventricular tissue.^{94, 97}

However, defining scar using bipolar EGMs has several limitations, and these will be discussed below.

1.7.1 Using voltage for substrate mapping

1.7.1.1 Electrode tip size and inter-electrode spacing

Recent studies have elegantly demonstrated how the amplitude of a bipolar EGM within the same location can change dependent upon the catheter construct, specifically in relation to the electrode tip size and inter-electrode spacing.¹⁰² Figure 1-26 illustrates how EGM amplitude can change with increased bipole spacing. It is of note that the definitions for ventricular scar that guide substrate ablation were determined using widely spaced catheters.^{103, 104}

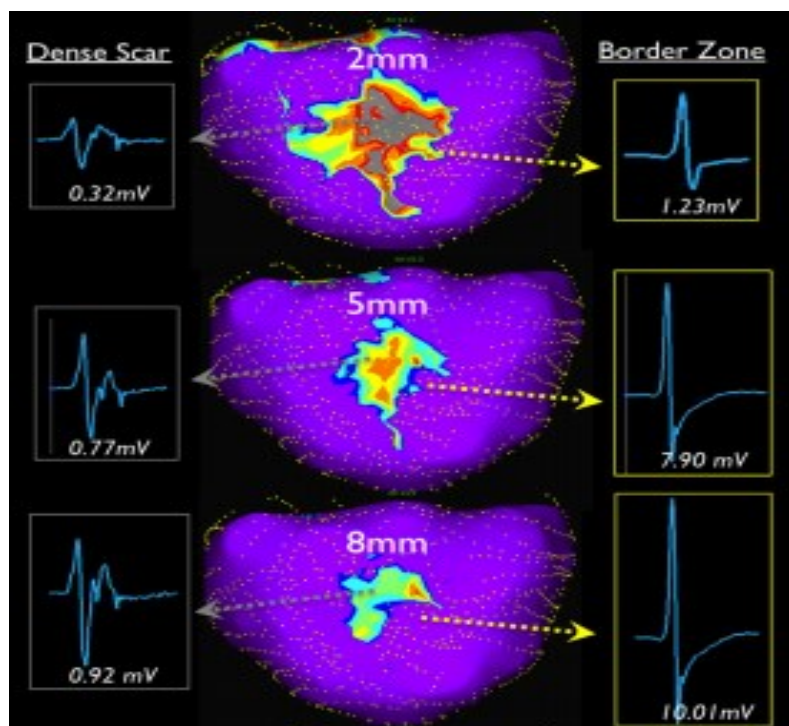


Figure 1-26: Influence of inter-electrode spacing on bipolar EGM amplitude
Top panel, 2mm inter-electrode spacing; middle, 5mm; bottom, 8mm. The amplitude of the far-field signal from surrounding tissue within the dense scar increases with increased inter-electrode spacing.¹⁰²

1.7.1.2 Far-field annotation

Regions of relatively higher voltage within and around areas of dense scar, as seen on voltage maps, have been considered surrogates for the channels of conduction through the scar. However, as voltage is annotated to the EGM peak, these regions may have reflected only far-field signal, and not these channels as previously thought.⁹³ Figure 1-27 illustrates a tiered voltage channel with far-field signal of higher amplitude than local signal.

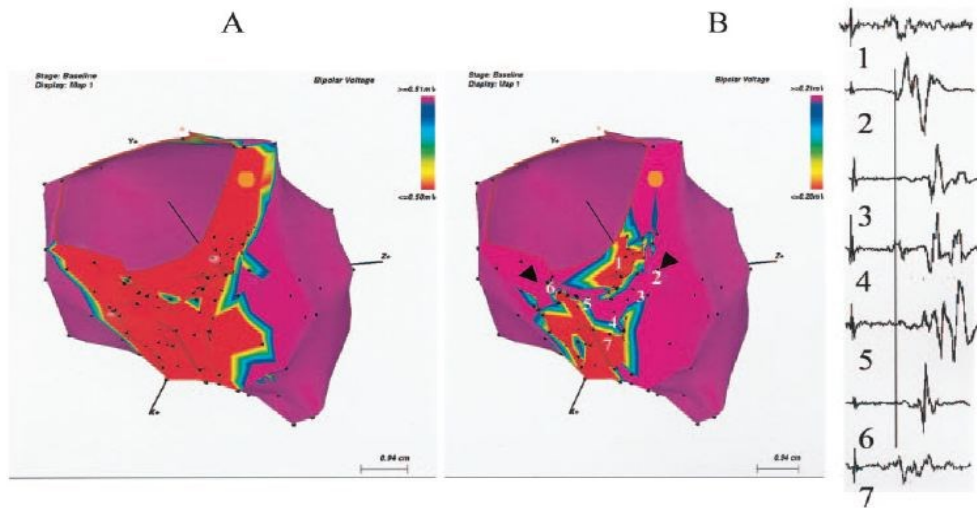


Figure 1-27: Voltage tiered channels

Bipolar voltage map showing the effect of scar voltage definition on identification of channel. Left image, the voltage was set at 0.5mV, and the right at 0.2mV. At this scar voltage definition, a channel spans from septum to lateral wall, defining a complete channel, with multiple-component EGMs recorded within. Activation time seems to follow from both entrances to inner part.⁹³ However, the far-field signal on EGMs 2, 3, 5 is of greater amplitude than the local signal and would have been the signal annotated in assigning the EGM voltage amplitude.

1.7.1.3 Electrode orientation

Whilst it is normally assumed that bipolar voltage is a measure of tissue health, it is only a measure of the potential difference between two electrodes. It can be influenced by multiple variables, leading to significant change in the recorded bipolar voltage amplitude at any single recording point.¹⁰⁵ This is of particular relevance within scarred sites.¹⁰⁶ Indeed, repeat mapping of the same scar may not necessarily create the same voltage display. Changes in polarity and amplitude of a bipolar signal can occur according to the electrode orientation, wavefront direction, wavefront collision and rate. Figure 1-28 illustrates the effect of electrode orientation in relation to the activation wavefront on the recorded bipolar signal.

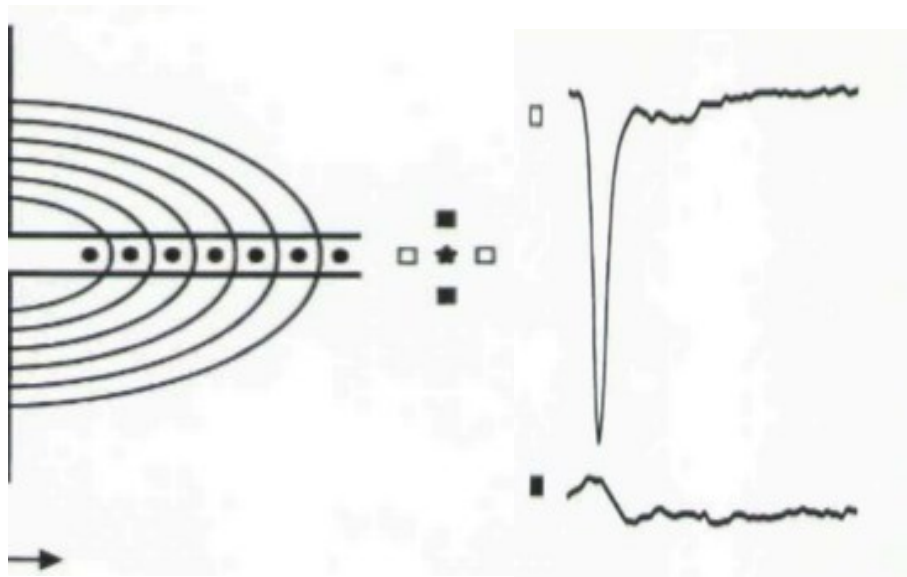


Figure 1-28: Effect of bipolar electrode orientation on recordings. A wavefront moves from left to right, parallel to the fibre orientation (arrow). Bipolar signals for two orthogonal electrode arrangements for longitudinal and transverse conduction are displayed. Open symbols = bipoles oriented parallel with the direction of the activation wave. Note the large amplitude EGM. Filled symbols = electrodes oriented perpendicular with the activation wave. Note the low amplitude EGM.¹⁰⁷

Electrophysiologists often interpret scar patterns by the voltage displays mapped in tachycardia. However, early validation studies of voltage displays compared histo-pathological specimens to scar patterns obtained in sinus rhythm.¹⁰¹ Whether areas of low voltage mapped in one rhythm are always concordant in other rhythms is unknown - recent studies have demonstrated variation in voltage displays between different rhythms.^{108, 109} An example of a study between atrial flutter and sinus rhythm from the same patient is illustrated in figure 1- 29.

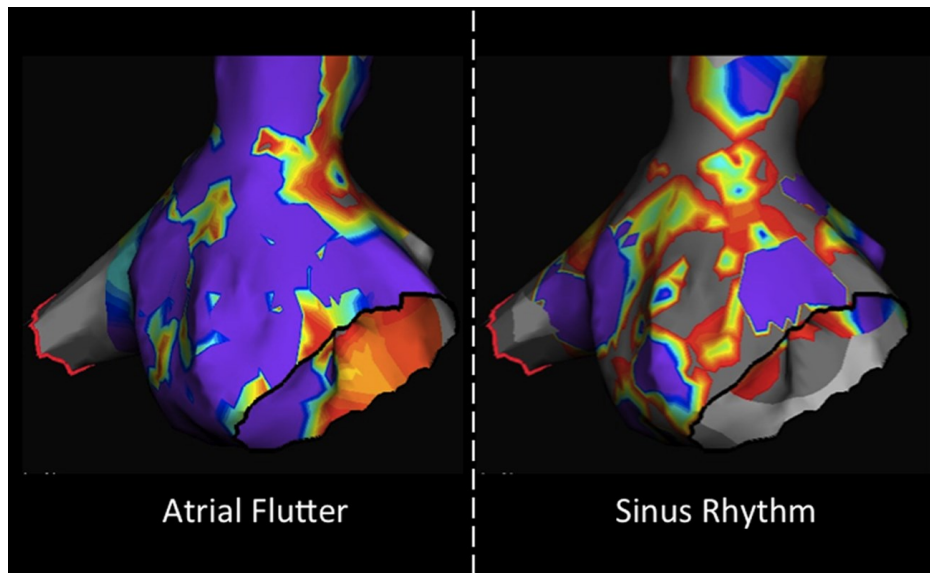


*Figure 1-29: Influence of underlying rhythm on appearance of voltage map
Bipolar voltage display (0.5-1.5mV) from the same patient collected (left) in atrial flutter, and (right) in sinus rhythm. There is marked discordance between the 2 displays.¹⁰⁸*

To correctly interpret areas of low voltage mapped in tachycardia, one must be able to differentiate fixed low voltage secondary to fibrosis from functional low voltage secondary to wavefront interaction.¹¹⁰

1.7.1.4 Unknown atrial scar voltage

There remains no consensus on defining atrial scar with voltage mapping. Normal atrial tissue has been suggested in the left atrium as containing EGM signal greater than 0.45 mV.¹¹¹ Atrial scar has previously been identified by a bipolar voltage of ≤ 0.05 -0.1mV in accordance with the baseline noise in early electro-anatomic mapping systems without published pathological validation.¹¹² Alternatively, defining scar as locations without pace capture (at 10mA/2ms) led to a suggestion of 0.15mV.¹¹³ The mean endocardial voltage within a CMR-confirmed chronic linear atrial ablation lesion was found to be 0.3 mV, though MRI resolution does not reproducibly offer the same accuracy as in ventricular scar in detecting scar in the thin wall atria.^{114,115}

1.7.2 Using activation for substrate mapping

Regions of delayed activation within scar often harbor areas of slow conduction. LAT maps have been used within ventricular scar to display sites of late activation by adjusting the WOI to highlight areas of tissue that activate post QRS (figure 1-30).¹¹⁶

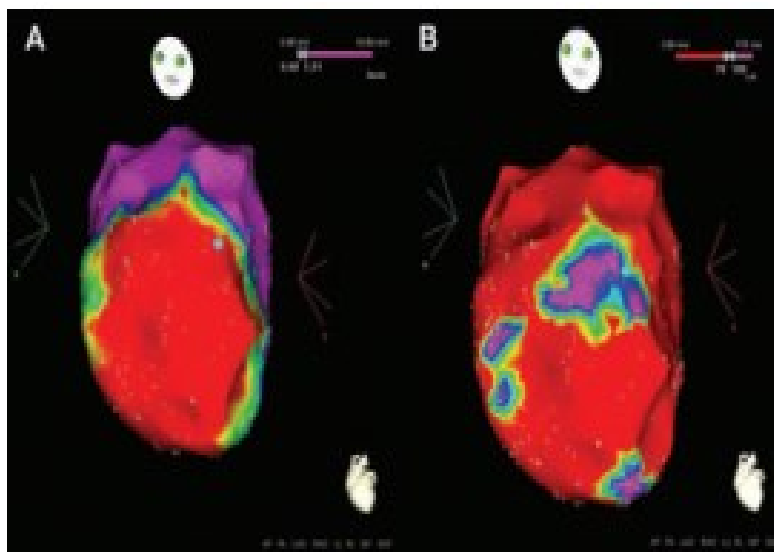


Figure 1-30: Late activation mapping

A patient with previous anterior myocardial infarction. (Left) Voltage mapping showed a large endocardial scar involving the left ventricular apex. (Right) The LAT map was adjusted to highlight all regions that activate post QRS in purple – this late activation zone was located within a small area of the scar and was targeted specifically for ablation.¹¹⁶

Whilst this may identify some late potentials, it ignores all local signals within the time-window spanned within the QRS complex, especially seen when the scar is located close to the breakout site of ventricular activation.

1.7.3 Functional block

Substrate ablation assumes that these regions of slow conduction that support reentry are bordered by fixed anatomical block. Previous studies, include those using a non-contact mapping system within our institution demonstrated that these lines of block can be partially functional with relatively normal EGMs in sinus rhythm (figure 1-31).

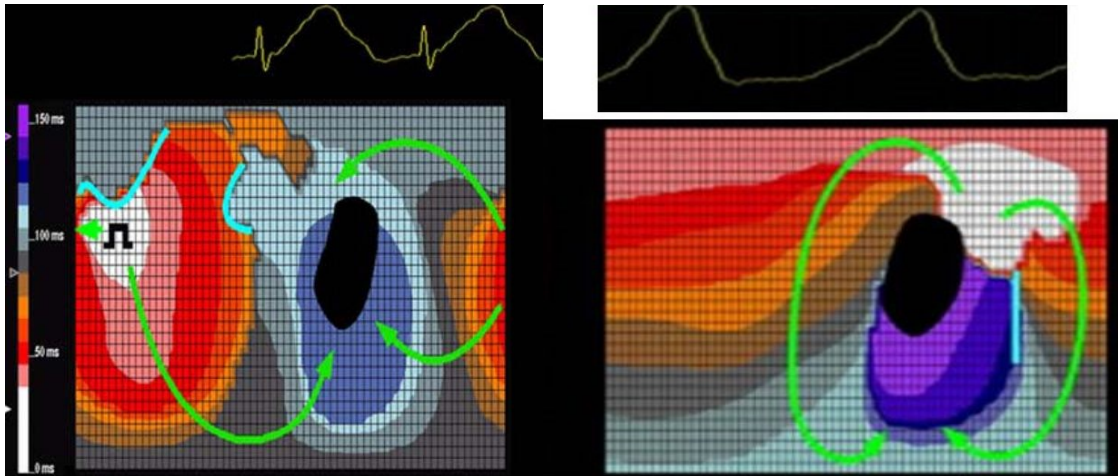


Figure 1-31: Functional lines of block

Areas at which lines of functional block form can be critical to VT formation. Black region represents scar (bipolar voltage <0.5mV). Light blue lines represent lines of functional block. Left: isochronal activation map of the last paced beat from a 300ms drive train. No lines of block are present around the infarct border zone (although one is present adjacent to the pacing site). (Right) Lines of functional block (in a region that previously conducted normally) created a protected zone of slow conduction allowing recovery of myocardial excitability essential for reentry.¹¹⁷

These functional boundaries can arise in regions of damaged tissue secondary to disrupted cellular properties and changes in anisotropy that can slow conduction in the absence of fibrosis.¹¹⁷⁻¹¹⁹ No current method of substrate mapping in sinus rhythm can identify regions of functional reentry during tachycardia. Therefore, despite elimination of all anatomically fixed channels, patients will still be susceptible to reentry.

1.8 Overcoming the present limitations in mapping and ablation within scar

1.8.1 Optimising mapping resolution

Multi-electrode mapping utilising smaller electrodes with closer inter-electrode spacing can offer higher resolution for scar mapping. This is because: 1) multi-electrode catheters offer increased sampling point density; 2) smaller electrodes have smaller electric fields of view; 3) closer inter-electrode spacing record data from smaller tissue diameters, and is therefore more sensitive to detect surviving myocardial fibres within scar. This allows for a more distinct EGM of higher amplitude and shorter duration that allows more accurate annotation of LAT.

Recently, a multi-electrode mini-basket catheter has been developed which comprises 64 mini-electrodes (Orion, Boston Scientific, Cambridge, MA) paired to a 3D contact mapping system (Rhythmia, Boston Scientific). Figure 1-32 presents a photograph of this mini-basket catheter.

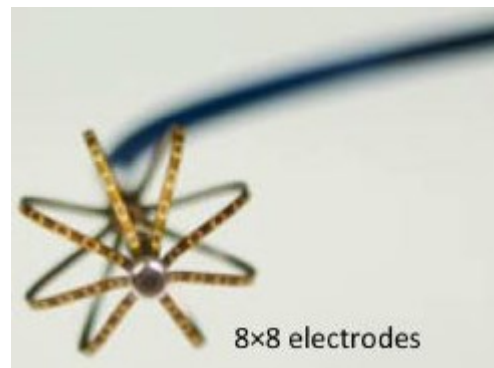


Figure 1-32: Orion Mapping catheter

The mini-basket mapping catheter contains 8 splines each with 8 small electrodes (0.4 mm^2 , 2.5mm centre-to-centre inter-electrode distance). (courtesy of Boston Scientific)

This new mapping system was first studied creating activation maps in the canine right atrium where it was able to acquire a very large number of EGMs (median 4227) in a short period of time (figure 1-33).¹²⁰ The combination of increased sampling density with small size electrodes and close inter-electrode spacing produced very high resolution EGMs. This allowed accurate definition of lines of block

and the presence of electrical gaps along prior ablation lines. The high density of data points minimised error from incorrect annotation of LAT.

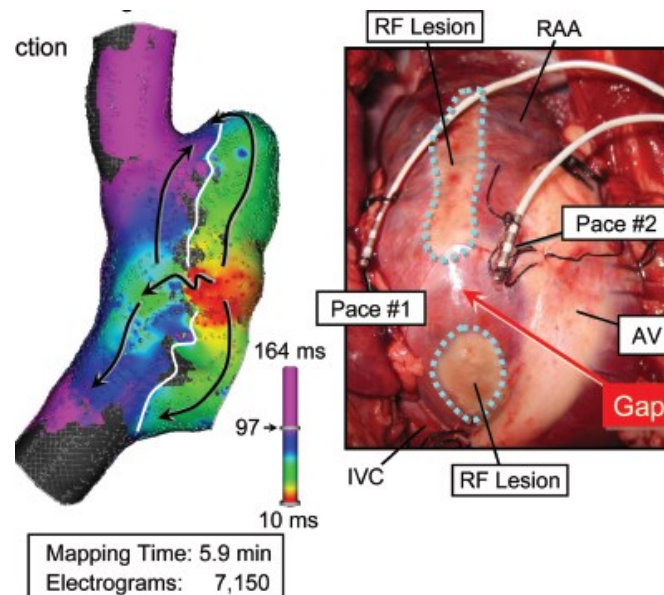


Figure 1-33: Rhythmia activation mapping
 (Left) LAT map collected after the creation of 2 linear ablation lesions, leaving a gap for conduction. (Right) Photograph of the epicardial surface of the RA shows the location of the 2 RF linear lesions (dotted blue lines) with a central gap (red arrow). Pacing anterior to the linear lesions revealed propagation (black arrows) around 2 lines of block (white lines) and across the gap (wiggly black arrow). The map contains 7150 EGMs and was acquired in 5.9 minutes.¹²⁰

The application of this “ultra-high” point density mapping system (often in excess of 10,000 points per map) and improved EGM resolution for activation mapping offers the potential to visualise different arrhythmic circuits within scarred myocardium with greater accuracy as a guide to ablation.^{121, 122}

1.8.2 Alternative approach to activation visualisation

Ripple Mapping (RM) is a novel and unique method of activation visualisation developed within our institution that is not reliant upon annotation of activation time within a WOI, and avoids interpolation within unmapped sites. RM displays the entire EGM voltage-time relationship as a moving bar at its mapped location, perpendicular to the reconstructed chamber geometry and relative to a fiducial reference signal.¹²³ When multiple data points are collected, this is presented as a movie. A “ripple” effect is seen as the bar movements traverse from one bar to the next, and propagation is understood using the human ability to detect and interpret this movement. An example of a Ripple Map of typical atrial flutter from our groups’ first published description of RM is seen in figure 1-34.¹²³

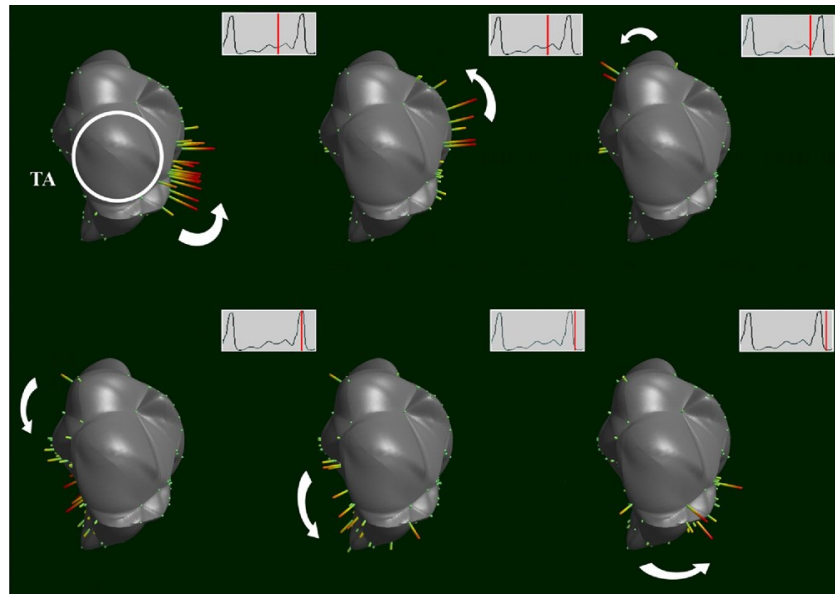


Figure 1-34: Ripple Map during typical atrial flutter.

A shell of the right atrium is displayed in grey. Coloured bars are seen protruding from the shell. The position of the coloured bars changes through time. When played as a movie, the movement of the bars across the map demonstrates anticlockwise activation of the atrium, encompassing the whole TCL.¹²³

Unlike LAT mapping, where activation is represented relative to a WOI , Ripple bars are analysed in relation to each other, therefore there is no concept of 'early' or 'late' but only of local activation direction.

In previous studies from our institution, RM has been tested offline using Matlab software across a spectrum of cardiac rhythms and demonstrated the feasibility to correctly display and interpret cardiac activation.¹²³ RM was subsequently incorporated into an offline CARTO-XP research platform and studied in AT, demonstrating a higher diagnostic accuracy (80%) in interpreting the correct mechanism of activation as compared to LAT maps (50%) in a retrospectively analysed series of ATs.^{124 125} An example of a mitral isthmus dependent flutter as depicted by RM using a CARTO XP platform is shown in figure 1-35.

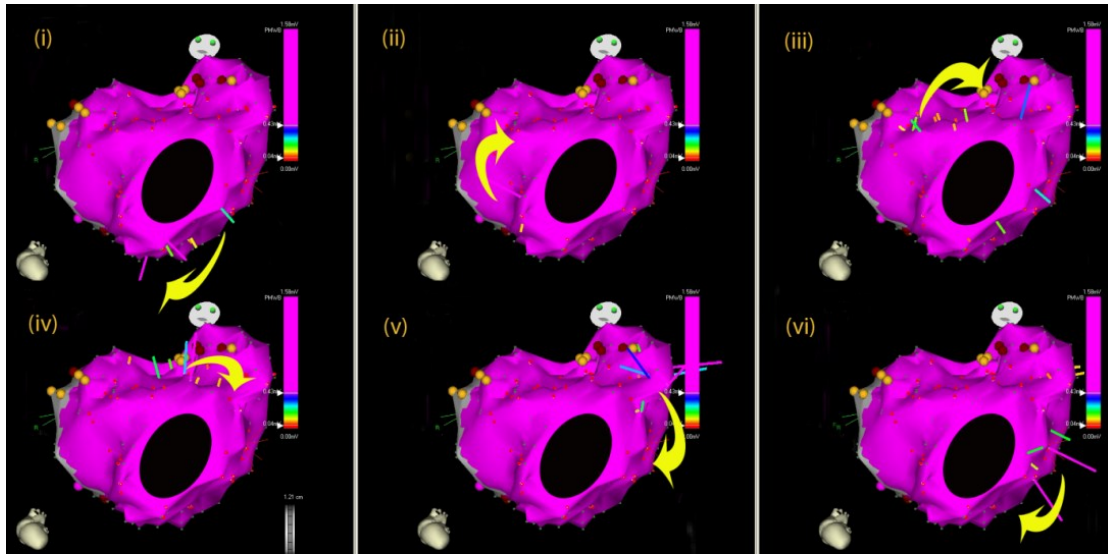


Figure 1-35: Ripple Map on CARTO-XP.

Mitral isthmus dependent flutter. En face view of the mitral annulus (cut out). Coloured bars are seen to rotate around the mitral annulus in a clockwise direction.¹²⁵

Detailed mapping studies of EGMs collected during sinus rhythm within ventricular scar have identified the putative path of slow conduction through the scar. Tung and colleagues positioned multipolar catheters in an orientation that recorded the largest number of late potentials with a gradient of early-to-late activation (figure 1-36), and demonstrated that local ablation targeting the “earliest” late potential eliminated neighbouring and remote areas of slow conduction, suggesting that EGM signals within scar are inter-connected.^{126, 127}

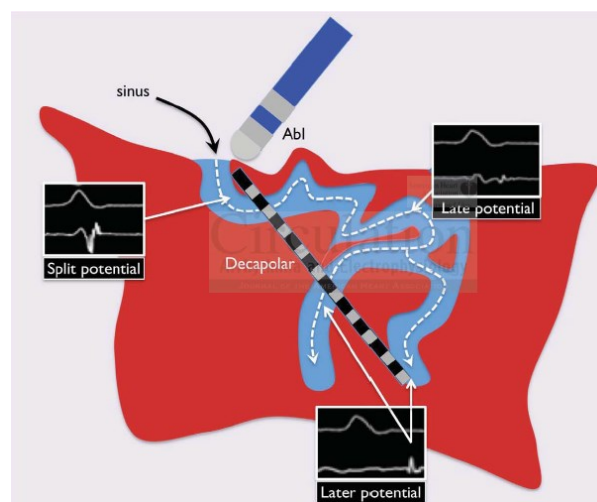


Figure 1-36: Schematic of activation within scar

Progressively late activation is seen after the QRS in sinus rhythm as EGMs are sampled further along the channel.¹²⁶

Another unique advantage of RM is that ripple bar activation can be superimposed on a bipolar voltage map, allowing the possibility of visualising activation directly over scar maps. Our group previously demonstrated that RM could be used to follow local activation through ventricular scar, and visualise “conducting channels” of EGM activation using the off-line Matlab system in a retrospective series of ventricular substrate maps (figure 1-37).¹²⁸

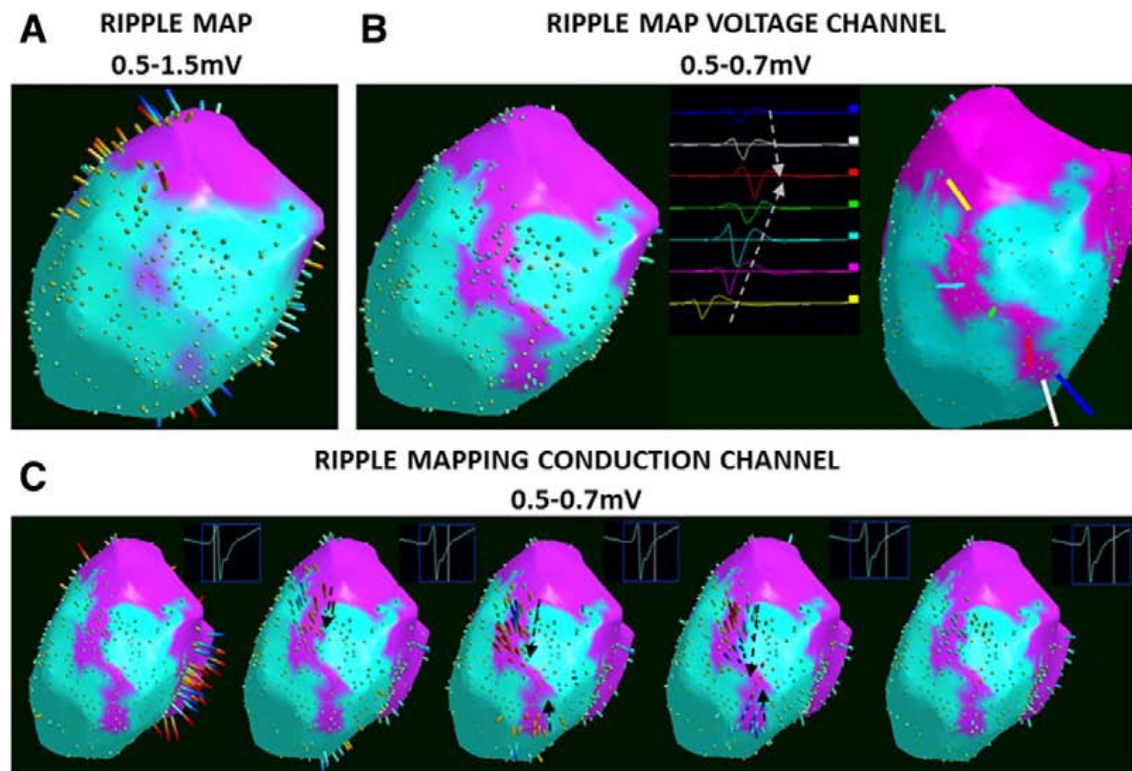


Figure 1-37: Matlab Ripple Map of the LV scar.

(A) The ripple bars can be played over a display of bipolar voltage (purple, healthy myocardium >1.5 mV; cyan blue, scar with a voltage <0.5 mV). (B) As the upper voltage threshold is reduced to 0.7 mV, a channel of higher voltage (purple) is visualised through scar. The EGMs within the channel demonstrate a chevron pattern, as activation moves in from both sides of the scar. (C) Ripple map played during the QRS interval demonstrate bidirectional activation of ripple bars within the channel.¹²⁸

Mapping without LAT annotation or setting a WOI, as well as displaying all EGM components on the map offers an alternative means of mapping scar based arrhythmias. Over the last 2 years, a clinical version of RM has been released on the CARTO3™ (Version 4) for prospective testing in scar based arrhythmia.

1.8.3 Optimal timing for ablation

The evolution of the arrhythmic scar post ablation or post myocardial infarction is complex and poorly understood. It has been studied, to some extent, within post infarct tissue. Within the first week post infarction, the existing extracellular matrix and vasculature is degraded, and replaced by collagen fibres from active myofibroblasts.⁴³ These myofibroblasts develop their own nervous and vascular network that provides for their metabolic activity to continue to turn over collagen long after scar tissue has restored the structural integrity of the infarcted myocardium (figure 1-38). Thus the concept of scar as an acellular and inert collagenous structure is incorrect, and studies have argued that post infarct scar is a “living structure” itself.¹²⁹

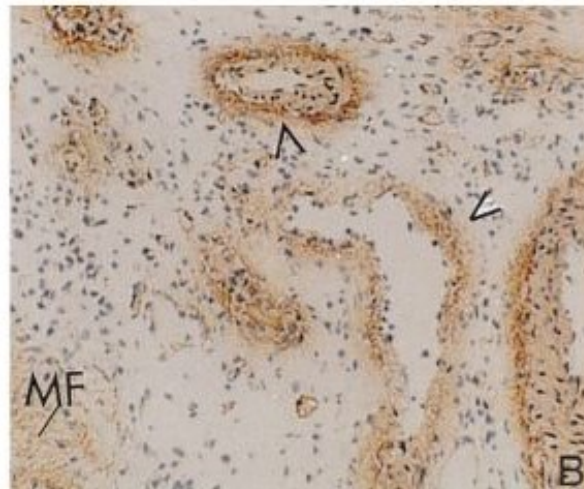


Figure 1-38: Histological staining within ventricular scar eight weeks post infarct. The scar still contains abundant myofibroblasts (MF) and remains vascularized (V)¹²⁹

Scar tissue composition is known to continuously change many years after infarction. The onset of sustained reentrant VT often arises after at least 10 years post infarction.¹³⁰ Animal studies of endocardial substrate have revealed that the area subtended with EGM fractionation increases with time.¹³¹ What this indicates is that the evolution of the arrhythmic substrate within scar is a progressive process, and some studies have suggested that, despite ablation, outcomes may be worse if the substrate becomes too advanced.^{130, 132} A retrospective study into the timing of ablation observed higher recurrence rates the longer the time ablation was performed after the initial episode of VT. Patients referred for VT ablation within 30 days after the first documented VT had higher acute success rates

compared with patients who underwent ablation late, as illustrated in the Kaplan Meir curves from figure 1-39.¹³²

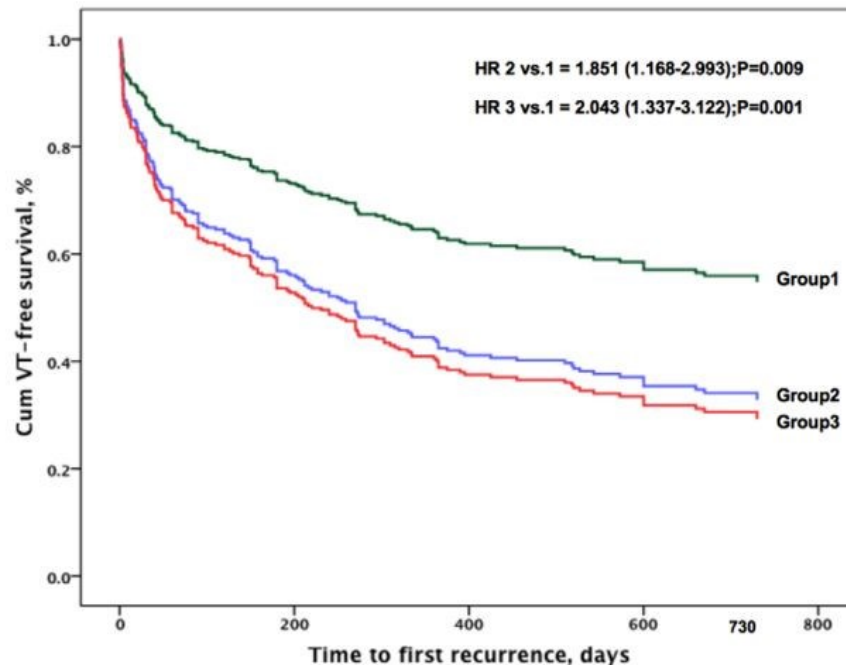


Figure 1-39: Kaplan–Meier curves of VT free survival according to the time to ablation. Patients referred earlier for ablation within 30 days after the first documented VT (group 1; green line) have better long-term VT-free survival as compared with those with delayed ablation between 1 month and 1 year after the initial VT (group 2; blue line), $P=0.009$, and very late ablation >1 year after the first documented VT (group 3; red line), $P=0.001$. HR indicates hazard ratio.¹³²

However, because of its complexity, VT ablation is usually performed in high-volume centres, in patients with high arrhythmia burden/storm and after failure to achieve effective suppression of the VT using anti-arrhythmic therapy. As a result, the majority of the patients experiencing VTs are referred relatively late into the disease course.

Despite these studies, the optimal timing for VT ablation remains unknown. The decision to proceed with ablation must weigh up the benefits of freedom from VT and ICD therapies against the procedural risks. Two randomised controlled trials reported that very early ablation before therapies had even occurred was effective in reducing future therapies.^{133, 134} However, many of the control patients from both trials did not receive any therapies during follow up, raising doubts about the clinical justification of this extensive ablation approach so early into the disease process. Arguments in favour of

early intervention include fewer lifetime ICD shocks (which are associated with a worse prognosis), fewer hospital admissions and potential avoidance of toxic anti-arrhythmics. The arguments against early intervention are related to mediocre mid-long term outcomes (50% recurrence rates), high complication rates (up-to 10% cumulative risk), and that ICD shocks are a marker of more advanced disease rather than a cause for worse prognosis.^{135, 136} Such issues can only be addressed by conducting randomised trials of VT ablation but these have been beset with recruitment challenges, and has led to the non-completion of multiple previous studies.¹³⁷

In our institution, a retrospective analysis of 106 post infarct ICD patients under long term review demonstrated that over an average of 2.5 years follow up period, only half received appropriate ICD therapy of any kind. However, of the remaining half who did have therapy, 89% had more than one episode suggesting that first appropriate therapy is an important predictor of subsequent therapy, and a potential optimal time to consider ablation.¹³⁸

1.8.4 Improving energy delivery by increasing catheter stability

The size and depth of an ablation lesion is dependent upon the magnitude and duration of power delivery, the contact force of the catheter on the tissue and the catheter stability.³⁵ Despite the use of irrigated ablation, durable lesions may not always be achieved, as is evident by the high rates of PV reconnection seen in redo AF ablation procedures despite isolation being documented during the index case.¹³⁹ Several studies have demonstrated that at least 10g of contact force is required to form a transmural lesion (figure 1-40).¹⁴⁰

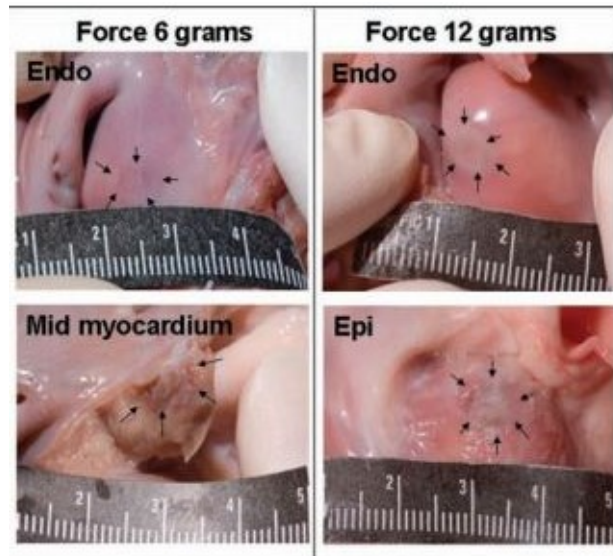


*Figure 1-40: Influence of contact force on achieving transmurality
Transmural lesions were not achievable at contact forces of 6 grams (ablated tissue was only observed upto the level of the mid-myocardium), whereas lesions were transmural at contact forces of 12 grams.⁴²*

The efficacy of contact force sensing during AF ablation was evaluated in the SMART-AF and TOCCASTAR trials.^{141 142} Delivering 10 grams of contact force was not easy, achieved in only 57% of cases in TOCCASTAR and 47% in SMART-AF. Furthermore, even if the average contact force applied was within the target range, catheter instability lead to large variability of the actual contact force value during an RF application. This can arise with sliding of the tip electrode over the endocardium, typically because of respiratory and cardiac motion.¹⁴³ Poor contact can lead to current loss into the blood pool, coagulum generation, and failure to achieve appropriate myocardial temperatures, despite using adequate voltage and power.

Stability of the catheter is particularly relevant in the scarred ventricle where the chambers are often markedly dilated and scars can be deep to the endocardial surface.^{46, 118, 119, 144} We previously reported on a post infarct patient who underwent endocardial VT ablation for shocks but continued to have multiple appropriate ATP therapies during follow up. The patient passed away from a non-cardiac cause and histology from myocardial strips taken post-mortem, displayed in figure 1-41, showed residual normal healthy tissue within the mid-myocardial and epicardial regions of these previously ablated sites.¹⁴⁵ Failure to achieve adequate lesion depth may have been the reason for VT recurrence.

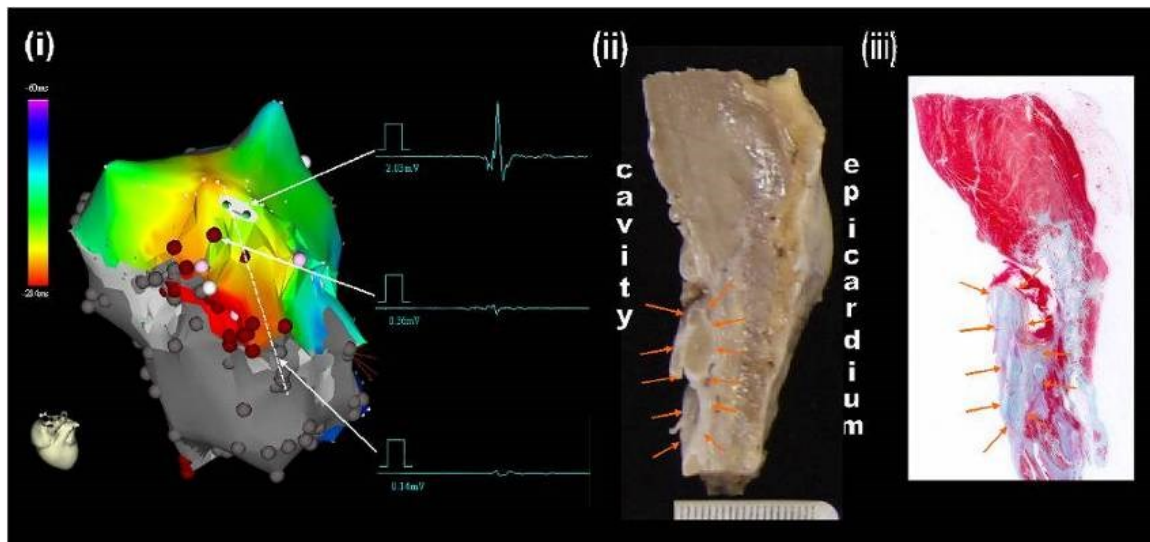


Figure 1-41: Histological study of ablated ventricular scar
 (Left) LAT map in VT with ablation lesions marked as red dots (superior view). Signals taken across scar border from healthy tissue (top) to scar border (middle) to scar (bottom) are correlated with a myocardial strip (ii) taken post-mortem and its corresponding histology (iii).¹⁴⁵ (Sections were stained with Masson's trichrome - myocardium is stained red, scar tissue stained blue.) There were areas of fibrotic scar tissue endocardially and viable myocardium epicardially. Residual normal healthy tissue (stained red) is seen in the company of ablation related scar (stained blue).

Multiple studies have demonstrated high VT recurrence rates despite ablation, and as we have shown using post-mortem histology, one of the reasons for these high rates of recurrence may be sub-optimal catheter stability. One of the biggest prospective studies assessing the effectiveness of post infarct VT ablation enrolled 231 patients. During a 6-month follow-up period, only 49% of patients were free of VT.¹³⁶ VTACH examined whether prophylactic substrate ablation in patients with secondary prevention ICD's reduced the incidence of future ICD therapies. Whilst patients who underwent ablation did have fewer recurrences than those that did not, after 2 years the recurrence rate in the ablation arm was 50%.¹³⁴ Even in the more recent VANISH study, a 60% recurrence rate was seen in the ablation arm at 2yr follow up – and this only included recurrence of VT storm or ICD shocks, and does not even account for those additional patients with ATP treated VT episodes.¹⁴⁶ In the CALYPSO pilot study, recurrence rates were higher in the ablation arm as compared to the control.¹³⁵ We have shown that increased stability of the ablation tip using robotic manipulation in the atria is associated with greater EGM diminution (figure 1-42). This raises the option of improving ablation outcomes within the post infarct ventricular scar by increasing catheter stability.

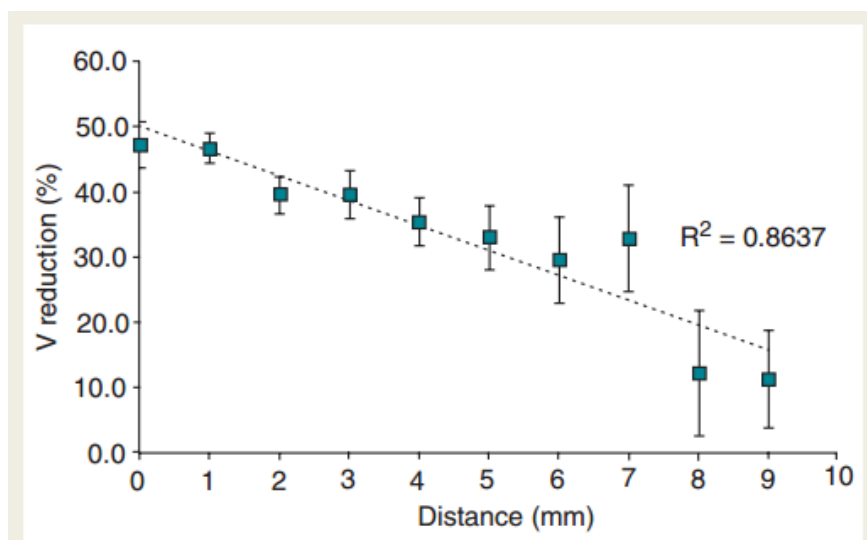


Figure 1-42: Influence of catheter stability on EGM signal attenuation

A graph comparing the distance moved by the catheter tip on the myocardial surface during energy delivery with the corresponding bipolar EGM signal attenuation percentage. With increased catheter movement during ablation, the % voltage reduction achieved is less. Thus greater catheter stability is associated with greater signal amplitude reduction.¹⁴⁷

Precise placement and catheter control are required for effective ablation delivery. Improved catheter control can be supported by deflection mechanisms integrated within the handle of the catheter, allowing the operator to navigate the catheter to the desired position guided by fluoroscopy. Furthermore, a variety of sheaths with different shapes and additional deflectable mechanism have been developed to increase catheter manoeuvrability and support, but rely on operator skill and stamina to maintain stability. Chamber dimensions are often dilated in patients with structural heart disease and the targets for ablation can be both small and hard to reach. To address some of the challenges of achieving increased catheter stability, robotic technologies were developed. The use of robotics offers potential advantages that include stability, precision and the ability to perform procedures remotely.

In the first report of a robotically controlled “master-slave” catheter system in ex-vivo hearts, robotic navigation demonstrated a greater range of motion and increased control of the catheter tip than with a standard catheter and deflectable sheath, as it eliminated the need to apply manual torque on the catheter or sheath shaft in order to reach a given target.^{148 149} Two systems for remote navigation of catheters within the heart have been developed; the first is based on a magnetic navigation system

(Niobe, Stereotaxis, Saint-Louis, Missouri, USA) that involves magnetic tipped catheters that are directed within a magnetic field, and the second is based on a steerable sheath system (Sensei, Hansen Medical, Mountain View, CA, USA). Both systems have been integrated with 3D navigation systems.

The magnetic navigation system consists of 2 magnets positioned on either side of the fluoroscopy table, controlled inside a fixed housing. A uniform magnetic field of approximately 15 cm is generated inside the chest of the patient. A soft and non-irrigated mapping and ablation catheter, equipped with its own magnet at the tip, aligns itself in the direction of the magnetic field. Catheter movement is achieved by changing the orientation of the magnetic field by moving the outer magnets. The system is remote controlled by a joystick.¹⁵⁰

We have tested the steerable sheath system extensively in our institution.¹⁵¹ This Hansen Sensei® X Robotic Catheter system (figure 1-43, Hansen Medical Inc., Mountain View, CA, USA) comprises the physician's workstation, remote catheter manipulator (RCM) and a steerable guide catheter (Artisan™ Control Catheter) in which the ablation catheter is locked in. The movements of a joystick within the physician's workstation are transferred into movements of the catheter manipulator, a robot that controls pull wires within the steerable sheath, manipulating the position of the ablation catheter tip.

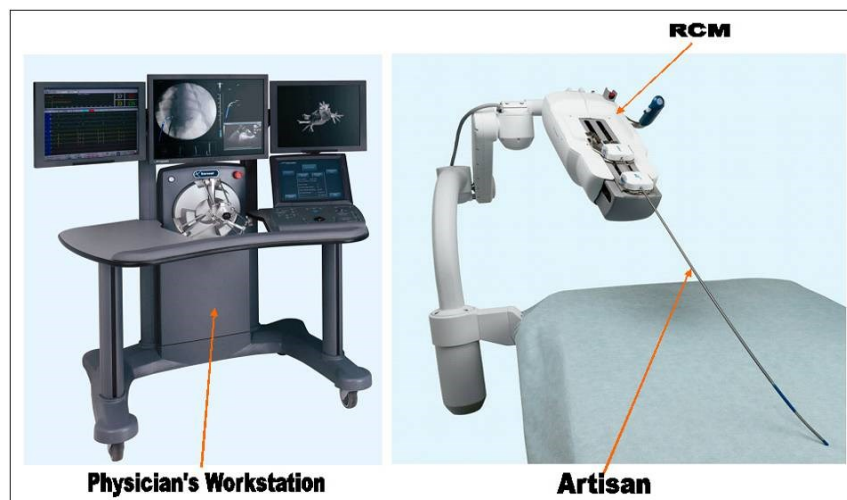


*Figure 1-43: The Hansen Sensei X Robotic Catheter system.
(Left) The physician workstation comprising screens to display fluoroscopy, EP data and the 3D mapping system, as well as a joystick control that controls the Artisan (Right), within the remote catheter manipulator.¹⁵¹*

In animal studies, we have previously demonstrated that at equivalent ablation settings, a more rapid and greater reduction in local EGM amplitude during robotic ablation compared with manual. Macroscopic examination of robotic lesions was also associated with greater lesion transmuralty (figure 1-44).^{145 152}

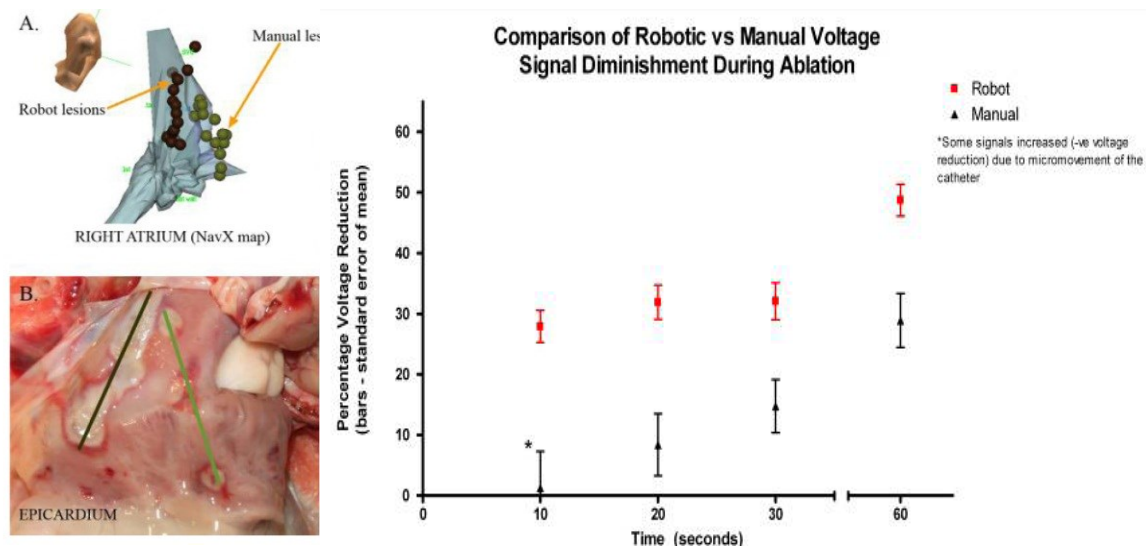


Figure 1-44: Voltage signal attenuation and lesion transmuralty between robotic/manual. (Left - A) NavX map of the right atrium (RA) showing robotic posterior ablation line (brown) and manual line (green). (Left - B) Epicardial surface of the RA (same orientation as A) showing transmuralty from robotic ablation, but there is little evidence of manual lesions anteriorly.¹⁵² (Right) A graph comparing the % voltage reduction in EGM signal following robotic (red square) and manual ablation (black triangle) over a time period of 60seconds. After 10secs, there is clear separation in % voltage reduction between the two ablation approaches, which continues through time.

We and others have demonstrated the feasibility of robotic catheter navigation within the left atrium during AF ablation.^{151, 153-155} Robotic navigation limits the amount of fluoroscopy exposure and fatigue associated with prolonged ablation procedures. Comparative outcome studies between robotic and manual procedures have been undertaken in several common arrhythmias, including AF, demonstrating that whilst procedural times and success rates have been similar, this has been achieved with reduced fluoroscopy time, thought related to improved catheter stability.^{156 157-159} Feasibility and safety in using robotics in performing LV endocardial mapping and ablation has been documented in only a few case reports and a single case series.^{160, 161} Because the catheter is rigid when not being manipulated, it retains its position in any anatomic location, mostly unaffected by blood flow or cardiac motion. This is in contrast with magnetic navigation systems, in which the catheter shaft is necessarily soft by design (in

order to allow its pulling by magnetic fields), and that softness makes it subject to motion by blood flow. Persistent tissue–catheter contact without excess applied force prevents substantial ectopy and myocardial wall distortion; this permits accurate electro-anatomical mapping of even very low voltage signals, with a high degree of precision and safety. Whether this translates to improved procedural outcomes during VT ablation is unknown.

1.9 Original Hypothesis

This thesis is based on the following observations:

1. Regions of slow conduction within scar are often critical to the reentrant arrhythmic substrate.
2. Failure to achieve transmural ablation within these regions can lead to arrhythmia recurrence.
3. This electro-architecture appears to evolve with time.
4. Mapping within scar is limited by conventional activation and voltage mapping approaches.

We hypothesized that increased catheter stability with robotic navigation, an earlier ablation approach, and better electrophysiological characterisation of the scar was needed to improve outcomes.

1.10 Scope of the thesis

In order to address this hypothesis, the arrhythmogenic substrate within both atrial and ventricular scar was studied in patients presenting with post-ablation AT and post-infarct VT respectively.

In ventricular scar, it was assumed that regions of myocardium with bipolar voltage between 0.5mV-1.5mV formed the arrhythmogenic substrate, and trans-mural ablation within these areas would prevent VT recurrence. Chapter 3 investigates the use of the Hansen Sensei robotic system within ventricular scar during ischaemic VT ablation by comparing acute and long-term outcomes of ablation to a cohort of patients who underwent manual ablation. The optimal timing of VT ablation was also studied in a randomised, multi-centre trial of robotic VT ablation in patients after their first episode of VT.

Chapter 4 investigates the effectiveness of improving activation mapping resolution to better delineate arrhythmogenic activation within scar using the ultra-high density Rhythmia mapping system to improve outcomes. This was tested in the mapping of localised reentry within iatrogenic atrial scarring post AF ablation, involving slow conduction around small scars.

It was apparent that improved resolution alone would not overcome the limitations in scar mapping. Ripple Mapping is not dependent on timing annotation, and can integrate activation and voltage displays on the same map. Chapter 5 investigates the effectiveness of Ripple Mapping within atrial scars during AT procedures as a means to guide ablation delivery, in both single centre and multi-centre cohorts.

Chapter 6 studies RM within ventricular scar as a novel approach to substrate ablation in post-infarct VT.

Chapter 7 uses RM to consider whether a substrate based approach is best to improve outcomes, by questioning whether the identification of slow conduction mapped outside of tachycardia remains specific for the arrhythmic substrate.

Chapter 8 summaries the conclusions from each chapter within this thesis and considers a future study to explore from this knowledge.

Chapter 2

2 - General Methodology

In this chapter, our general approaches used within post-infarct VT and post-ablation AT procedures are summarized, followed by a description of each mapping and ablation technique employed. This includes the Hansen robotic catheter control system, the Rhythmia ultra-high density mapping system, and the CARTO3 mapping system with the ConfiDENSE and Ripple Mapping module. Further detail specific to each study is presented within the methods section of each relevant chapter.

2.1 Procedural details

2.1.1 Study population

VT: The study population consisted of patients with previous myocardial infarction related to coronary artery disease with primary or secondary prevention ICDs referred by their clinical electrophysiologist from clinic or the cardiac ward for VT ablation. Reason for referral included one or more documented episodes of sustained VT or appropriate ICD therapy (including VT storm). The use of anti-arrhythmics prior to ablation was at the discretion of the responsible cardiologist, in line with current guidelines.¹⁶² Coronary angiography was performed to exclude an ischaemic trigger where necessary, and patients were excluded if revascularization was required. Transthoracic echocardiography with contrast assessment was used to determine the left ventricular (LV) ejection fraction, distribution of regional akinesia as a surrogate for scar, and exclude patients with identified cardiac thrombus or severe valvular heart disease. Patients with end stage renal failure, intractable heart failure (New York Heart Association Class IV), malignancy or bleeding disorders were also excluded. Pre-procedural cardiac magnetic resonance imaging was not feasible in our institution owing to the presence of the ICD.

AT: The study population consisted of patients with symptomatic paroxysmal or sustained AT, at least more than 3 months after previous AF/AT ablation, referred by their clinical electrophysiologist for AT ablation. Patients thought to have cavo-tricuspid isthmus dependent atrial flutter or with variable AT cycle lengths were excluded.

2.1.2 Set-up

All anti-arrhythmic drugs, except beta-blockers, were stopped 5 days before the procedure. Patients were studied in the post-absorptive state under general anaesthesia. Trans-oesophageal echocardiography was used to exclude left atrial appendage thrombus and guide atrial transseptal puncture. Arterial and venous sheaths were placed in the groin for intra-cardiac access and systemic pressure monitoring. Surface ECGs and bipolar EGMs were monitored continuously on a LabSystem Pro (Bard Electrophysiology, Lowell, MA), sampled at 1 KHz and band-pass filtered at 30–250 Hz, with the notch filter switched off. A standard decapolar catheter was placed in the coronary sinus. The left side heart was accessed via atrial transseptal puncture (BRK Needle, St. Jude Medical) and/or retrograde approach from the aorta. Heparin boluses were administered intravenously to target an activated clotting time >300 seconds.

2.1.3 Induction

VT: Induction was performed from 2 sites, including the right ventricular (RV) apex, and either the RV outflow tract (OT), or within the LV where pace capture was consistent. This included 2 pacing drive trains, with up to 3 extra-stimuli decremented to ventricular refractoriness or 200ms. If a stable VT was induced, an attempt at mapping the arrhythmia was undertaken. If an unstable VT was induced, it was terminated by overdrive pacing or defibrillation, and no further attempts to induce VT were performed until after substrate mapping and ablation.

AT: Those patients who presented in sinus rhythm on the day of the procedure underwent induction protocols prior to mapping. This was performed from the coronary sinus and included atrial extra-stimulus testing or burst pacing to 200ms. Following termination of tachycardia post ablation, re-induction of AT was at the discretion of the operator.

2.1.4 Mapping and ablation

Operators had the choice of mapping with linear catheters, multi-electrode catheters, or both. Consideration between catheter type was based on chamber location, chamber size and operator preference. Power controlled RF energy was delivered (Stockert 70 RF generator, Biosense Webster) through an irrigated ablation catheter (discussed below). Power was titrated between 25–35W in the

atrium, and between 30W for 60secs (17/ml/min) or 50W for 30secs (30ml/min) in the ventricle. A contact force of 10-20g was targeted.

2.1.5 Endpoints

Post procedural inducibility testing using the same induction protocols were performed to determine an acute procedural endpoint. Following VT ablation, ICD interrogations were conducted every 3 months or as symptoms dictated. Endpoints were defined by the time to first VT episode recurrence (first ATP or shock therapy, or sustained VT captured within a monitor zone or 12 lead ECG) and the total therapy burden. All patients were offered remote monitoring. No follow up was conducted in the AT studies.

2.2 Hansen Robotic navigation

The Hansen Sensei Robotic Catheter system comprises 3 components – the physician's workstation (Sensei robotic control system), remote catheter manipulator (RCM) and a steerable guide catheter, known as the Artisan Control Catheter. The physician's workstation incorporates screen displays for the 3D mapping system, electrophysiology data, and fluoroscopy with a superimposed live model icon of the Artisan.¹⁵¹

The Artisan Control catheter is a robotic hollow catheter consisting of a steerable inner and outer guide sheath system. Conventional 8Fr or smaller mapping and ablation catheters can be locked within the Artisan. The inner sheath is controlled by four orthogonal pull wires that deflect the catheter in x and y directions, allowing a tight bend radius of up to 270° in virtually any direction, and 10 cm extension. The tensile strength of the pull-wires within the sheath maintains its shape, allowing improved catheter stability and increased lesion depth. Control of the Artisan from the workstation involves a 3-dimensional hand operated joystick. The position of the joystick is registered from internal sensors, which guide the RCM, a robot designed to accept the Artisan. The movement of the RCM is transferred to the Artisan pull wires, which determines the position of the catheter tip.¹⁵¹ A photo of the RCM and the Artisan sheath in maximal flexion is presented in figure 2-1.

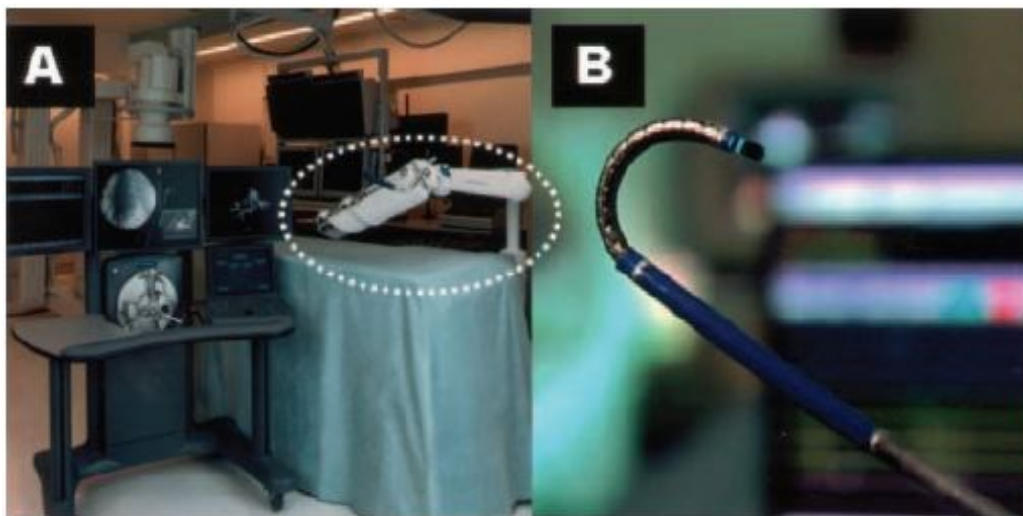


Figure 2-1: Various components of the Hansen robotic system.

A, The mobile physician workstation and the robotic arm (circled) mounted to the foot of the x-ray fluoroscopy table. B, Example of the Artisan sheath demonstrating a degree of deflection, with an ablation catheter protruding from the tip.¹⁵⁴

One of the limitations of robotic catheter navigation is that, in separating the human operator from the ablation catheter, the tactile sense of catheter tip/tissue contact is reduced. This can be of particular concern owing to the rigidity of the Artisan sheath. Prior to the introduction of contact force sensing, operators applied the integrated Intellisense Fine Force Technology which used two force sensors that gripped the shaft of the ablation catheter as it protruded from the Artisan to determine coaxial force data. A reading of continuous force feedback allowed the operator to maintain adequate catheter tip-tissue contact, and prevent excess pressure. Figure 2-2 illustrates how real-time contact force data is presented to the operator. This was the first contact force measurement available in electrophysiology.

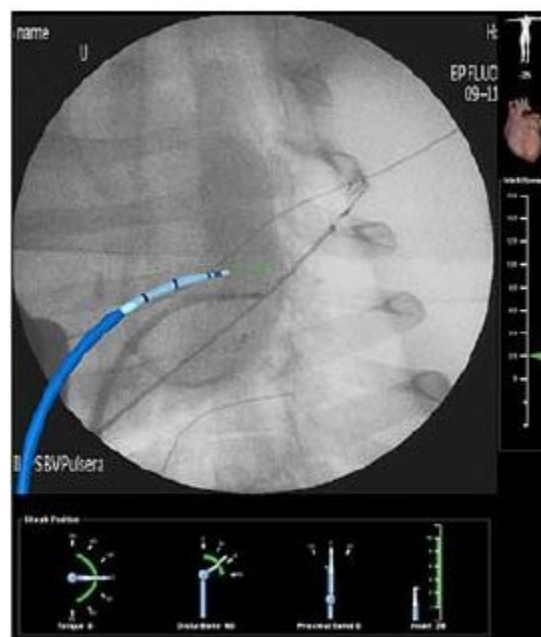


*Figure 2-2: Contact force visualisation using the Hansen system
The steerable guide catheter can be seen on the central “control view” display. Real-time data on catheter orientation, catheter-tip pressure, and contact force are observed.¹⁵¹*

With robotically guided ablation, as a result of increased catheter stability, a greater current can potentially be delivered to the tissue, with an increased risk of overheating. Animal studies using the robotic system demonstrated greater risk of charring or perforation with a power of 45W.¹⁶³ Owing to the stability afforded by the robotic system, the power delivered can probably be lowered with the same resultant attenuation of myocardial signal.

When using the Hansen system during VT ablation in our institution, a standard transseptal puncture was performed from a right femoral venous access and J-wire was placed in the left upper PV. The

Artisan sheath was loaded with the ablation catheter and introduced through a long 14F sheath via the left femoral vein. The robotic catheter was steered along the J-wire to enter the left atrium. The robotic sheath was steered into the left ventricle with the outer sheath of the Artisan positioned within the left atrium to support access to all parts of the left ventricle. Irrigated catheters were used for mapping and ablation within the ventricle. The Hansen system's integrated contact force feature, Intellisense, was used for contact force feedback initially, and latter cases used catheters capable of sensing contact force. In view of the fact that we were likely to achieve greater catheter stability and endocardial RF energy delivery with the robot, we intentionally reduced the power delivery during robotic ablation to no more than 30W, and delivered each lesion for no more than 60 seconds.

2.3 3D navigation and localisation - CARTO3

System design: The CARTO mapping system (Biosense Webster, Inc., Diamond Bar, California) uses an electromagnetic method to determine catheter location to create a 3D anatomic shell of the cardiac chamber. Magnetic fields are generated by a “location pad” placed under the patient table. Catheters designed for use with CARTO are equipped with a location sensor embedded in the tip of the catheter that provides real-time information to triangulate the catheter location, based on the magnetic fields generated by the location pad. CARTO3 is the latest generation mapping platform (following on from CARTO XP and CARTO MEM), offering a mean magnetic-based catheter location accuracy of 1mm. Additional localisation technology integrated within the system uses high-frequency/low-power current emission from each catheter electrode detected by 6 location patches placed on the patient’s chest and back (figure 2-3). A proprietary algorithm integrated within the system is used to equate catheter location based on the relative measured current emanating from each patch. To warn the operator of a map shift, the relative location between the back patches and location pad is used to determine a “virtual location reference.” When the system detects a map shift, by virtue of a change in the relative distance between the back patches and reference, it recommends a new map is collected.



Figure 2-3 CARTO Locator pad

Left: CARTO locator pad placed under the patient table generates a low amplitude magnetic field. Right: CARTO location setup page that illustrates this pad and its relation to the chest (yellow) and back (green) patches on the patient. (Courtesy of Biosense Webster)

A Patient Interface Unit (PIU) stationed in the operating room is used to interface catheters and other EP equipment, and is the processing unit for implementing all real-time location and ECG calculations (figure 2-4). The PIU enables:

1. Output of intra-cardiac and body surface signals to the EP recording systems via an intra-cardiac out cable connected from the PIU to the EP polygrapher system.
2. Integration of location data from the six patches via a patch sensor unit.
3. Connection to the workstation, often housed in an adjacent observation room via a fibre-optic cable.
4. Control of RF energy delivery for catheters with a thermocouple sensor via an indifferent electrode applied to the patients back.



*Figure 2-4: CARTO PIU
(Courtesy of Biosense Webster)*

Geometry construction: A 3D reconstructed shell of the chamber of interest is created by dragging catheters around the cardiac surface. Computer software visualises and tracks the various positions reached by the catheter, and then applies an algorithm to overlay a shell upon these points. Although the shell inferred from catheter movement tends to overestimate the actual volume, a respiratory gating algorithm can correct for the movement of the heart that occurs with ventilation. Maps created can be rotated and re-orientated to better visualise heart anatomy or to closely examine a part of the map in detail. Electro-anatomical (EA) maps are constructed by combining and integrating information from the cardiac EGMs seen during geometry acquisition with their respective location data. CARTO then presents an on-screen, real-time geometric representation of the heart chamber containing both LAT and voltage information. When a linear mapping catheter is used, each point reflects the location

and electrical data of the tip electrode. When a multi-electrode mapping catheter is used, several points are acquired with each acquisition.

CARTO offer two types of geometric displays – “Fast Anatomical Maps” (FAM) or “point by point” displays. Point by point geometric displays create a shell precisely where the mapping catheter has acquired a data point. FAM smoothens out the geometric shell. The degree of smoothing is adjustable, defined by the system using an arbitrary range from 0-20. The lower this value, the greater the degree of surface smoothing. Figure 2-5 illustrates examples of the same shell displayed with high resolution and low resolution.

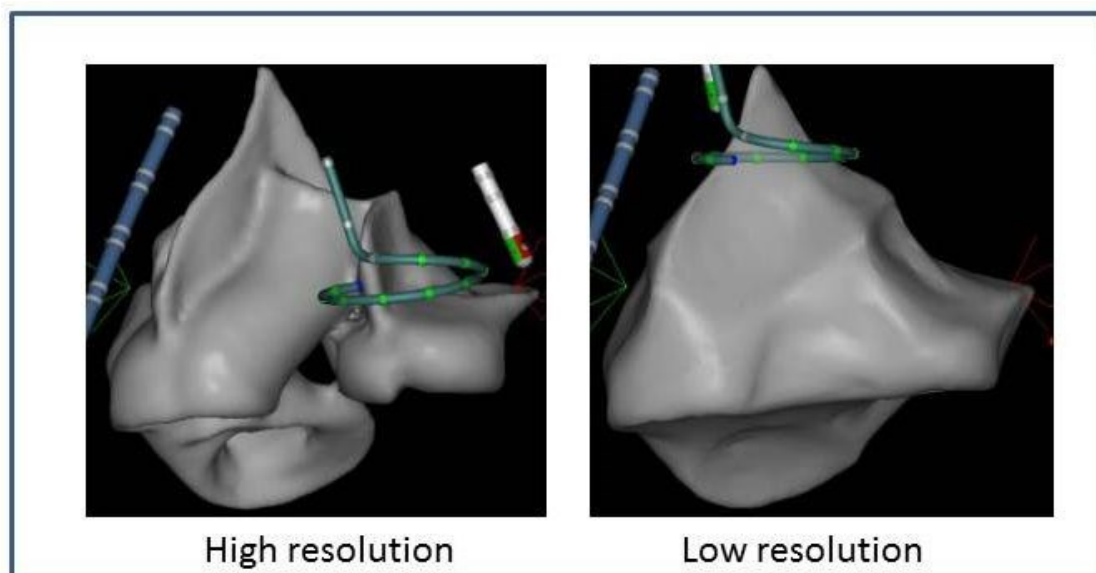


Figure 2-5: FAM resolution

The level of detail of the FAM reconstruction can be adjusted globally, for the entire reconstruction, or regionally, for a specific area of interest. A high level of detail (high resolution) generates a detailed reconstruction that tightly fits the acquired data. A low level of detail (low resolution) generates a less detailed reconstruction with more interpolation between the acquired data. The image depicts the same geometric shell at high and low resolution.

Mapping: CARTO voltage and LAT maps are coloured from red (assigned to the minimum value in the designated window) to purple (assigned to the maximum value in the designated window) along the rainbow colour spectrum (figure 2-6). A colour scale bar displays the range of electrical data collected and their associated colour along this spectrum. The minimum and maximum limits in the displayed map can be manually adjusted by dragging sliders across the colour bar.

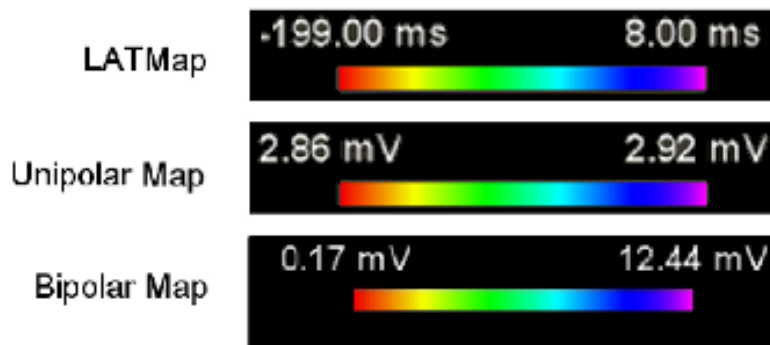


Figure 2-6: Examples of colour scale bar values
(Courtesy of Biosense Webster)

CARTO LAT propagation maps present a cine-like version of electrical propagation in the heart, as a continuous loop. The map is coloured red and blue with red representing activated tissue at that time point, and blue representing inactivate tissue. An example is presented in figure 2-7.

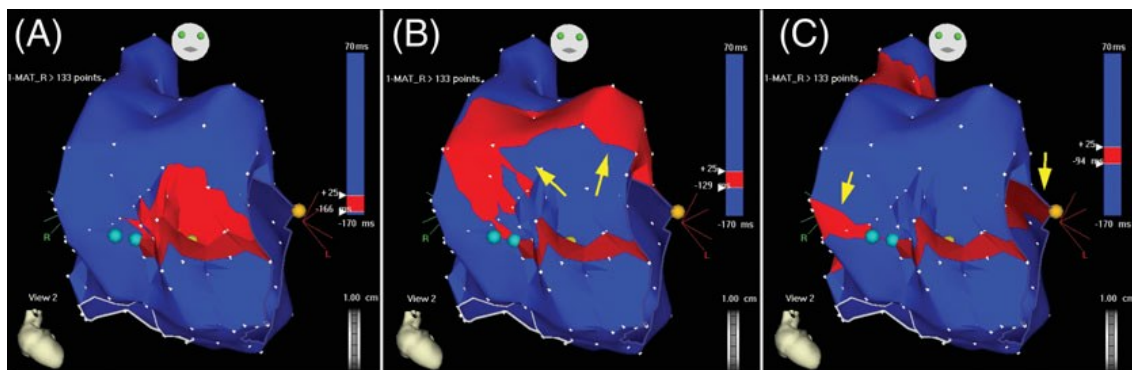


Figure 2-7: CARTO Propagation map
Sequential frames of a macro-reentrant propagation map. The propagation wavefronts are represented by the red bands, and the timing in the tachycardia cycle is indicated by the scale on the right-hand side of each frame.

A “colour threshold” function limits the degree of background colour interpolation on the acquired geometry, defined by the system again using an arbitrary range from 0-20. The lower this value, the less interpolation of colour is evident between data points.

Tagging: Low voltage EGMs below an arbitrary and adjustable amplitude can be highlighted on the map as scar, where the associated electro-anatomical point is tagged in grey. In doing so, these points only

contribute anatomical information to the map. Coloured point tags can also be used to mark a specific point in the map for easy reference.

Internal points filter: Internal points are those points collected within the blood pool away from the endocardial surface. EGMs from these sites are likely to be of lower amplitude, and their projection on the map may mislead operators to considering the projected EGMs arose from a region of scar. An internal point filter sets a threshold for inclusion of points in proximity to the anatomical shell based on the distance from the surface reconstruction according to a 0 – 30mm scale.

CARTO Catheters: There are three CARTO based catheters commonly used for mapping with the CARTO system. The Thermocool-Smarttouch catheter (Biosense Webster) is a linear contact force sensing catheter. It is composed of a 3.5mm irrigated tip which houses an electrode dipole for mapping. The catheter tip is mounted on a precision spring that deflects both axially and laterally. Micro-deformations of the precision spring are converted to a contact force value every 50ms, displayed continuously in real time in grams.⁴¹ Location sensors within the shaft determine the precise angulation of the catheter tip in relation to the shaft orientation. The catheter is deployed through an 8Fr sheath for mapping and ablation in any chamber.

The Lasso (Biosense Webster) is a 20-pole platinum electrode deflectable catheter. The electrodes are housed at the distal tip on a 4.5Fr circular spine. Each electrode is 1mm in size, and can be used for pacing and recording. A nitinol loop allows expansion and contraction of the circular spine to custom-fit veins with different sizes, ranging from 25mm to 15mm diameter, and adjusted using a mechanism within the handle. The catheter is deployed through an 8Fr guiding sheath for mapping exclusively within the atrium. Care is required to avoid catheter snagging within valvular apparatus close to the ventricle.

The Pentaray is also a 20-pole catheter, organized along 5 soft and flexible branches arranged as a star to provide full and atraumatic surface coverage. Each branch is composed of 4 electrodes, 1mm in size, and spaced either 4mm apart, or in a 2mm by 6mm by 2mm configuration. The catheter can be used within all 4 chambers and can record signals with high resolution.

These three CARTO based mapping catheters are shown in figure 2-8.



Figure 2-8 CARTO based catheters

Linear and multi-electrode types (courtesy of Biosense Webster)

2.3.1 CARTO3 ConfiDENSE module

CARTO3 incorporates the ConfiDENSE module, a feature designed to improve the EGM signal quality incorporated within the map, and subsequent mapping accuracy. The module consists of a series of filters that review each passing EGM picked up by the mapping catheters. These beat acceptance filters include 1) “cycle length range” that measure the cycle length between 2 beats and accepts those within a predefined limit; 2) “LAT stability” that compares the LAT of each new beat to the previous beat and rejects those with LAT more than a pre-defined stability time (set between 0-10ms); 3) “position stability” filter that rejects points collected outside of a specified area (set between 1-12mm) between consecutive beats; and 4) “density” that defines the minimum inter-point density (between 1-4mm) between projected points. The ConfiDENSE filter display is depicted in figure 2-9.

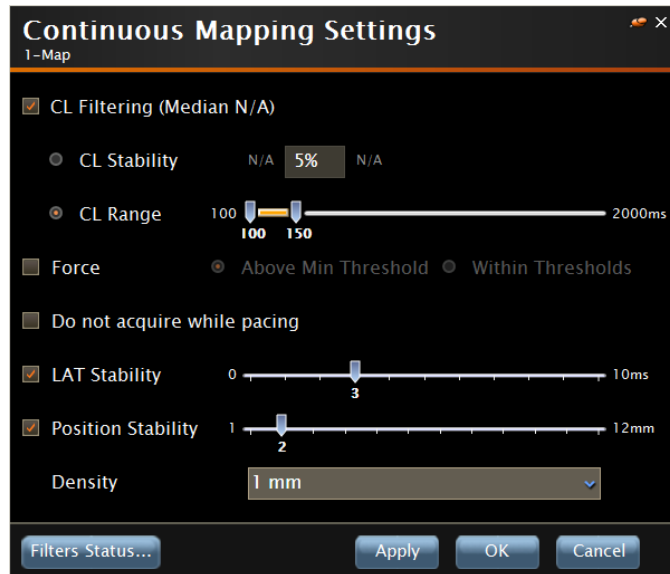


Figure 2-9 ConfiDENSE Continuous Mapping Settings

ConfiDENSE also includes a catheter Tissue Proximity Indicator (TPI) for use with multipolar electrodes that minimizes the acquisition of points when the catheter is not in contact with the tissue surface. TPI uses impedance measurements to determine an electrode's proximity to cardiac tissue. If the distance is less than the radius of the electrode, the electrode is considered to be touching.

ConfiDENSE also offers several enhancements to improve LAT mapping. This includes an automated algorithm designed to use the unipolar EGM to annotate LAT, but avoid far-field signal. This is achieved by assigning timing annotation at the maximal negative distal unipolar derivative that is only seen by the time window spanned by the bipolar EGM. This is known as Wavefront annotation. Annotation of the unipolar EGM is preferred as its maximum negative dV/dT correlates with the upslope of the local intracellular action potential, but has previously been avoided owing to the concern of far-field mis-annotation (figure 2-10).

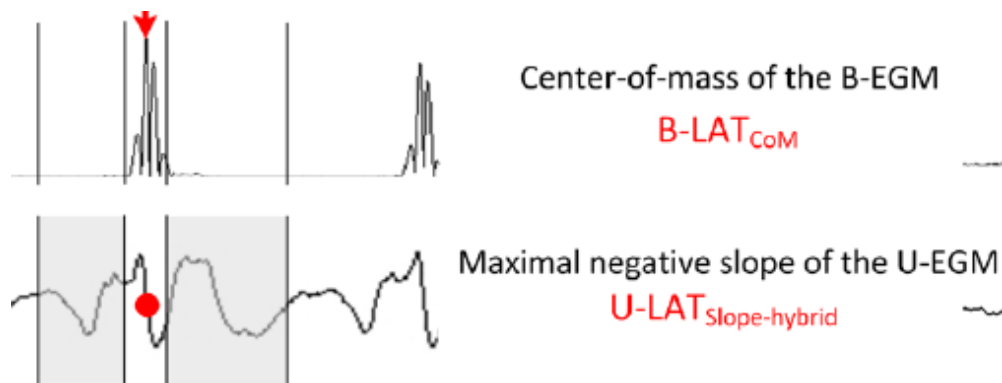


Figure 2-10: Assignment of unipolar EGM LAT

Most recent 3D mapping systems have incorporated annotation algorithms that consider both the unipolar and bipolar EGMs – here annotation is marked at the maximum negative unipolar downslope (lower panel) that is only seen within the time window spanned by the bipolar EGM (upper panel).⁸⁸

To minimize noise annotation, where the maximum unipolar slope $< 0.03\text{mV}$, the system avoids LAT assignment, replacing it with a grey square on the map. A comparison between conventional bipolar timing annotation and this novel approach to unipolar annotation is presented in figure 2-11.

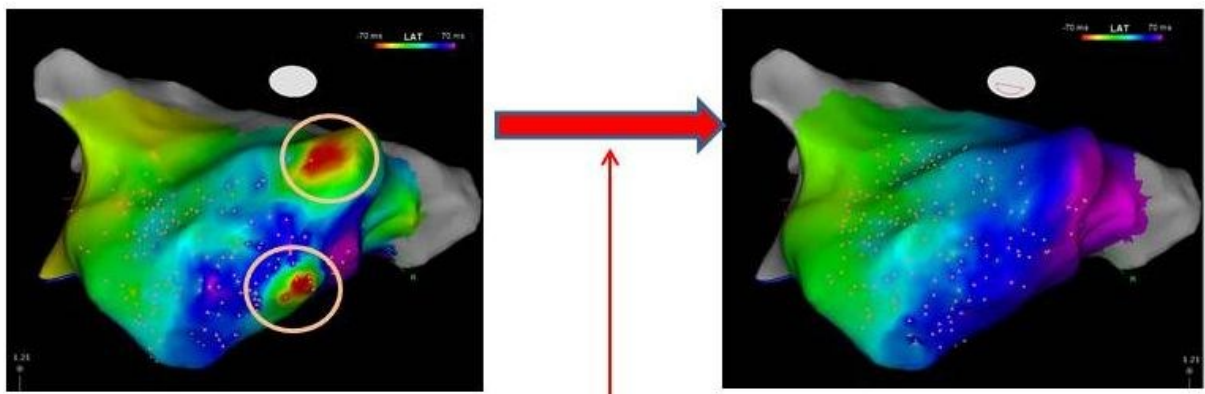


Figure 2-11: Wavefront annotation

LAT maps of the LA posterior wall were collected and annotated (left) using the maximum bipolar peak and (right) using the Wavefront algorithm found on the ConfiDENSE module. Neither map has been manually adjusted. Unlike the map annotated to the bipolar signal, where regions of unclear propagation have been encircled, the “Wavefront” map displays clear propagation of activation around the posterior wall.

The consistency of each measured LAT point relative to its neighbouring points can be assessed automatically using a “map consistency” filter, which highlights outlier points with LAT very different to its surrounding neighbours for review and deletion/re-annotation as required (figure 2-12).



Figure 2-12: Map consistency

The left sided image demonstrates an automated LAT map without adjustment. Having applied a “Map Consistency” filter, a collection of yellow points were immediately highlighted as LAT outliers on the map (encircled). These points could be reviewed and adjusted. The image on the right presents the map post re-annotation/deletion of these points, where the pattern of propagation is more apparent.

Finally, ConfiDENSE allows the WOI, and the subsequent LAT of each projected point to be re-calculated at any time during map acquisition. By convention, the tachycardia reference point is positioned in the middle of the WOI - changing the position of the reference changes the subsequent appearance of the colours on the activation map which can be of value depending on the mechanism of the tachycardia.

2.4 Rhythmia ultra-high density mapping

The Rhythmia ultra-high density mapping system is composed of a 3D mapping system paired to the Orion catheter which offers ultra-high density. The Orion catheter (Boston Scientific, Cambridge, MA) consists of an 8-F shaft with a bidirectional deflection mechanism and a mini-basket array with 64 mini-electrodes arranged on 8 splines. These electrodes have a surface area of 0.4mm^2 with a 2.5-mm centre to centre inter-electrode spacing. The electrode array can be deployed into a spherical configuration through mechanical flexion of the splines. Maximal spherical diameter of the basket is 22mm when measured at its equator. Mapping can be performed in any stage of deployment, from linear (completely un-flexed) to spherical (maximal flexion). Figure 2-13 demonstrates the Orion catheter at various degrees of flexion. A combination of magnetic and impedance based sensors are used to locate each of the 64 electrodes: a magnetic sensor in the distal region of the catheter and impedance sensor on each electrode. Localisation of each electrode is predicted to be accurate to within 1mm^2 . Systemic intravenous heparinisation, targeting an ACT>300secs is required independent of the chamber being mapped.

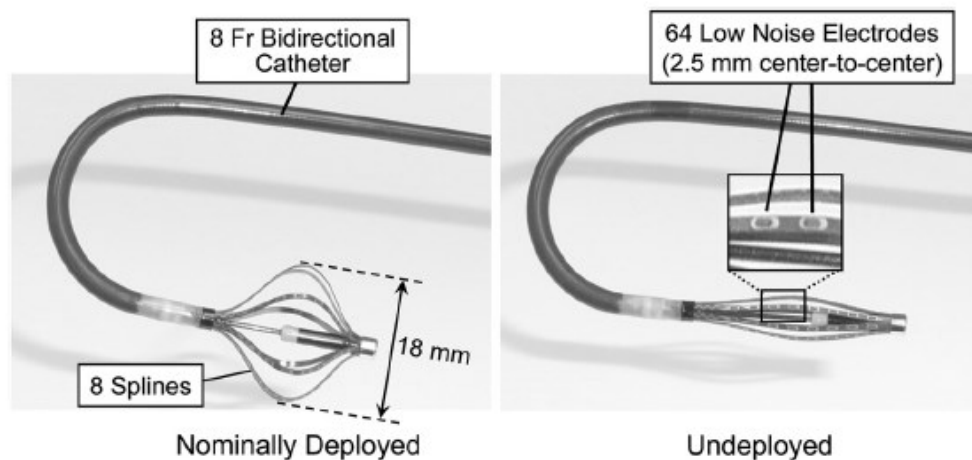


Figure 2-13: Orion Mapping catheter

The mini-basket mapping catheter contains 8 splines each with 8 small electrodes (0.4 mm^2 , 2.5 mm centre-to-centre inter-electrode distance).¹²⁰

The Rhythmia system is comprised of 2 major component groups: a Signal station, typically used near the patient in the EP lab; and a workstation, typically used in the EP lab control room (figure 2-14). The signal station accepts signals from the Orion Catheter and ECG electrodes connected to the system, and

amplifies and digitises these signals, providing them to the Workstation for real-time processing and display.



Figure 2-14: Rhythmia signal station and workstation

The signal station is pictured on the left; the workstation that projects the map during a procedure is pictured on the right (Courtesy of Boston Scientific)

Catheter location is determined using magnetic localisation (similar to CARTO), based on magnetic fields generated by a Localisation Generator positioned under the patient table. A location reference patch is applied on the patient's back and is connected to the Signal Station, serving as a location reference for the tracking system. The magnetic location sensors within the Orion measure the magnetic fields, and internal software uses this information to determine the position of the catheter relative to the Localisation Generator. The mean magnetic-based location accuracy of the Rhythmia Mapping System is $\leq 1\text{mm}$.

This system displays the geometry of the cardiac chambers based on the location of the outer-most electrodes. These displays are created by aggregating the tracked catheter locations recorded during a mapping session. Proximity of a mapping catheter to the shell is represented by a "halo" projected onto the acquired chamber geometry (figure 2-15).

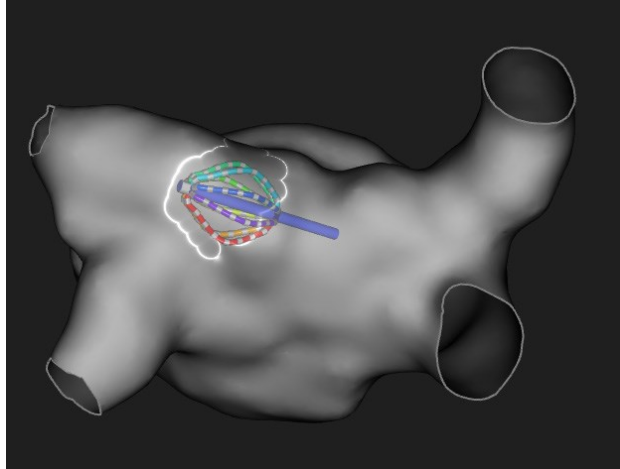


*Figure 2-15: Mapping catheter proximity represented by outline.
The 3D shall of the LA with the Orion close to the roof is displayed. The white halo around the Orion indicates proximity to the shell. (Courtesy of Boston Scientific)*

Collection of the chamber geometry is combined with collection of EGMs. LAT and voltage data from individual cardiac beats detected by the Orion mini-electrodes are acquired automatically, but only accepted for display on the map having passed through a series of beat acceptance criteria, similar to those employed by the CARTO ConifDENSE system. These include: (1) the stability of the electrode, (2) the stability in cycle length of the cardiac rhythm, (3) the stability in timing between the reference EGM and an additional bipole not involved in mapping, and (4) sampling during end-expiration (tracked by measuring impedance change across the chest). Only EGMs within a pre-assigned distance (between 1-5mm) of the surface geometry are projected, and this process is continuously updated as the surface geometry is acquired. These criteria are set by the operator before mapping has begun and can be adjusted, if needed, during mapping. In addition, the user can define timing intervals to avoid detecting beats on pacing artefact or ventricular far-field signal. The display of these beat acceptance criteria are shown in figure 2-16.



Figure 2-16: Rhythmia beat acceptance criteria

Left: An example of a beat to beat measurement in the timing difference between the designated reference EGM (R: CS 7-8) and a second stable signal that is not involved in mapping (R: CS 4-5) as seen whilst mapping an AT. The ΔR between the two EGMs for the sampled beat is 14.7ms – as this was consistent to the index measurement, the beat successfully passes this criteria. The system uses this to prevent ectopic beats, or data from a change in tachycardia activation being displayed on the map. Right: for each beat that passes, a green bar highlights whether that beat has passed the pre-assigned acceptance criteria (CL – cycle length stability; ΔR - timing reference stability; RSP – respiratory gating; M – catheter stability). Courtesy of Boston Scientific

Like CARTO, the Rhythmia system displays activation around the cardiac chamber by measuring the LAT at different sites in relation to a stable reference, presenting this information on a colour coded map. The system calculates the median TCL over 10sec and sets the duration of the WOI to 100% of the observed cycle length, centred on the timing reference electrode. The annotation of LAT is assigned automatically by the system, based on either the bipolar or unipolar EGM signal. For bipolar maps, EGMs with a single component are annotated at the maximum absolute peak of the bipolar EGM. For EGMs with more than 1 potential, annotation is guided by surrounding EGMs. For unipolar maps, in order to avoid far-field signal, the system applies the same timing algorithm used in ConfiDENSE, timing activation to the maximal negative unipolar derivative contained within the timing window spanned by the accompanying bipolar EGM..

Individual EGMs and their annotation of activation timing can be studied by roving a virtual probe (figure 2-17) at the desired location. Users can edit each point on the map, including changing the timing annotation for the selected EGM, deleting the selected EGM, or tagging the EGM as scar.

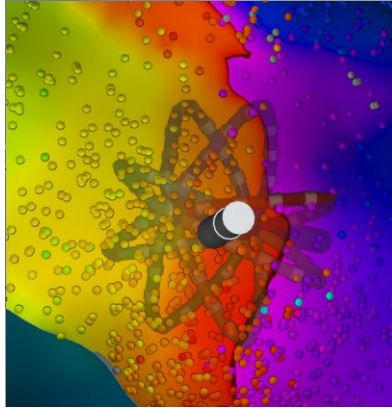


*Figure 2-17: Roving Probe
Courtesy of Boston Scientific*

The Rhythmia system utilizes a unique WOI display. The WOI is represented as a colour wheel running from red to purple, and spanning the colours of the rainbow (figure 2-18). These limits default to red being the earliest in the window and purple being the latest. However by representing the colour bar as a wheel, purple conveys activation 10ms before red for reentrant maps. These limits can be rotated around the colour wheel, and this has the equivalent effect of sliding the WOI without causing a full map re-compute. This function preserves the full colour spectrum on the propagation map. Wavefront activation can be followed by rotating the colour wheel and tracking the leading edge of a maroon coloured wavefront, distinguishable from the rainbow spectrum, around the cardiac chamber.

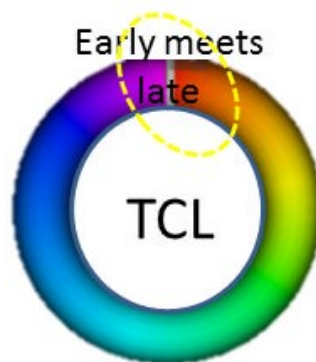


*Figure 2-18 Rainbow colour wheel
The wheel runs from red to purple within the WOI spanning the full TCL.*

Activation in regions of low voltage and/or inconsistent timing can be hidden from the map using a confidence mask. The default threshold is 0.03mV, and assumes that signal below this represents noise. Areas below this threshold are therefore displayed in grey and conventionally defined as scar.

2.5 Ripple Mapping

Ripple Mapping (RM) presents the entire EGM as a moving bar on the surface geometry. The height of the bar correlates with EGM amplitude through time. Negative deflections are presented as upward moving bars so no component of the EGM is lost. An example of EGMs presented as a ripple map are illustrated in figure 2-19 and video 2-19.

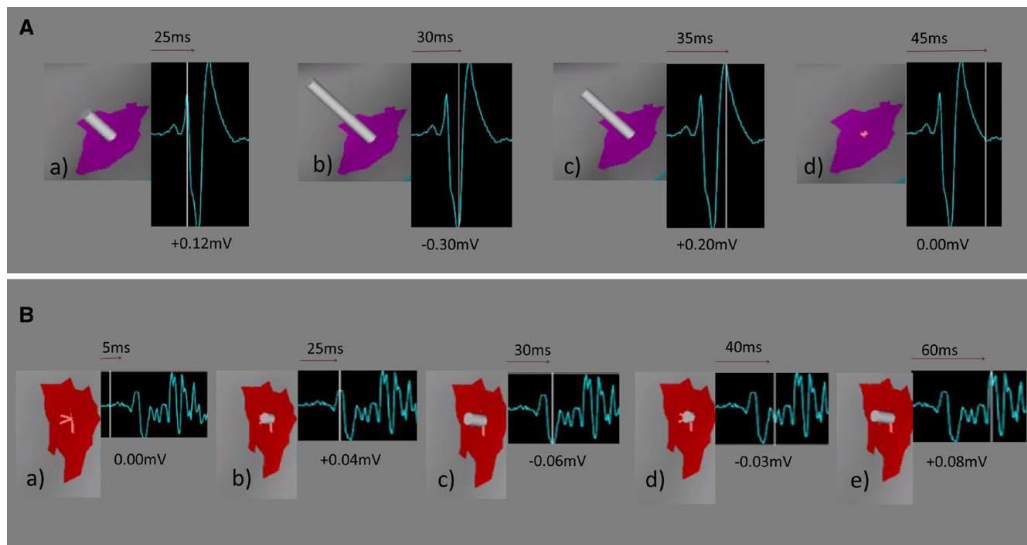


Figure 2-19: (see also video 2-19) Ripple bars

Panel I: Ripple bars representation of a bipolar EGM (peak amplitude 0.48mV). Four time frames (25ms, 30ms, 35ms, 45ms) are displayed (a-d). At each time frame, the amplitude of each deflection is +0.12, -0.30, +0.20, 0.00mV respectively. The corresponding Ripple bar for each time point is seen, overlying a CARTO voltage colour.

Panel II: Ripple bar representation of a fractionated EGM (peak amplitude 0.11mV). Five time frames (+05, +25ms, +30ms, +40ms +60ms) are displayed (a-e). At each time frame, the amplitude of each deflection is 0.00, 0.04, -0.06, -0.03, +0.08mV respectively. The Ripple bars have been set to show bars above 0.03mV.

RM has been integrated into a research module in CARTO3v4 for prospective testing. Electro-anatomical data is collected using any mapping catheter and projected on the cardiac geometry. Every EGM from each projected point is subsequently aligned relative to a fiducial reference signal. The Ripple Map of all points is then played through time and presented as a movie. When multiple points are collected over an area, a “ripple” effect is seen as the movement of bars traverses from one area to the next. Wavefront direction is understood by displaying all timing and voltage data dynamically, allowing the observer to use the human ability to detect and interpret movement to “see” activation. Unlike LAT

mapping, where activation is visually represented relative to the WOI, the Ripple bars are analysed in relation to each other. Local activation direction is established by the local sequence of bar movement, therefore there is no concept of 'early' or 'late' but only the local activation direction. Figure 2-20 and video 2-20 demonstrate how propagation can be visualised using RM.

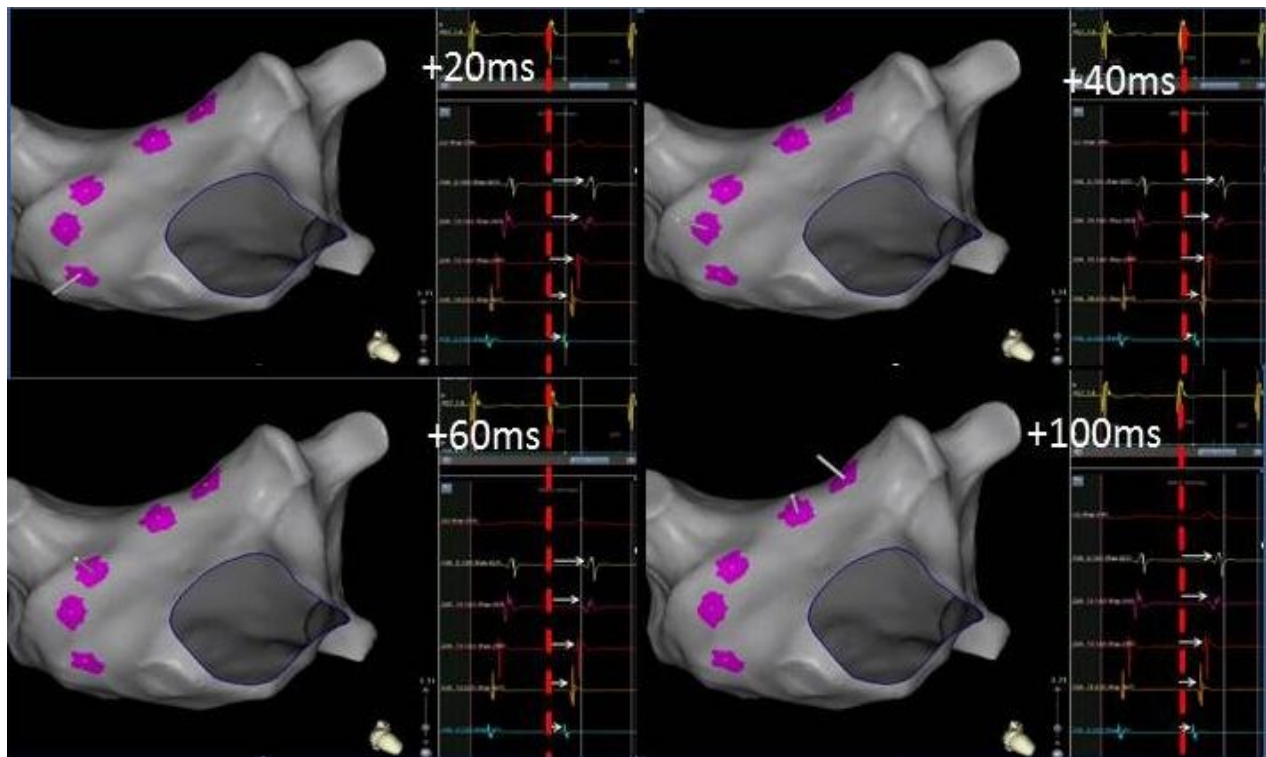


Figure 2-20: (see also video 2-20) Ripple Map propagation

5 EGMs have been collected across the anterior wall of the LA during tachycardia, and the location of each data point is projected on the anatomical shell. The RM algorithm aligns all the EGMs from each point according to a stable fiducial reference signal. In this example, a coronary sinus (CS) signal (yellow EGM) was chosen as reference – the system has aligned each of the 5 EGMs in line with CS with peak of the CS ref EGM (highlighted here with red dashed line). The Ripple Map for every EGM collected is played through time (0-100ms). Deflections (negative or positive) away from the iso-electric line from every mapped point are projected as a perpendicular white bar. As time progresses, bars are seen to ascend up the anterior wall. When played quickly as a movie, this gives the impression of propagation as the bar movement progresses in relation to its neighbouring points.

Ripple Map Preferences:

A series of Ripple map preference tools are integrated within the workstation that determine the voltage at which bars are visible and the voltage-height relationship. The 'show bars above' dialog box is used to enter the minimum voltage at which the Ripple bars become visible. The 'Clip bars above' option

limits the height of the bar at the assigned voltage. Figure 2-21 summarises the Ripple Map preference display.

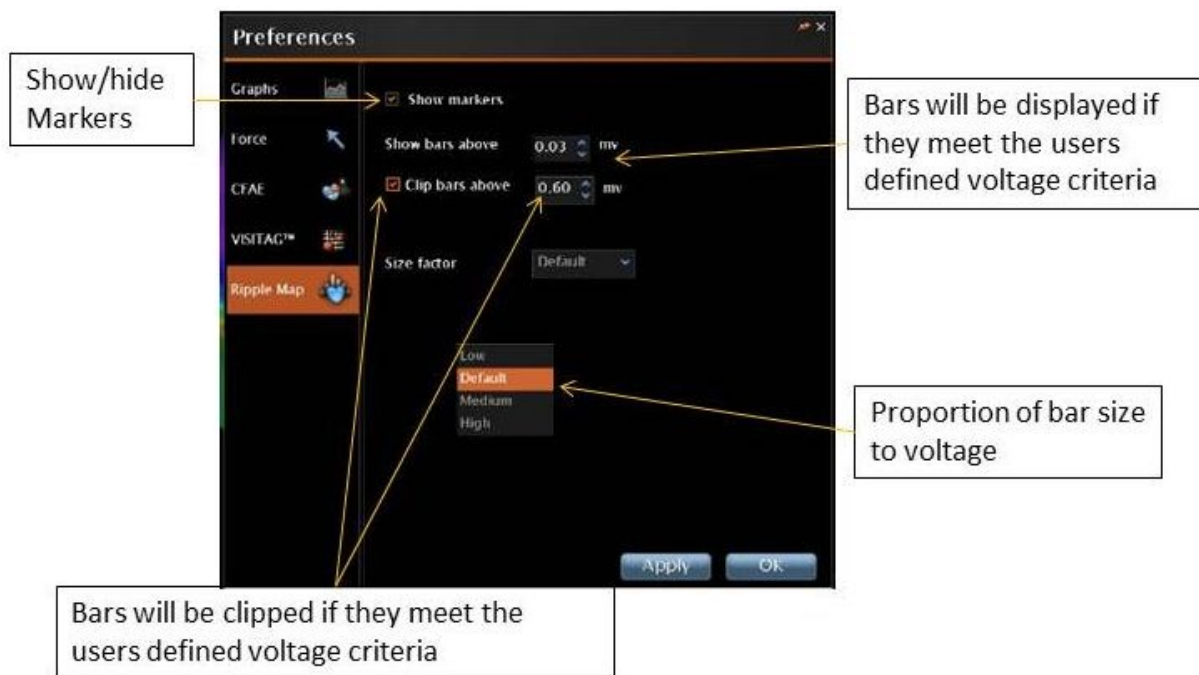


Figure 2-21: Ripple map preferences

For each point collected, 2.5seconds of intra-cardiac data is stored. When played, the Ripple Map automatically runs in a continuous loop, jumping back to the beginning with each revolution. The duration of intracardiac signal that is played as a Ripple Map can be adjusted using a “Ripple Viewer function” on the workstation The ripple viewer can also display mapping channels of points from different acquisitions, with each channel aligned according to the reference signal. This enables the operator to review a series of EGM signals from an area of interest with marked points side by side. (figure 2-22).

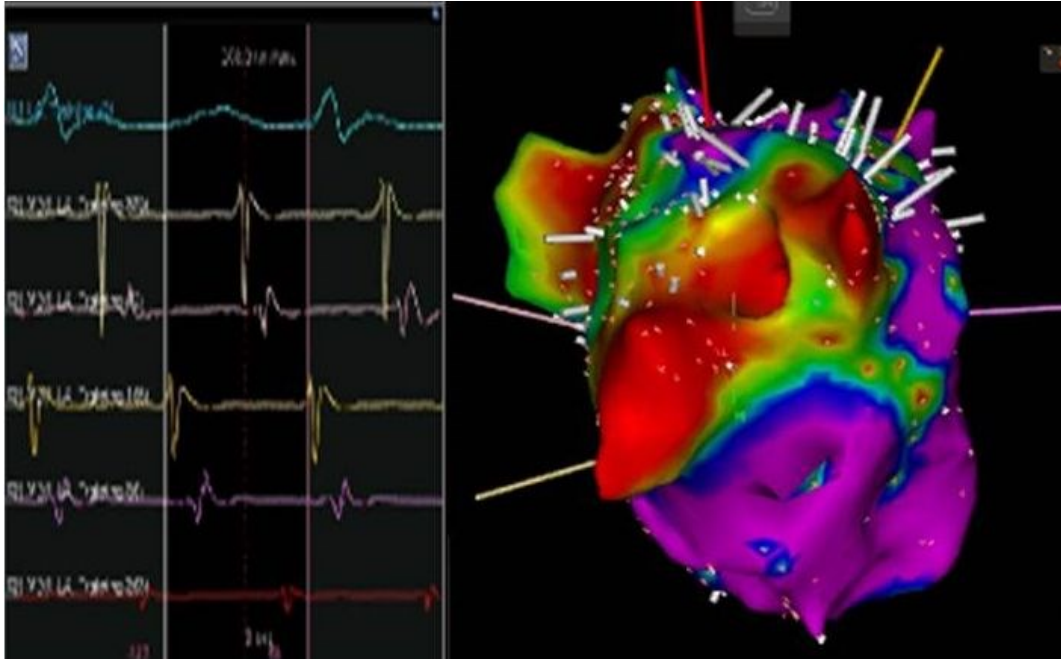


Figure 2-22: Ripple Viewer

Left atrium geometry (right lateral view) with 5 points marked in coloured bars (light grey, light purple, yellow, purple and red) and their corresponding EGM channel presented in the viewer, aligned according to the designated reference signal.

2.6 Summary

This chapter outlines our general approach to mapping and ablation within atrial and ventricular scar and outline some of the specific tools used in this thesis, namely the Hansen robotic catheter control system, the Rhythmia ultra-high density mapping system, and the CARTO3 mapping system with the ConfIDENSE and RM functions.

Chapter 3

3 Novel ablation approaches

In this chapter we study the efficacy of ablation supported by robotically controlled catheters, and then use this robotic system to explore the effectiveness of an earlier approach to substrate ablation after the first ICD therapy.

3.1 VT ablation using a robotically controlled catheter system

3.1.1 Introduction

Despite the introduction of cardiac mapping systems, irrigated tip catheters and substrate based ablation strategies, patients continue to experience on-going ICD therapies for VT recurrence in long term follow up.^{135, 164} We have previously shown that this may be attributed to an inability to achieve endocardial lesions with sufficient depth.¹⁴⁵ We have also demonstrated, in animal models, that robotically assisted ablation using the Hansen Sensei Robotic Catheter system improves catheter stability to increase lesion depth.^{147, 152, 151}

The use of this robotic system in atrial based arrhythmias is well described.^{158, 165, 166} Limited data exists of its clinical efficacy within ventricular scar during VT ablation.¹⁶⁰ Mapping and ablation using a robotically controlled “master-slave” catheter system is potentially more advantageous within the scarred ventricle where the chambers are dilated and scars can be small, hard to reach, and deep to the endocardial surface. Persistent tissue–catheter contact might permit more accurate electro-anatomical mapping of low voltage signals and the potential to target regions of slow conduction with deeper lesions. This study aimed to assess the feasibility and safety of using the Hansen robotic system to guide VT ablation in a series of patients with post-infarct related scar, and compare acute and long-term outcome data to a cohort of patients who underwent manual ablation.¹⁶⁷

3.1.2 Methods

3.1.2.1 Patient sample

Robotic VT ablation started at our institute in 2010. It had previously been used for AF ablation. The Imperial College Electrophysiology procedural database was reviewed to identify all patients who underwent post infarct scar related VT ablation using the Hansen System between January 2010 to January 2014. All non-robotic cases over the same time interval were also identified. These patients included those presenting acutely to our centre either directly, or from neighbouring local hospitals, or electively following assessment in ICD clinic. Patients were excluded if they were involved in any other VT ablation study, or if they were followed up outside of our institution. Patients were also excluded if they failed to undergo a programmed electrical ventricular stimulation to assess inducibility post ablation, owing to the absence of an acute procedural endpoint for comparison. Long term outcome data was gathered from the patients' clinical case notes, or their ICD device downloads from clinic or remote monitoring.

3.1.2.2 Electrophysiology Study and Mapping

Our standard procedural setup and VT stimulation protocol was described in Chapter 2.1. The CARTO mapping system was used in combination with a Thermocool catheter (Biosense Webster) for mapping and ablation in all cases. A bipolar voltage map was created using established peak-to-peak bipolar voltage criteria for dense scar (<0.5mV), scar-border (0.5mV-1.5mV) and healthy tissue (>1.5mV). The integrated contact force feature, Intellisense, was used for contact force feedback. Following the release of contact force sensing, Thermocool Smarttouch catheters were used instead, with a target contact force of 10-20g.

3.1.2.3 Ablation strategy and settings

During stable VT, CARTO LAT maps were combined with entrainment manoeuvres to define the target ablation sites, ideally at sites with mid diastolic potentials. For poorly tolerated VT, the voltage map collected in sinus rhythm was used to perform substrate ablation using one or more of the following; scar border location, presence of a late potential, and local capture with a 12/12 pacemap to the clinical or induced VT. All patients undergoing robotic procedures were limited to 30W at 60secs with a flow rate of 17mls/min and a temperature limit of 40°C. In the manual group, power output and delivery time was at the discretion of the operator.

ICD programming post procedure was left unchanged.

3.1.2.4 End Points

The immediate ablation outcome was assessed following programmed ventricular electrical stimulation. Patients were defined as either “non-inducible”, “inducible for non-clinical VT”, or “inducible for clinical VT”.

Long-term outcomes were defined by the cumulative burden of appropriate ICD therapies (anti-tachycardia pacing (ATP) + shocks). This was assessed from 6 months pre-ablation and compared with the post ablation therapy burden till their most recent device interrogation or redo procedure. ICDs were interrogated whenever symptoms suggested delivery of device therapy in addition to routine follow-up in ICD clinic and by remote follow up. A 6 month proportion of each patient’s total therapy burden during follow up was calculated for each patient ((6/follow-up duration (mths)) x total therapies post ablation)) allowing direct comparison with the 6 month pre-ablative burden.

3.1.2.5 Statistical Analysis

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median $\pm$ interquartile range for non-parametric data. Paired non-parametric data were analysed using the Wilcoxon Signed Ranks test. Unpaired continuous variables were analysed using a student’s t-test for parametric data and Mann-Whitney U-Test for non-parametric data. Fisher’s Exact test was used for categorical data. A value of $p \leq 0.05$ was considered significant.

3.1.3 Results

60 patients underwent scar related VT ablation during the study period. A total of 36 patients met exclusion criteria. This included 18 patients with non-ischemic cardiomyopathy and 9 patients involved in a concurrent VT ablation trial that commenced during this study interval in our institution. 2 patients presented with VT below the device detection zone. 2 patients had their ICD implanted post ablation. The procedure was abandoned in 3 patients owing to transeptal puncture related complication. This included 1 patient who was a planned robotic procedure. 2 patients were followed up externally. This exclusion data is summarised in figure 3-1.

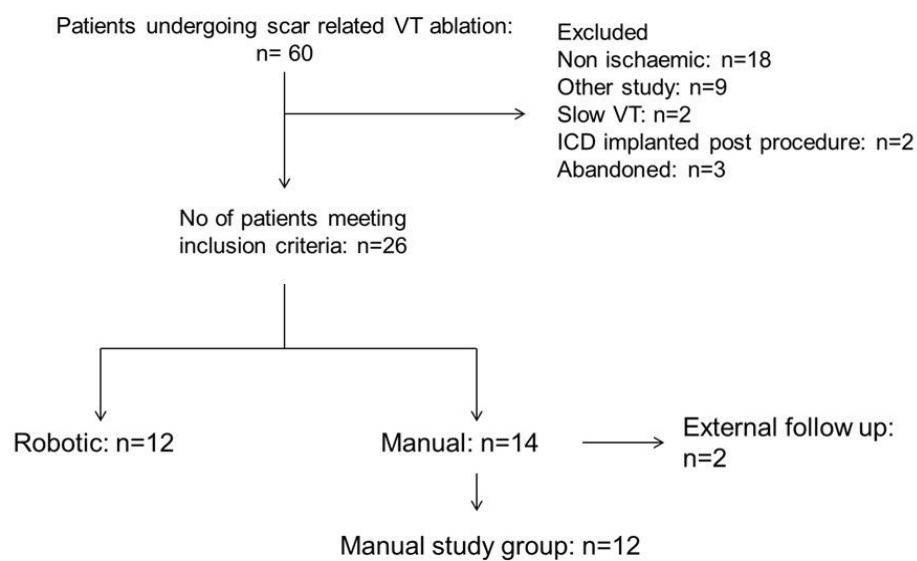


Figure 3-1: The number of patients within each exclusion criteria.

Of the remaining 24 patients, 12 underwent robotically guided ablation. The majority of patients were male (9/12, 75%) with a mean age of 70.8 ± 5.5 years at the time of the procedure. 42% (5/12) had diagnosed essential hypertension and 50% (6/12) type II diabetes mellitus. The mean body mass index (BMI) was 29.0 ± 5.3 kg/m². Most patients had severely impaired left ventricular ejection fractions ($28 \pm 14\%$) and 67% (8/12) had undergone coronary artery bypass grafting (CABG) with the remainder having undergone percutaneous coronary intervention (PCI). 42% (5/12) were biventricular paced prior to the procedure. There were no significant differences in baseline characteristics and comorbidities between the robotic ablation cohort and the 12 remaining patients in the manually ablated cohort. This is illustrated in table 3-1.

Clinical Characteristics	Robotic	Manual	p value
N	12	12	1*
Male	9/12 (75%)	12/12 (100%)	0.22*
Age/yrs (mean±SD)	70.8±5.5	73.8±6.7	0.24+
BMI (kg/m ²)	29.0±5.3	26.2±4.8	0.18+
HTN	5/12 (42%)	5/12 (42%)	1*
DM	6/12 (50%)	6/12 (50%)	1*
CABG	8/12 (67%)	7/12 (58%)	1*
LVEF 2D echo: (mean±SD)	28.1±13.7%	31.2±10.7%	0.53+
AAD pre ablation	7/12 (58%)	8/12 (67%)	
Amiodarone	12/12 (100%)	12/12 (100%)	1*
Beta blocker	4/12 (33%)	1/12 (8%)	1*
Mexilitine			0.32*
Cardiac resynchronisation	5/12 (42%)	7/12 (58%)	0.68*

Table 3-1: Baseline clinical characteristics

AAD – Antiarrhythmic drug. BMI - Body mass Index; CABG – Coronary artery bypass grafting; DM - Diabetes Mellitus; HTN – Hypertension; LVEF – left ventricular ejection fraction;

*Fisher's exact test; +Students t-test.

3.1.3.1 Pre-procedural therapy burden

During this time period, the Hansen system was often preferred for ablation in those who had failed manual procedures, and those presenting urgently with multiple ICD therapies/storm. In those who failed manual procedures, the coronary angiograms were also reviewed for consideration of intracoronary ethanol. A total of 9/12 robotic ablations (75%) were undertaken in those presenting urgently, whereas only 4/12 (33%) were as such in the manual arm (p=0.01). 4/12 (33%) of the patients had undergone failed manual procedures compared 1/12 (8%) in the manual group undergoing a redo ablation (p=0.32). A numerically higher median pre-ablation therapy burden was evident in the robotic arm (n=32 therapies (IQR=5-400)) as compared to the manual arm (n=14 therapies (IQR=10-25)) (p=0.49).

3.1.3.2 Procedural data

In the cohort that underwent robotic ablation, scar (<1.5mV) was located around the anterior wall (including anterolateral and antero-septal walls) in 4 patients, around the inferior wall (including inferoseptal and inferolateral walls) in 4 patients, and apically (including 2 apical aneurysms) in 4 patients. There were 2.4±1.9 different VT morphologies induced in each patient. All patients underwent substrate ablation, and ablation was also delivered in VT in 4 patients. All areas could be reached by robotic manipulation and procedures were all completed robotically. An average of 35±25 RF applications were delivered with a maximum temperature of 38.3±2.4°C, power of

29.6±2.7 Watts and duration of 59.4±3.4 seconds. The intra-procedural data for both robotic and manual groups are summarised in table 3-2.

Characteristics	Robotic	Manual	p value
No. of VT's induced (mean±SD)	2.4±1.9	1.7±1.0	0.31 +
VT CL of clinical tachycardia/ms, (mean±SD)	439±143	422±70	0.73 +
Scar location:			
Anterior	4	3	1 *
Inferior	4	7	0.41 *
Apical	4	2	0.65 *
Number of CARTO points collected (mean±SD)	168±97	209±107	0.54+
Total LV mapping times/ mins (mean±SD)	51±31	51±34	0.95 +
Ablation strategy:			
During VT	4	4	1 *
Substrate ablation	12	12	1 *
RF ablation lesions (mean±SD)	35±25	23±9	0.15 +
Maximum temp/ °C (mean±SD)	38.3±2.4	38.9±4.2	0.66 +
Maximum power/ W (mean±SD)	29.6±2.7	44.6±10.0	<0.001 +
Duration of ablation lesion/sec (mean±SD)	59.4±3.4	71.9±19.1	0.05 +
Fluoroscopy time/mins (mean±SD)	42.6±11.4	32.7 ±18.6	0.13 +
Cumulative X ray dose/ cGycm2 (mean±SD)	4567±3601	2931+/-2329	0.20 +
Overall procedure duration/ min (mean±SD)	312±91	218±93	0.02 +

Table 3-2: Intra-procedural data for both robotic and manual groups

*VT CL – Ventricular Tachycardia cycle length; *Fisher's exact test; +Students t-test.*

There was no significant difference in ventricular mapping times (51(±31) vs. 51(±34) mins, p=0.95) and the number of CARTO points collected (168 (±97) vs. 209 (±107), p=0.54) between the robotic and manual approaches. Owing to the restriction in power output and ablation duration, RF delivery in patients undergoing robotically guided ablation was of significantly shorter duration (59.4±3.4 vs. 71.9±19.1sec, p=0.05) with lower power output (29.6±2.7 vs. 44.6±10.0W, P<0.001) compared to those undergoing a manual ablation. A greater number of ablation lesions (35±25 vs. 23±9, p=0.15) were delivered over a significantly longer procedural duration (312±91 vs. 218±93mins, p=0.02) in the robotic cohort (defined as the time the patient arrived in the electrophysiology laboratory to subsequent exit). There was a trend towards an increased median fluoroscopic time (42.6±11.4 vs. 32.7±18.6mins, p=0.13) in the robotic group as compared to the manual.

3.1.3.3 Acute and long term Outcomes

In the robotic arm, following programmed ventricular stimulation at the end of the procedure, 6/12 (50%) had no VT inducible, 5/12 (42%) had non-clinical VT only, and 1/12 had clinical VT still inducible. 6/12 (50%) were maintained on amiodarone post procedure. Patients were followed up for a mean of 24.1 ± 19.1 months. Data was available from patient attendances or ICD downloads from an average of 6.8 ± 3.9 device interrogations. The total therapy burden (ATP + shocks) fell to a median of 3.5 (1-11) events. The calculated averaged 6 month post procedural therapy burden fell significantly to a median of 2.5 (0-11) ($p=0.015$). This represented a 95% therapy burden reduction. 3/12 (25%) patients required a further ablation procedure during this follow up period.

In the manual arm, following programmed ventricular stimulation at the end of the procedure, 8/12 (67%) had no VT inducible, 3/12 (25%) had non-clinical VT only, and 1/12 (8%) had clinical VT inducible. 5/12 (42%) were maintained on amiodarone post procedure. Patients were followed up for a mean of 21.1 ± 14.6 months. Data was available from patient attendances or ICD downloads from an average of 4.3 ± 3.2 occasions. The total therapy burden (ATP + shocks) fell to a median of 1 (0-14) events. The averaged 6 month therapy burden fell significantly to median of 1 (0-5) ($p=0.023$). 4/12 (33%) patients required a further ablation procedure during this follow up period. A comparison between the acute and long term procedural outcomes between the robotic and manual groups is detailed in table 3-3.

Characteristics	Robotic	Manual	p value
Total ATP's 6 mnths pre abl. (median (IQR))	19 (4-396)	11 (8-22)	0.56 +
Total shocks 6 mnths pre abl. (median (IQR))	1.5 (1-4)	1 (0-3)	0.73 +
Prior failed manual ablation	4/12 (33%)	1/12 (8%)	0.32 *
Urgent (multiple ICD therapies/ICD Storm)	9/12 (75%)	4/12 (33%)	0.01 *
Post proc VT non-ind:	6/12 (50%)	8/12 (67%)	0.68 *
Post proc non-clinical VT ind:	5/12 (42%)	3/12 (25%)	0.67 *
Post proc clinical VT ind:	1/12 (8%)	1/12 (8%)	1 *
Post proc complications	0/12	0/12	1 *
Post proc Amiodarone continued	6/12 (50%)	5/12 (42%)	1 *
Follow up (months): (mean±SD), (median (IQR))	24.1±19.1, 27 (5-40)	21.1±14.6, 22 (9-32)	0.77 +
Total ATP's post abl. (median (IQR))	3.5 (1-10)	0.5 (0-11)	0.38 +
Total Shocks post abl. (median (IQR))	0.6 (0-1)	0 (0-2)	0.52 +
Total ICD therapies post abl. (median (IQR))	3.5 (1-11)	1 (0-14)	0.38 +
Absolute therapy reduction (median (IQR))	22 (3-388)	12 (5-25)	0.51 +
6mth averaged ICD therapies (median (IQR))	Pre proc: 32 (5-400) Post proc: 2.5 (0-11) p=0.015 §	Pre proc: 14 (10-25) Post proc: 1 (0-5) p=0.023 §	0.49 + 0.60 +
Further ablation procedure	3/12 (21%)	4/12 (29%)	1 *
Mortality Months: mean±SD	4/12 (33%), 16±12.2	4/12 (33%), 15.5±7.0	1 *

*Table 3-3: Comparison of robotic and manual ablation acute and long-term outcome data. abl – ablation, ATP – Anti-tachycardia Pacing, ICD – Implantable Cardioverter Defibrillator, ind – inducible, proc – procedural, *Fisher's exact test, +Mann-Whitney U-Test, §Wilcoxon signed rank test*

Figure 3-2 demonstrates pre and post ablation therapy burdens for each robotic and manual patient averaged over 6 months.

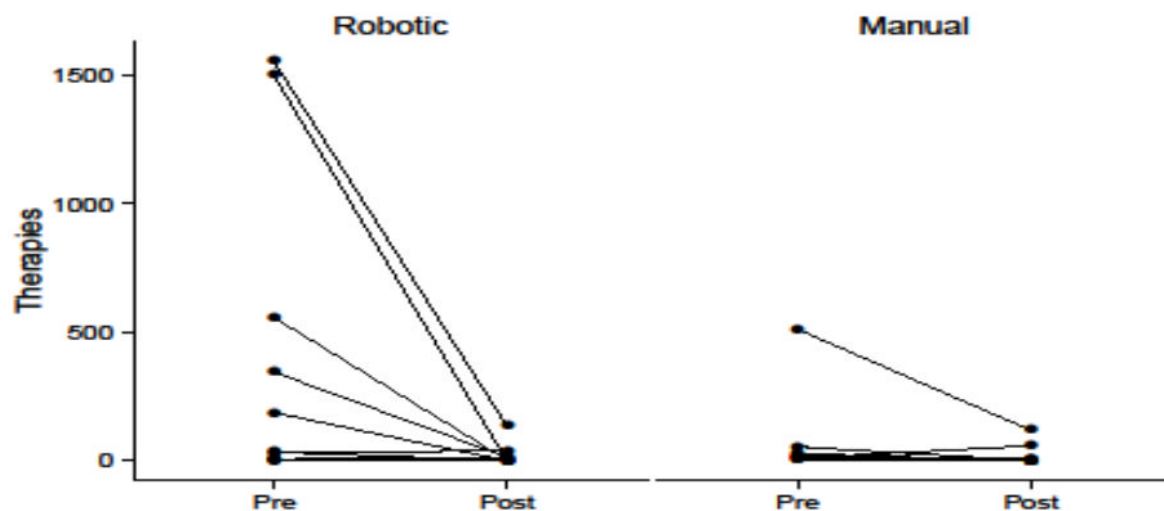


Figure 3-2: Pre and post ablation therapy burdens for each robotic and manual patient averaged over 6 months.

3.1.3.4 Procedure-Related Complications and Death

There were no peri-procedural complications related to ablation delivery in either of the groups in this study. The 30-day procedural mortality was nil in both arms. In the robotic group 4/12 (33%) patients died during this follow up interval, an average 16.0 ± 12.2 months remote of the procedure. 3 died from end stage heart failure and 1 died following a stroke. In the manual group, 4/12 (33%) patients died an average 15.5 ± 7.0 months remote of the procedure. 3 died from end stage heart failure and 1 died from mitral valve endocarditis.

The intra-procedural and long term outcomes for each patient have been categorised per group and summarised in table 3-4 and table 3-5.

Pt	No. of prev Abl	ICD Rx 6 mth	Elective/urgent	VT Morph	VT CL	Ablation lesions	Scar Location	X-ray (cGycm 2)	skin dose (cGycm 2)	fluoro (min)	Duration (min)	Amio. Post Abl	Total F/u mth	Total ATP Post Abl	Total Shock Post Abl	Total Rx Post Abl	Rx post 6 mth	Rx fall 6 mth	Redo Abl	Death (mth)
1	0	10	Elective	2	286	29	IS	2151	234	41	390	0	31	1	0	1	0	10	0	
2	2	346	Urgent	0	X	33	A	2318	252	40	240	1	2	5	0	5	15	331	1	27
3	3	5	Elective	1	538	31	A S	5117	675	40	420	1	41	0	0	0	0	5	0	
4	2	1501	Urgent	1	560	12	AL	2250	272	38	305	1	52	9	1	10	1	1500	0	
5	0	2	Elective	2	470	51	Ap A, AS, AL	2898	271	54	330	0	1	0	1	1	6	4	1	
6	0	188	Urgent	1	406	29	IS	1272	152	33	228	0	25	3	0	3	0	188	0	
7	0	33	Urgent	7	536	30	AL	2258	231	36	266	1	40	1	0	1	0	33	0	
8	1	5	Urgent	3	364	12	IS	7944	100	24	196	0	49	73	0	73	9	4	0	
9	0	30	Urgent	3	498	37	L	6855	759	67	397	0	2	12	1	13	39	9	0	4
10	0	5	Urgent	2	636	50	Ap A Aneurys m	1992	209	37	236	0	29	1	0	1	0	5	0	
11	0	1557	Urgent	5	130	101	Ap I	6167	593	54	480	1	11	249	4	253	136	1421	2	26
12	0	561	Urgent	2	404	7	Ap A Aneurys m	13584	148	48	252	1	6	4	0	4	4	557	0	7

A=anterior; AL=anterolateral; Ap=Apical; IL=inferolateral; IS=inferoseptum; L=lateral; abl=ablations; Amio=Amiodarone; ICD=Implantable Cardioverter Defibrillator; Rx = Treatment (ATP (anti-tachycardia pacing) +shocks); VT CL=ventricular tachycardia cycle length.

Table 3-4: Pre, intra and post procedural data for each patient in the robotic group.

Pt	No. of prev Abl	ICD Rx 6 mnth	Elective/urgent	VT 's Morph	VT CL/ Ms	Ablation lesions	Scar Location	X-ray (cGym 2)	skin dose (cGym 2)	fluoro time (min)	Duration (min)	Amio. post Abl	F/u mnth	Total ATP Post Abl	Total Shock Post Abl	Total Rx Post Abl	Rx post 6 mnth	Rx fall 6 mnth	Radio Abl	Death (mnth)
1	0	15	Urgent	1	480	26	I	1394	151	20	206	0	39	1	0	1	0	15	0	
2	0	17	Elective	1	440	23	IL	540	62	10	174	0	43	0	0	0	0	17	0	
3	1	26	elective	2	420	29	IS	4156	403	53	346	0	34	0	0	0	0	26	0	
4	0	12	Elective	1	320	23	S	2806	389	42	242	0	32	15	2	17	3	9	0	
5	0	24	Urgent	1	398	4	I	175	18	6	36	0	10	0	0	0	0	24	0	
6	0	9	Elective	3	564	12	IL	4857	308	26	246	0	9	73	7	80	57	-48	0	9
7	0	514	Elective	0	X	26	S	1660	192	35	250	1	3	49	11	60	120	394	1	
8	0	11	Urgent	2	364	36	AS	2393	292	66	310	1	1	0	1	1	6	4	1	
9	0	6	Elective	2	400	21	IS	2238	201	22	160	0	30	5	0	5	1	5	0	
10	0	3	Elective	4	470	25	Ap, L, IS	1494	180	28	137	1	8	0	0	0	0	3	1	16
11	0	58	Urgent	2	364	32	Ap, AS	5072	384	57	353	1	22	0	0	0	0	54	0	12
12	0	10	Elective	2	423	23	S	8387	1154	27	153	1	22	10	3	13	4	6	1	25

A=anterior; AL=anterolateral; Ap=Apical, IL=inferolateral; IS=inferoseptum; L=lateral; abl=ablations; Amio=Amiodarone; ICD=Implantable Cardioverter Defibrillator; Rx = Treatment (ATP (anti-tachycardia pacing) +shocks); VT CL=ventricular tachycardia cycle length.

Table 3-5 Pre, intra and post procedural data for each patient in the manual group.

3.1.4 Discussion

This study demonstrates the feasibility of using the Hansen Sensei Robotic System in performing LV endocardial ablation within the post infarct scar. The robotic system was often utilised in patients presenting urgently with multiple ICD events/storm, and those who had recurrence of VT despite a previous ablation procedure, and still resulted in a significant reduction in total ICD therapy burden compared over a 6 month averaged interval. To our knowledge, this study is also the first to compare acute and long-term robotic outcome data with a matched cohort of manual ablations. Despite a potentially more complex arrhythmic substrate in the robotic arm, the acute and long-term procedural outcomes between the two groups were similar.

We intentionally reduced the power delivery during robotic ablation to no more than 30W, and delivered each lesion for no more than 60 seconds. This was based on previous animal studies where, at 45W, charring, popping and perforation were seen.¹⁶³ As there was no restriction in the manual arm, both power output and duration were significantly higher for each ablation lesion delivered. The only other case series of robotically guided VT ablation did allow for a higher power output (50W) and also demonstrated a significant reduction in the frequency of patient VT episodes.¹⁶⁰ The absence of any acute procedural complications directly attributable to the robotic system or during ablation in both studies series is notable.

The mean procedural duration and fluoroscopic times in the robotic arm were greater than in the manual arm. This was not the result of mapping times, which were similar. There are additional steps in a robotic procedure which include the introduction of a 14F femoral long sheath, advancing the Artisan sheath to the right atrium, navigation of the catheter and Artisan-sheath across the trans-septal puncture site and repositioning the outer sheath remotely during manipulation within the LV, all of which may have been responsible. Furthermore, although non-significant, there were more VTs induced in the robotic arm implying more complex procedures in the robotic group.

Operators reported that movement of the ablation catheter within the left ventricle using the Hansen robotic sheath easier than manual manipulation of the ablation catheter within a deflectable sheath particularly for maintaining stability during RF delivery. Manoeuvrability around the papillary muscles was not more difficult with robotic ablation and there were no papillary muscle related complications.

Reaching the outflow tract and mitral annulus required adjustment of the outer sheath and torque settings so that the inner sheath turned back on itself, but this was still easier to do robotically than manually, and, more importantly, with greater stability.

Long-term freedom from VT, as opposed to just VT burden reduction, is often used as a marker of ablation success. However, in this study, our patients had advanced disease with a high therapy burden, and a reduction of total ICD therapy burden was considered a clinical success. This endpoint has been applied in other studies as well, including the Thermocool VT ablation Trial and Euro VT, which also included patients with severe left ventricular impairment secondary to remote myocardial infarction, experiencing multiple ICD episodes, similar to our own.^{136, 168} Furthermore, outcome data from both these studies is comparable to our robotic cohort, with similar rates of non-inducibility (49% in the Thermocool trial) and 6 month reduction in therapy burdens (>75% reduction in 67% of patients in the Thermocool trial, and from 60±70 events pre-ablation to 14±15 events post ablation in Euro VT).

3.1.5 Limitations

The data presented is a small series from a single centre where cases were performed by experienced operators. There is a learning curve required to become proficient with the system and hence the results may not be reproducible in less experienced centres. Comparison between the robotic and manual data sets must take into consideration the retrospective nature of this study, the absence of a standardized protocol with regards to long-term anti-arrhythmic and device programming management, and the heterogeneous spread of the data between the groups.

Larger, prospective and randomised studies are required to more accurately understand the clinical utility of robotically guided ablation over a conventional manual ablation, though the number of VTs performed in the 4 years illustrates the potential challenge of recruiting to such a VT ablation study.

3.1.6 Conclusions

We have demonstrated that ablation of post-infarct scar-related VT using the Hansen Sensei Robotic Catheter System in patients with severe ventricular dysfunction is feasible with long term outcomes comparable to previous studies, as measured by a significant reduction in ICD therapy burden post ablation, and this includes patients who have failed manual ablations and presented acutely with multiple ICD therapies/storm. Despite a higher pre-procedural therapy burden, when compared to a series of patients who underwent manual guided ablation, acute and long-term outcomes were similar. Furthermore, it offered reduced operator radiation exposure for these long procedures.

Whether robotically guided ablation performed earlier into the disease process in patients who have experienced fewer ICD therapies (i.e. before the substrate becomes too advanced) improves outcomes is studied in the next section.

3.2 Early VT ablation after the first ICD therapy (ERASE-VT)

3.2.1 Introduction

The evolution of the arrhythmic scar post myocardial infarction is complex and poorly understood. Scar tissue composition is known to continuously change many years after infarction. Some studies have suggested that, despite ablation, VT recurrence is inevitable once the substrate has become too advanced, no matter how ablation is attempted (e.g. robotically) or delivered, partly owing to the challenges of completely eliminating the extensive arrhythmic substrate at this stage.^{130, 132} However, because of its inherent complexity, VT ablation is usually performed late into the disease course in patients with high arrhythmia burden, and after failure to achieve effective suppression using anti-arrhythmic medication.

Randomised controlled trials comparing the effectiveness of early VT ablation against conservative therapy have demonstrated mixed results with regard to long-term reduction in VT recurrence.^{133, 134, 169} There is thus a need for further studies to help ascertain the optimal timing of ablation. Two randomised controlled trials reported that very early ablation before therapies had even occurred might be a more effective strategy in preventing future therapies by addressing the substrate before it becomes too complex.^{133, 134} However, many of the control patients from both trials did not receive any therapies during follow up, raising doubts about the clinical justification of this approach so early into the disease process. Furthermore, a repeat study from the same investigators seven years after of one of the earlier trials did not show any benefit to earlier ablation.¹⁶⁹

A retrospective study of our post infarct ICD population demonstrated that the first appropriate therapy is an important predictor of subsequent therapy, and this may be a more acceptable time to consider early ablation, knowing that VT recurrence is likely to occur.¹³⁸ However, patients who have experienced only a single ICD therapy are quite different to those reported in most VT ablation studies involving individuals with multiple VTs.^{168, 170, 171} These studies aggressively targeted non-inducibility of all VTs, often requiring extensive ablation delivery.⁹⁴

In this study, we tested the hypothesis that early substrate based ablation after the first ICD therapy is effective in eliminating the arrhythmic substrate and prevent further episodes as compared to a non-ablative approach. Having demonstrated the safety and effectiveness of the Hansen robotic system we planned the ablative approach using this robotic system. We chose to avoid an aggressive ablation strategy in patients so early into the disease process, and planned a standardized procedure in which a target of 30 minutes of RF ablation was delivered within the substrate.^{147, 161}

3.2.2 Methods

3.2.2.1 Study Design

This was a prospective and randomised control trial. Three centres participated in this study, including:

1. Imperial College Healthcare, London;
2. John Radcliffe Hospital, Oxford;
3. Barts Heart Centre, London.

Patients were enrolled after their first episode of VT post ICD implantation, and were randomised in a 1:1 manner to an un-blinded treatment strategy of either VT ablation or non-ablative approach (conservative) approach. Randomisation was performed electronically (InForm electronic data capture system). The centres involved in the study routinely performed robotic ablations using the Hansen Sensei system. The primary endpoint of the study was the time to first appropriate ICD therapy or sustained VT episode (>30seconds). Patients were followed for a maximum of 2 years, or till they had sustained either 2 subsequent ICD shocks or 5 ATP episodes (considered a treatment failure). All ICDs were programmed to a standard setting based on the EMPIRIC trial.¹⁷² All patients enrolled after providing informed consent to participate in the study.

3.2.2.2 Inclusion Criteria

Post infarct ICD patients between the ages of 18-80 years after their first appropriate therapy (ATP/shock) from the device or sustained episode lasting more than 30 seconds captured in the monitor zone or by 12 lead ECG.

3.2.2.3 Mapping and Ablation Protocol

The same pre-procedural, mapping and ablation protocols as described in section 3.1.2.2 & 3.1.2.3 were used for those patients randomised to robotic ablation in this trial. Once an episode of sustained VT was induced, the VT stimulation study was stopped, and the tachycardia was terminated by ATP or DC reversion. Both CARTO and NAVX systems were used to map the ventricular scar. No mapping was performed in VT. A target of 30 lesions (30W for 60 seconds) were delivered at sites with voltage $\leq 1.5\text{mV}$ and one of: a) capture with stim-QRS>30ms; b) capture with pace-map consistent with induced or clinical tachycardia;⁹⁶ c) scar border location;⁹⁷ d) presence of a late potential;^{89, 173} e) completing a linear lesion.⁹⁵ A contact force of 10-20g was targeted, aiming for the local signal to diminish. The VT

stimulation was then repeated and further ablation was performed as clinically indicated, with the minimum target of eliminating the induced VT. No epicardial mapping or ablation was performed.

3.2.2.4 Follow-up

Patients were scheduled for follow-up visits at set intervals (3/6/12/18/24 months) from randomisation for ICD interrogation. In both the ablation and conservative arms, whilst patients may have already been on anti-arrhythmic therapy prior to enrollment, no changes (either additions or removal/ dose changes) were allowed subsequent to enrollment within the study till the primary endpoint was reached. Therefore, AADs were continued post ablation and during follow up in those who were already on them. In the conservative arm, once the primary endpoint was reached, patients could receive amiodarone if not already started, but no change was allowed in the ablation arm. If a patient re-presented in ICD storm, or sustained a cumulative of either 2 shocks or 5 ATP episodes during follow up, then either further anti-arrhythmics or VT ablation were allowed in both arms, according to the discretion of the investigator.

3.2.2.5 Statistics

Categorical variables were expressed as percentages and analysed using a Pearson Chi Squared Test or Fisher's Exact Test where the minimum expected count was <5. All data were unpaired: parametric continuous variables were expressed as mean $\pm$ 1 standard deviation and were analysed using a student's T-test. Skewed continuous variables were expressed as median (interquartile range) and analysed using the Mann-Whitney U-Test. The primary endpoint was time-to-event (with standard censoring at the time of latest visit, dropout or death), displayed by the Kaplan-Meier method, and statistical testing carried out by the Cox Proportional Hazards model. Analysis was performed as intention to treat. A value of $p \leq 0.05$ was considered significant. SPSS Version 23 (IBM) was used for statistical analysis.

3.2.3 Results

A total of 51 patients (age 69yrs (IQR=62-74); LVEF 32±10%; LVEDD=6.1±0.6cm; MI 18±11yrs previous) were recruited into this study (October 2011-November 2015) following their first detected ICD therapy (17mths (IQR=4-35) post implant; (ATP (n=24), shock (n=24)) or sustained VT episode below a therapy zone (n=3); VT 192±40bpm), and randomised into the two arms (ablation (n=26), conventional (n=25)).

Baseline demographics and co-morbidities between the groups were similar and are listed in Table 3-6.

	Ablation	Conventional
No.	26	25
Age (yrs)	68 (62-71)	71 (59-75)
male	96%	100%
Years since previous MI	17.3±10.9	18.9±10.8
Time to first ICD therapy (mnths)	14.8 (3.7-40.1)	18.2 (3.8-35.1)
VT Rate (bpm)	193 (164-228)	188 (167-203)
CABG	10 (38%)	8 (32%)
Diabetes	11 (42%)	9 (36%)
Ejection Fraction (%)	33.6±10.7	30.3±8.6
EF≥30%	16	14
EF<30%	10	11
LVEDD (cm)	6.1±0.79	6.2±0.51
NYHA (class)	II (II-III)	II (I-III)
CRT	10 (38%)	9 (36%)
Amiodarone	12 (46%)	12 (48%)
Creatinine (umol/L)	101 (87-126)	100 (87-131)

Table 3-6: Patient Demographics

All patients were on a beta-blocker, ACE inhibitor, statin and anti-platelet/anticoagulant as therapy for heart failure and coronary disease. Amiodarone was the sole anti-arrhythmic prescribed. There was no

difference in amiodarone usage (ablation n=12, conventional n=12; p=0.895) or EF% (ablation: 33.6 ± 10.7 ; conventional: 30.3 ± 8.6 ; p=0.244) between the two groups. The proportion of patients with left ventricular dysfunction and EF<30% (n=21; ablation: 10 (47%), conventional: 11 (53%)), and left ventricular dysfunction but with EF $\geq 30\%$ (n=30; ablation: 16 (53%), conventional: 14 (47%)) between the 2 groups were similar from the start (p=0.688). All ICDs were programmed to a standard setting. A further therapy zone was programmed in 2 patients owing to very slow symptomatic VTs.

Ablation was performed in 24pts at a median of 32 days (IQR=25-58) post enrollment. 1pt died prior to ablation and 1pt was withdrawn due to end-stage heart failure. VT was induced in 15/24pt (63%) pre-ablation (CL: 320ms (275-454)) and was subsequently pace terminated or defibrillated as per protocol. The entire LV was mapped robotically in all patients and scar was delineated accordingly (anterior/septum 30%; inferior/posterior 48%, apical 22%). An average 30 ± 11 lesions (1min RF duration per lesion) were delivered per scar, targeting scar border (49%), late potentials (9%), stim-QRS >30ms (32%), linear lesions (4%), and pace-match sites to the induced VT (7%) (Figures 3-3 and 3-4)

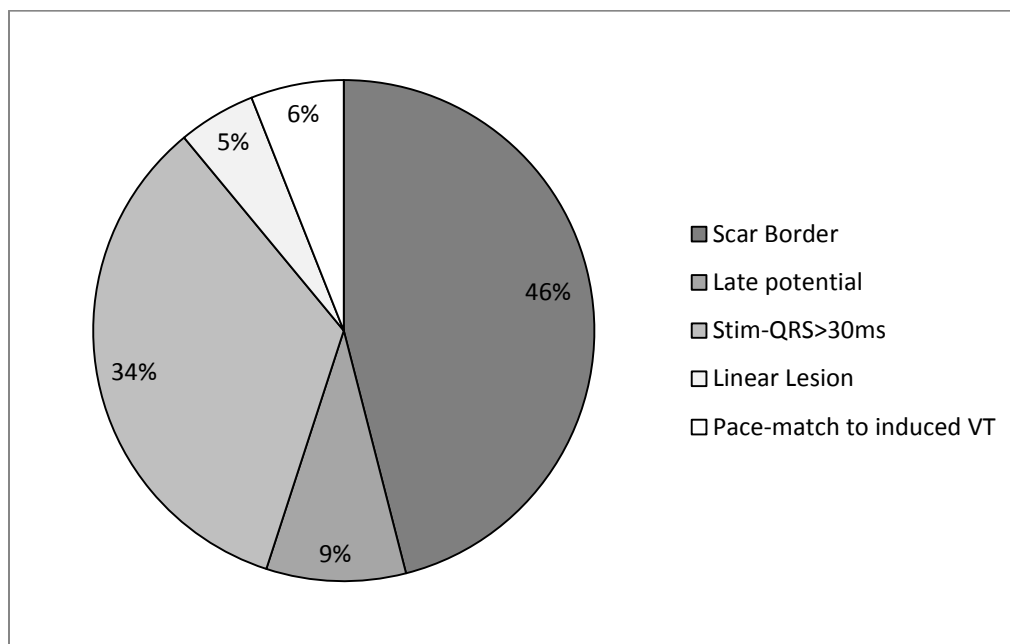


Figure 3-3: Substrate ablation targets

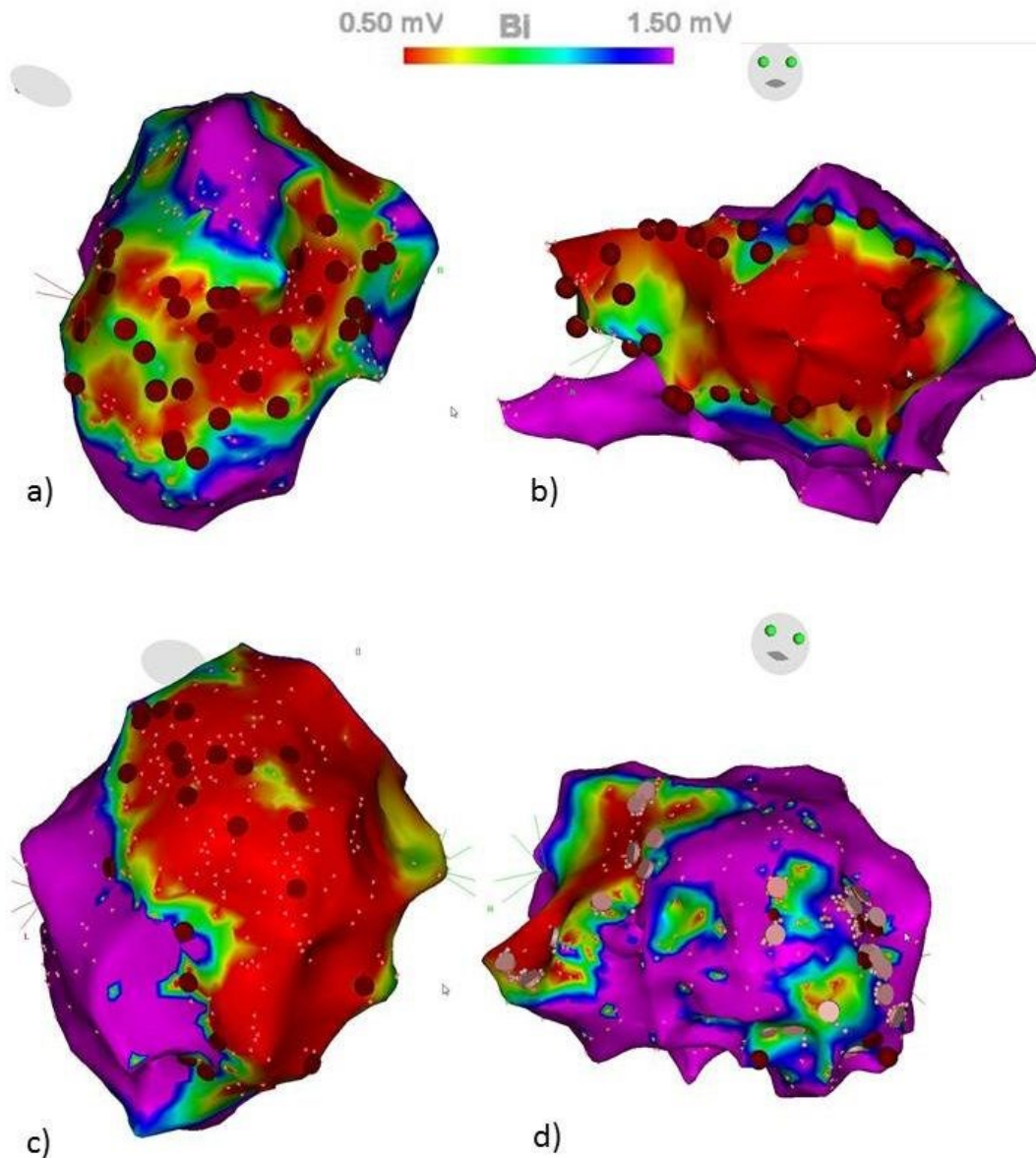


Figure 3-4: CARTO bipolar voltage maps of endocardial LV scar.

4 examples of substrate guided ablation in this study: a) scar border zone, stim-QRS >30ms; b) scar border zone; c) late potentials; d) scar border zone and sites with stim-QRS >30ms

Limited scar was seen in 2/24 endocardial substrates prohibiting dense substrate ablation. Total procedural duration was 159 ± 84 mins. The total fluoroscopic time was 32.2 ± 16.5 mins. The pre-ablation induced VT was no longer inducible in 13/15 (87%) post ablation. Within this group, VT was completely non-inducible in 5/13 (28%). There were 2 patients where the clinical VT remained inducible – difficult catheter manipulation and poor reach towards the anterior mitral valve region were noted with both

the Artisan and manually during these procedures. Two cases were stopped early (1 case with multiple spontaneous VT requiring recurrent defibrillation, and 1 case with a transient blood pressure fall without any reversible cause). Complications occurred in 2/24 (8%) (1 cardiac tamponade and 1 groin hematoma) that delayed discharge from hospital. The tamponade occurred prior to ablation and was assumed related to the transeptal puncture. There were no mortalities recorded within the first 30 days.

All patients were followed up for at least 1 year or until treatment failure. Follow up was terminated after 2 years. The median follow up time was 15.0months (IQR=9.3-24.0). A summary of the treatment outcomes within the study is presented in Table 3-7.

	Total	Ablation	Conventional	P value	Survival analysis
Follow up/ mnths (median (IQR))	15 (9.3-24)	18.5 (12-24)	12 (6-24)	0.23 ^a	
Deaths	6/49 (12%)	2/24 (8%)	4/25 (16%)		HR 0.47, 95% CI 0.09 – 2.56, p=0.37
Freedom from VT/ mnths (med (IQR))		12.0 (9.4-24.0)	6.0 (2.4-18.0)		HR 0.55, 95% CI (0.25-1.26), p=0.16 ^c
VT recurrence	24/49 (49%)	10/24 (42%)	14/25 (56%)	0.31 ^b	
Proportion of VT recurrence within 3 mnths	14/24 (58%)	3/10 (30%)	11/14 (79%)	0.035^d	
VT recurrence EF ≥30% (29pt)	14/29 (48%)	5/15 (33%)	9/14 (64%)	0.096 ^b	
Freedom from VT (EF≥30%)		12.8 (8.0-24.0)	2.6 (1.4-10.5)		HR 0.31, 95% CI (0.10-0.92), p=0.035^c
VT recurrence EF <30% (20pt)	10/20	5/9 (50%)	5/11 (50%)	0.80 ^b	
Freedom from VT (EF<30%)		12 (10.3-18)	12.2 (4.5-21)		HR 0.89, 95% CI (0.24-3.33), p=0.87 ^c
ICD storm	6/49 (12%)	3/24 (13%)	3/25 (12%)	0.96 ^b	
# Tot. therapies per pt (median/IQR)		0 (0-3)	1 (0-5)	0.16 ^a	
# Tot therapies per pt EF≥30% (29pts)		0 (0-1)	4 (0-6)	0.024^a	
# Tot therapies per pt EF<30% (20pts)		2 (0-3)	0 (0-2)	0.50 ^a	
Treatment failure	18/49 (37%)	8 (44%)	10 (56%)	0.63 ^b	

Table 3-7: Treatment Outcomes

Mann Whitney U Test=a; Pearson Chi Squared Test=b; Cox Proportional Hazards=c; Fishers Exact Test=d

Total therapies = (ICD shocks + ATP episodes). Slow VT episodes were recorded as 1 therapy. ICD storm was recorded as 3 therapies. Once patient reached Treatment failure, no further therapies were recorded.

There was no difference in the overall follow up time between the two groups (ablation=18.5mths (IQR=12.0-24.0); conventional=12mths (IQR=6.0-24.0); $p=0.23$). There was no significant difference in mortality between the two arms (HR 0.47, 95% CI 0.09 – 2.56, $p=0.37$). During this follow up period, there were 2 (8%) deaths in the ablation group (month 18 - cardiogenic shock, month 24 - end stage heart failure); and 4 (16%) deaths in the conventional group (month 12 – sepsis, month 18 - end stage heart failure, month 18 – sepsis, month 24 – metastatic cancer) ($p=0.41$). There was a single patient withdrawal (month 6) within the study, occurring within the conventional arm. Two patients were lost to follow up (month 6 and month 18), both from the conventional arm. A summary of the follow up period is presented in figure 3-5.

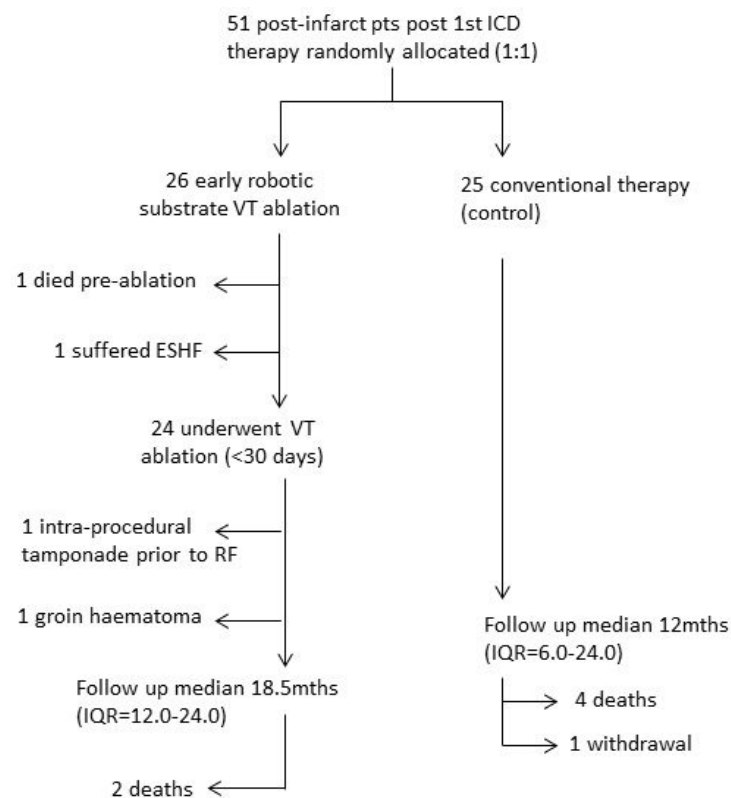


Figure 3-5: Patient groups

Freedom from VT recurrence was longer in the ablation arm (12.0months (IQR=9.4-24.0)) compared to the conservative arm (6.0months (IQR=2.4-18.0)) though this difference did not reach statistical significance (HR 0.55, 95% CI (0.25-1.25), $p=0.16$). Freedom from VT recurrence has been presented as Kaplan Meir Survival curves in Figure 3-6. This VT recurrence (CL: 172 ± 42 bpm) presented as ICD shocks in $n=3$ (ablation), and $n=2$ (conservative). The numerical difference between the two groups was driven by a high recurrence rate in the conventional arm within the first 3 months (proportion of VT

recurrences by 3 months = 14/24 (58%); ablation n=3/10 (30%); conventional n=11/14 (79%); p=0.035). Stratifying each group by ejection fraction severity, ablation significantly delayed the time to recurrence in patients with ejection fraction $\geq 30\%$ (6.0 months (IQR=2.4-18.0); HR 0.31, 95% CI (0.10-0.92), p=0.035), although the delay was not significantly different between the two EF subgroups (p=0.11 for interaction).

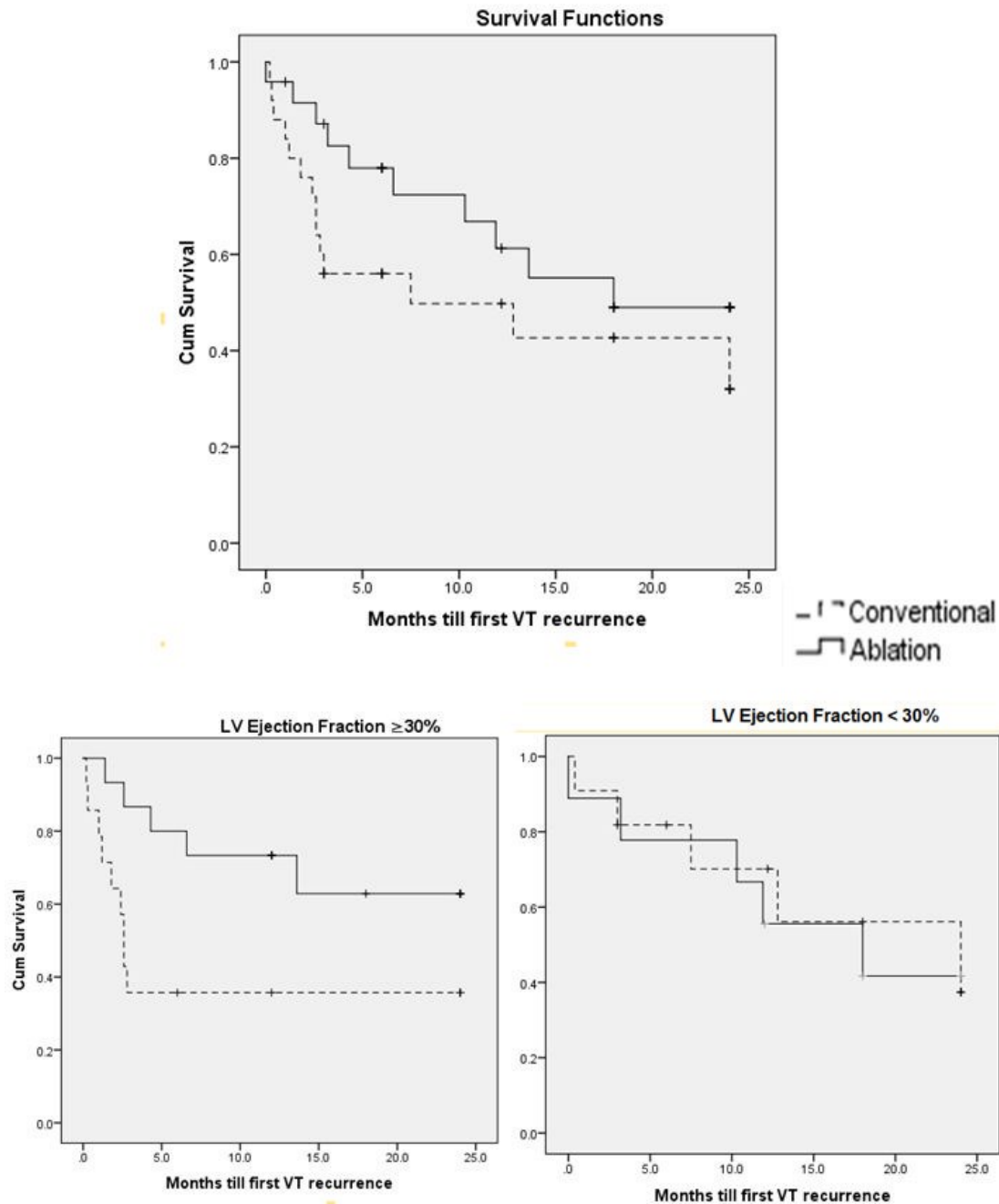


Figure 3-6 Kaplan Meir Survival curves: Freedom from VT recurrence
(Includes sub-analysis of groups separated by ejection fraction of 30%)

Early VT ablation reduced the burden of total ICD therapies over follow up, but this did not reach statistical significance (median therapies per patient: ablation n=0 (IQR 0-3); conservative n=1 (IQR: 0-5); p=0.16). Stratifying each group by ejection fraction severity (figure 3-7), ablation significantly reduced the total therapy burden in patients with ejection fraction $\geq 30\%$ (median therapies per patient: ablation n=0 (IQR 0-1); conservative n=4 (IQR: 0-6); p=0.024). This analysis of total therapy burden between the two arms was significantly skewed by an ICD storm event (3 or more therapies within 24hours), especially where VT failed to terminate with appropriate therapy prior to the patient seeking medical attention. As there were equal number of storm episodes between groups (n=3), to avoid these extreme outliers, we compared the total therapy burden above by recording an ICD storm event as “3” ICD therapies.

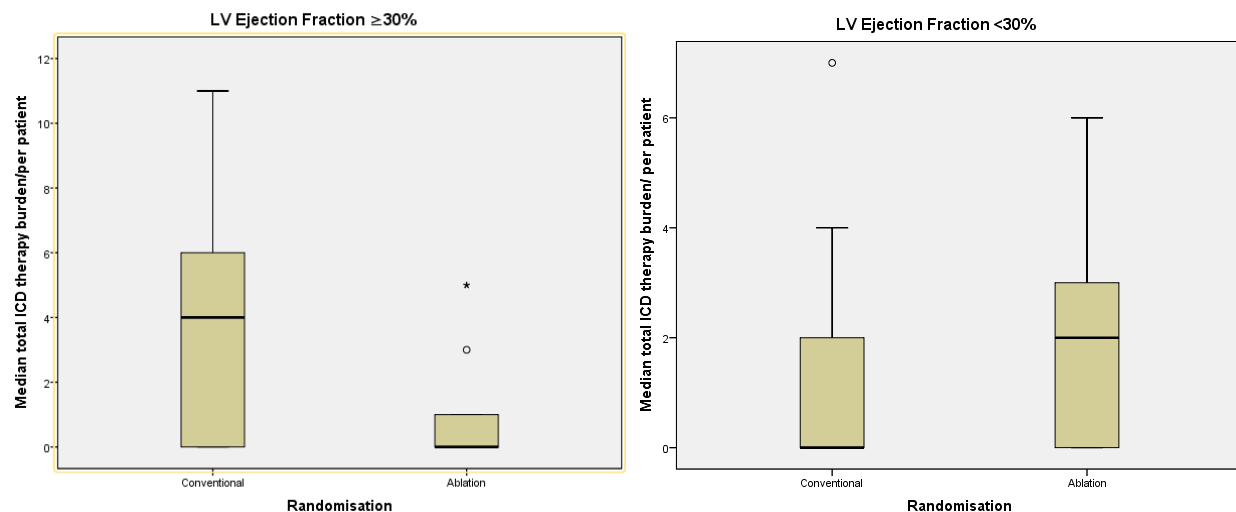


Figure 3-7: Total therapy burden stratified by LV Ejection Fraction. Modified box and whisker plots of the ablation and conventional distribution stratified by EF%, demonstrating the smallest observation, first quartile, median, third quartile, and largest observations, with outliers plotted as isolated points.

Following treatment failure, defined as either x5 ATPs or x2 shocks (ablation n=8/18 (44%); conventional n=10/18 (56%); p=0.628) 8/10 patients in the conventional group underwent VT ablation, and 2/8 patients in the ablation arm underwent redo-procedures.

3.2.4 Discussion

Early robotic post-infarct VT ablation following the first appropriate ICD therapy using a fixed dose of 30 minutes of RF energy demonstrated a non-significant delay till VT recurrence compared to a non-ablative approach. Furthermore, post hoc analysis of those patients with EF $\geq 30\%$ demonstrated a statistically significant delay in time to VT recurrence, and reduction of overall therapy burden post ablation, suggesting that elimination of the arrhythmic substrate is more likely in patients with higher EF%.

There exists clinical equipoise about whether an early invasive approach is of net clinical benefit in significantly reducing long-term arrhythmia recurrence. This study now further adds to the debate. To date, there have been only three completed randomised controlled trials; VTACH (Catheter Ablation of Stable Ventricular Tachycardia Before Defibrillator Implantation in Patients With Coronary Heart Disease) recruited from a population of patients with only stable VT; SMASH-VT (Prophylactic Catheter Ablation for the Prevention of Defibrillator Therapy) and SMS (Substrate Modification Study) also recruited patients with more unstable VTs, more typical of a general ICD population.^{133, 134, 169} Whilst VTACH and SMASH-VT demonstrated that prophylactic ablation before ICD implantation was effective in reducing future therapies, SMS did not.^{133, 134} The study designs within these trials were similar to ERASE-VT, though each recruited a higher number of patients.

One of the first challenges we encountered in this early VT ablation trial was deciding the endpoint. Non-inducibility of VT is associated with greater freedom from VT recurrence, but is limited by poor reproducibility, especially related to general anesthesia.^{89, 174, 175} In this study, VT was already non-inducible in 37% at the start of the procedure. Extensive ablation (~70mins of RF time) has been required in previous studies to achieve non-inducibility.^{94, 176} We decided against using such an aggressive endpoint in our cohort of patients early into the arrhythmic disease process, and we chose a fixed RF dose of 30mins (operators were allowed to deliver more than 30mins in order to render any clinical VT non-inducible). The high recurrence rate, especially in those with EF<30%, may have been a reflection of this decision. However, this needs to be weighed against the greater risk of long procedures in patients with low EF%.

A retrospective study of our post infarct ICD population demonstrated that the first appropriate therapy is an important predictor of subsequent therapy. In this study, ICD therapy recurrence occurred within the first 3 months in approximately 30% of all patients, which included 4 times more patients from the conventional arm than the ablation arm. The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias has included that “catheter ablation should be considered after a first episode of sustained VT in patients with ischaemic heart disease and an ICD (Class IIa, level of evidence B).”¹⁶² Remarkably, in our study, after the first 3 months, VT recurrence in the conventional arm was much slower, suggesting that in about 30-40% of patients, first ICD therapy is still relatively benign. This is in-keeping with SMASH VT, where the event rate in the conservative arm of patients with secondary prevention ICDs was only 33%.¹³³ This is important as it underlines the challenge of avoiding aggressive endpoints with higher risks in this cohort when ablation is being considered.

The current study findings appear to advocate early VT ablation after the first ICD therapy specifically in those patients with EF $\geq$ 30%. Interestingly, this is similar to the VTACH trial in which there was a wide separation of the curves between ablation and conventional arms in those with EF $\geq$ 30% and has led to the proposal of Berlin VT targeting those patients with EF $\geq$ 30% alone.¹³⁴ Prior studies have demonstrated that worsening left ventricular ejection fraction has been associated with a higher burden of myocardial scar, and increased susceptibility to ventricular arrhythmia including storm.¹⁷⁷⁻¹⁷⁹ This suggests that despite attempts at early intervention, the arrhythmic substrate may already be too advanced in patient with EF <30% to address with a single ablation attempt.

There are multiple reasons for VT recurrence post ablation. This may be due to new arrhythmic substrate developing with time or ablation causing regions of slow conduction and reentry.¹⁶⁷ Alternatively it may be a reflection that VT inducibility is an unreliable endpoint to define acute success, as evident by the fact that almost 40% of the patients were non-inducible from the start. Most importantly, this may be a reflection that our mapping approaches did not reliably identify the arrhythmic substrate. In both ERASE VT and our robotic VT feasibility study, the arrhythmic substrate was broadly defined using established peak-to-peak bipolar voltage of <1.5mV.⁹⁵ This value originated from previous studies that used widely spaced catheters, as we did in these studies, that may have under-estimated the scar area. Furthermore, in the robotic feasibility study reported in section 3.1, approximately only 200 data points were collected within the complete LV cavity during each ablation procedure, and fewer still within the scar itself. Whilst not reported here in ERASE VT, a similar low

number of data points were accrued in each map. A more detailed characterization of the activation patterns within the scar with higher point density and smaller tip/narrower spaced catheters may help define a more targeted ablation.¹⁸⁰

3.2.5 Limitations

This study is limited by a relatively small sample size. The analysis of outcomes between groups, especially by severity of left ventricular dysfunction is underpowered with wide confidence intervals to make any firm conclusion. Recruitment to the study was considerably lower than anticipated and hence continued over a 4year interval. We continued the study till 50 patients, having to stop owing to cessation of financial support. Difficulties with recruitment and follow up have resulted in the failure of several other important trials leading to completion, and the current paucity of data in this field.¹³⁷ A systematic review of all completed randomised controlled trials, including our own, would increase the power of any common trends between studies, and is described in the next section.

Mapping and ablation in VT was not performed in this study. Whilst this offers the advantage of avoiding hemodynamic instability in sustained VT, efficacy of ablation in previous studies has been measured by combining both substrate and VT based approaches where feasible.

Multiple approaches to substrate based ablation were used in this study. There is currently no data on the optimal substrate based strategy to minimize the risk of future VT recurrence. Multiple novel techniques have been developed since the advent of this study which have all demonstrated means of improved ablation outcomes. These have included combined endo-epicardial approaches, mechanical circulatory support, multi-polar catheters and high density mapping systems, and delayed non-invasive inducibility tests.^{94, 174, 181}

3.2.6 Conclusions

Robotic VT substrate ablation following the first ICD therapy in the post infarct population has demonstrated a non-significant delay in time to VT recurrence in patients receiving a standard RF dose of 30 lesions at 30W for 60 seconds. The first ICD therapy was an important predictor of early recurrence (within 3 months) in only a third of patients. However, another third of patients remained free of further VT recurrence without ablation over a 2 year follow up, suggesting that the first ICD therapy is still relatively benign in some. Post hoc analysis of those patients with EF $\geq$ 30% demonstrated a statistically significant delay in time to VT recurrence and reduction of overall therapy burden post ablation. Therefore, early ablation does appear beneficial after the first ICD therapy in patients with EF $\geq$ 30%, though this finding was under-powered to make any firm conclusion. The higher than expected overall recurrence rates post ablation may have been a reflection of the RF dose restriction, or sub-optimal mapping of the scar to identify suitable substrate ablation targets. Methods to improve our understanding of activation patterns within scar are likely required to improve outcomes, and the Rhythmia ultra-high density mapping system as a means to increase resolution is studied in the next chapter.

3.3 A meta-analysis of early catheter ablation in post infarct VT

3.3.1 Introduction

The difficulties in conducting large trials of early VT ablation in post-infarct patients means that there remains a paucity of controlled trials assessing the efficacy of catheter ablation.¹³⁷ We therefore conducted a systematic review of all completed randomised controlled trials exploring the efficacy of early ablation on recurrent episodes of VT as well as death in the post infarct patient. We included our data from ERASE VT.

3.3.2 Methods

We identified all reports of randomised controlled trials investigating the role of VT ablation in patients with ischaemic cardiomyopathy and a single episode of suspected VT/VF, using the search strategy outlined below. Only articles in English were considered. Reference lists and systematic reviews were hand-searched for additional publications.

Wolters Kluwer's Ovid ® was used to search MEDLINE ® (from 1947 to present) and EMBASE (from 1946 to present) using the following search strategy on 13th June 2017.

1. *Ablation*
2. *AND Ventricular tachycardia*
3. *AND*
 - a. *ischemic heart disease*
 - b. *OR ischaemic heart disease*
 - c. *OR myocardial infarction*
 - d. *OR coronary artery disease*
4. *AND*
 - a. *trial*
 - b. *OR randomised*
 - c. *OR randomised*
 - d. *OR randomly*

We sought data on the following outcomes: all-cause mortality, survival free of VT/VF and survival free of ICD therapy. Where available, we extracted data for patients with ejection fractions $\leq 30\%$ and ejection fractions $>30\%$ separately. We extracted reported hazard ratios with confidence intervals, and appropriately transformed them for meta-analysis. We quantitatively synthesised the extracted hazard ratios using a random-effects meta-analysis. Heterogeneity was assessed using the

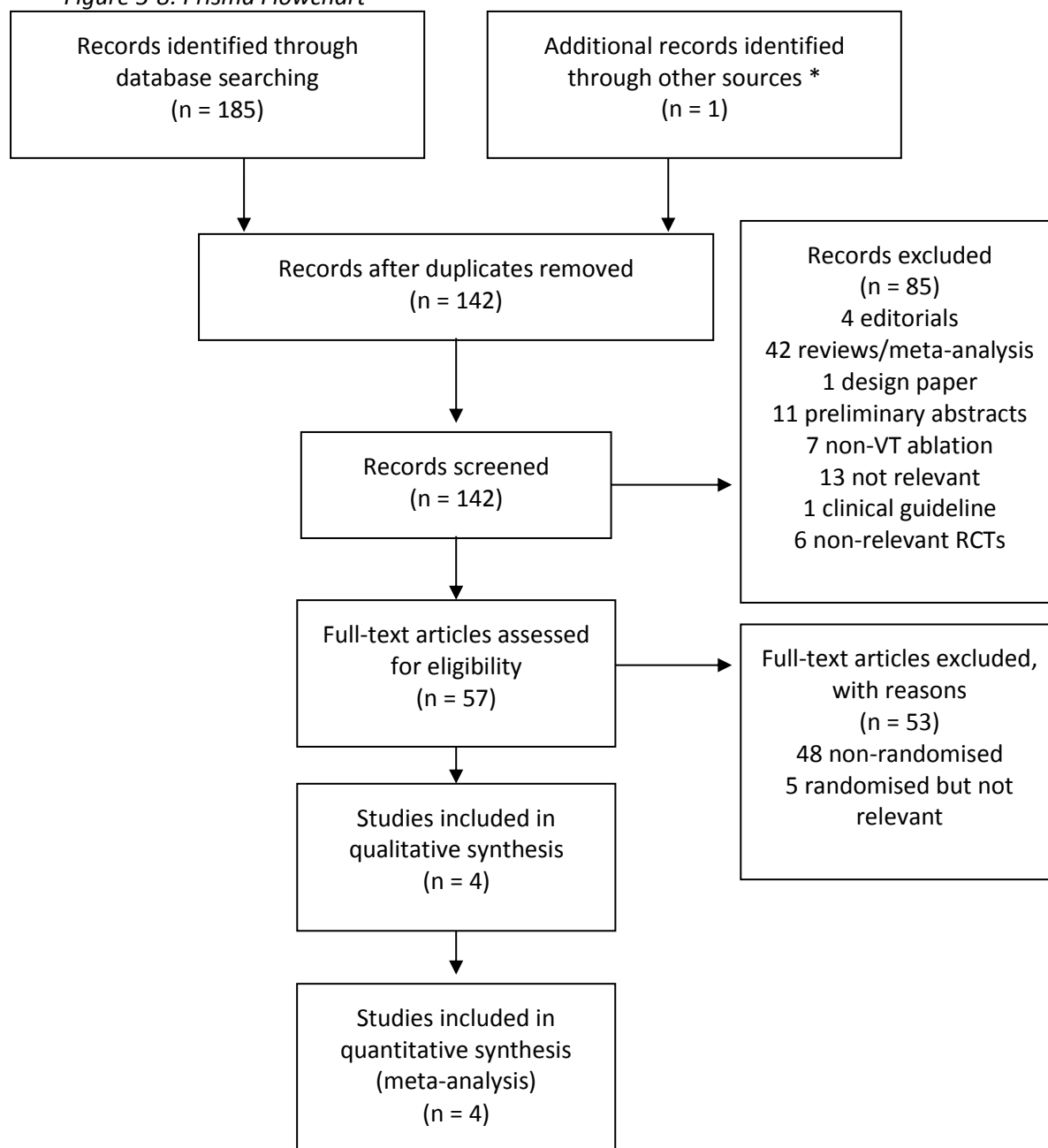
I^2 statistic. Data was analysed using the R Programming Language and the “metafor” meta-analysis package.

3.3.3 Results

Our search strategy identified 185 reports, which were processed as shown in the study flow chart (Figure 3-8). We also included the ERASE-VT trial. A total of 8 randomised clinical trials involving VT ablation were eventually identified, of which 5 trials were excluded from this meta-analysis. The VANISH trial recruited patients all of whom were already on AADs (anti-arrhythmic drugs) and compared ablation to higher dose AADs.¹⁴⁶ In the CALYPSO trial, whilst the control arm received AADs, the ablation arm did not, obscuring the effect of ablation alone.¹³⁵ In the remaining three trials, patients in both arms underwent VT ablation, where different approaches to ablation were subsequently compared.^{176, 182, 183} A total of 4 studies were eligible for meta-analysis.^{133, 169, 184} The baseline and procedural characteristics are shown in Table 3-8 and 3-9.

A total of 400 participants were enrolled, with 198 patients allocated to early VT ablation, and 202 patients allocated to the control arms of the trials. Across the 4 trials, the mean age was 66.9 years. Each trial recruited from a post-infarct population, and included patients following the first documented or inducible ventricular arrhythmia and randomised patients to an ablation vs non-ablation approach. For those patients randomised to ablation, this was performed endocardially alone, consisting of pace-map guided linear lesions or late/fractionated EGM abolition. All trials aimed to eliminate the clinical VT as a minimum. AAD usage was controlled and ICD programming was standardized between arms during follow up.

Figure 3-8: Prisma Flowchart



* The contemporaneously conducted ERASE-VT trial was included in our analysis

Study	Year	Presenting arrhythmia	Number of subjects		Age (years)		Years from MI		Baseline (%)		EF		Amiodarone use		Beta-blocker use	
			Stable or unstable VT	active	control	active	control	active	control	Active	control	control	active	control	active	control
SMASH-VT	2007	Both	64	64	67	66	8.8	7.9	30.7	32.9	0 (0%)	0 (0%)	60 (94%)	63 (98%)		
VTACH	2010	Stable	54	56	67.7	64.4	12.6	13.3	34	34.1	18 (33%)	19 (34%)	39 (72%)	41 (73%)		
SMS	2017	Unstable	54	57	68.4	65.9	11.1	8.6	32	30.4	16 (30%)	20 (35%)	49 (91%)	52 (91%)		
ERASE-VT	2017	Both	26	25	68	71	17.3	18.9	33.6	30.3	12 (46%)	12 (48%)	26 (100%)	25 (100%)		

Table 3-8: Baseline characteristics

Study	VTACH	SMASH VT	SMS	ERASE
VT type	Stable VT (BP >90mmHg and no syncope)	All VTs	Unstable VTs (ventricular fibrillation (VF) or VT with a systolic blood pressure <90 mm Hg)	All VTs
Ablation timing	Pre secondary prevention ICD implantation	Pre secondary prevention ICD implantation	Pre secondary prevention ICD implantation	Post first ICD therapy (primary or secondary prevention device)
Ablation approach	VT + substrate	VT + substrate	VT + substrate	Substrate
Substrate ablation method	"standard criteria" - pacemap guided linear lesions referenced	pacemap guided linear lesions. late / fractionated potentials	standard criteria - pacemap guided linear lesions referenced	As per operator preference: a) capture with stim-QRS>30ms; b) capture with pace-map consistent with induced or clinical tachycardia; c) scar border location; d) presence of a late potential; e) completing a linear lesion
Acute endpoint	Non-inducibility of any VT	Unknown	Non-inducibility of the clinical VT	Non-inducibility of the clinical VT
AAD	at the discretion of the investigator - restricted use recommended	No AADs allowed (pre or post enrollment)	No restriction documented, though similar use in both groups	Following enrollment, no AAD till primary endpoint
ICD programming	All SUM ICDs - VF zone 200 beats per min. VT zone 60 ms above the slowest documented VT (ATP followed by shocks)	"Standardized to ensure at least one VT zone in which ATP could occur" - no rate documented	All Medtronic ICDs - VF zone >200bpm, VT zone >160bpm/60ms above slowest VT documented	As per EMPiRIC trial
Acute endpoint	non-inducibility of any VT	Unknown	Non-inducibility of the clinical VT	Non-inducibility of the clinical VT

Table 3-9: Procedural characteristic and follow up

3.3.3.1 Effect on all-cause mortality

All 4 trials reported hazard ratio and 95% confidence intervals for all-cause mortality. Meta-analysis showed no significant difference in all-cause mortality between patients in the active and control arms of the 4 trials (HR 0.76, 95% CI 0.43 to 1.32, $p = 0.74$, $I^2 = 0.0\%$, Figure 3.9). There was no significant heterogeneity between trials.

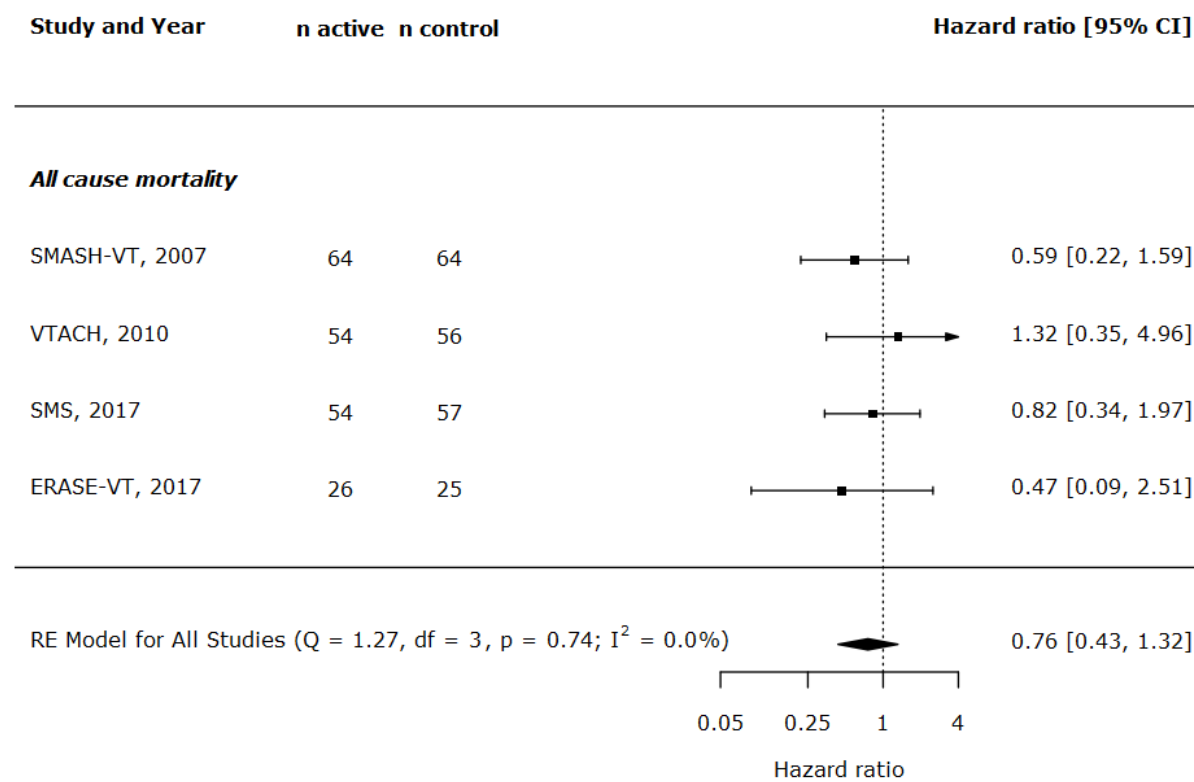


Figure 3-9: Impact of an early ablation strategy on all-cause mortality

3.3.3.2 Effect on primary endpoint of trials.

Meta-analysis showed a significant improvement in the survival from the primary endpoint of trials (either freedom from ICD therapy or freedom from VT/VF) for patients in the ablation arms across the 4 trials (HR 0.63, 95% CI 0.43 to 0.91, $p = 0.01$, $I^2 = 28.3\%$, Figure 3-10). There was no significant heterogeneity between trials.

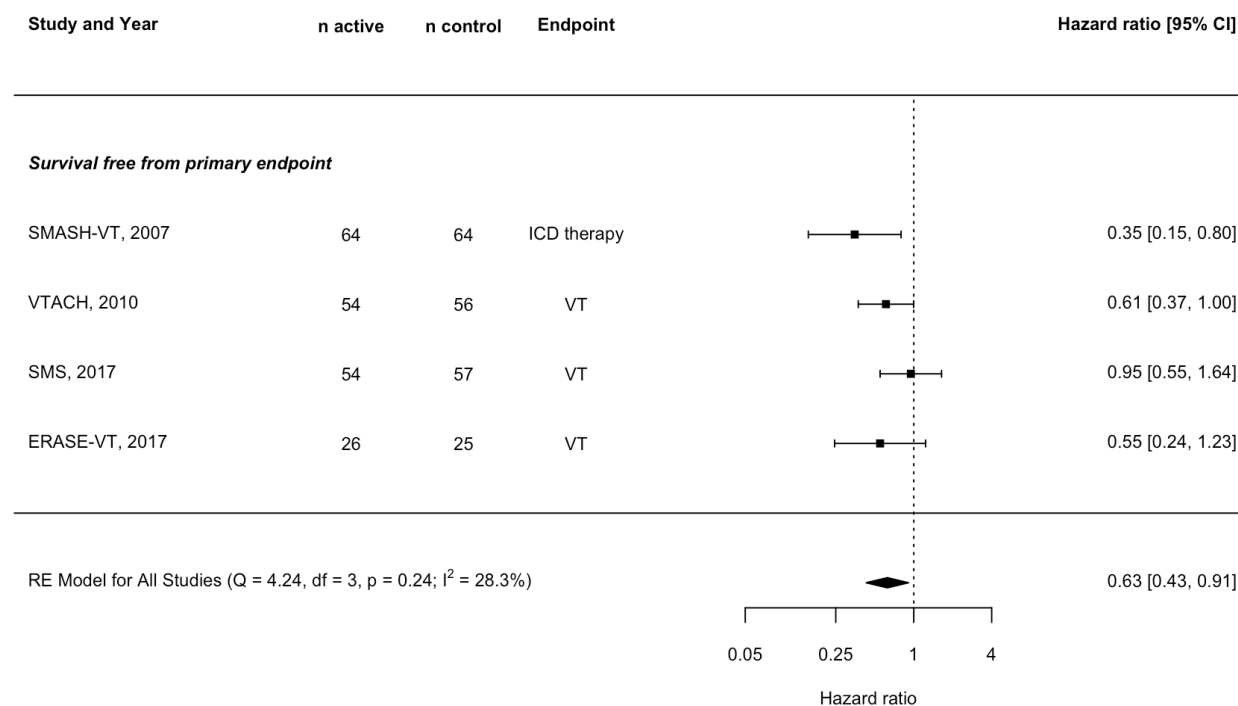


Figure 3-10: Impact of an early ablation strategy on primary endpoint

3.3.3.3 The effect of ejection fraction on survival from primary endpoint of trials

Three of the four trials (all except SMS) gave hazard ratios and 95% confidence intervals for freedom from their specified primary endpoint, stratified by ejection fraction category ($\leq 30\%$ versus $> 30\%$). One of these trials (SMASH-VT) did not provide the hazard ratio and 95% confidence interval for the $\leq 30\%$ ejection fraction subgroup; however, using the Kaplan-Meier plots from the publication and the supplied 'number at risk' data, we calculated these measures using Plot Digitizer. Meta-analysis showed a significant improvement in the survival from the primary endpoint of trials for patients with an EF $>30\%$ (HR 0.38, 95% CI 0.23 to 0.64, $p = 0.0003$, $I^2 = 0.0\%$, Figure 3-11 top panel). There was no significant improvement in the survival from the primary endpoint of trials for patients with an EF $<30\%$ (HR 0.78, 95% CI 0.44 to 1.41, $p = 0.415$, $I^2 = 0.0\%$, Figure 3-11, bottom panel).

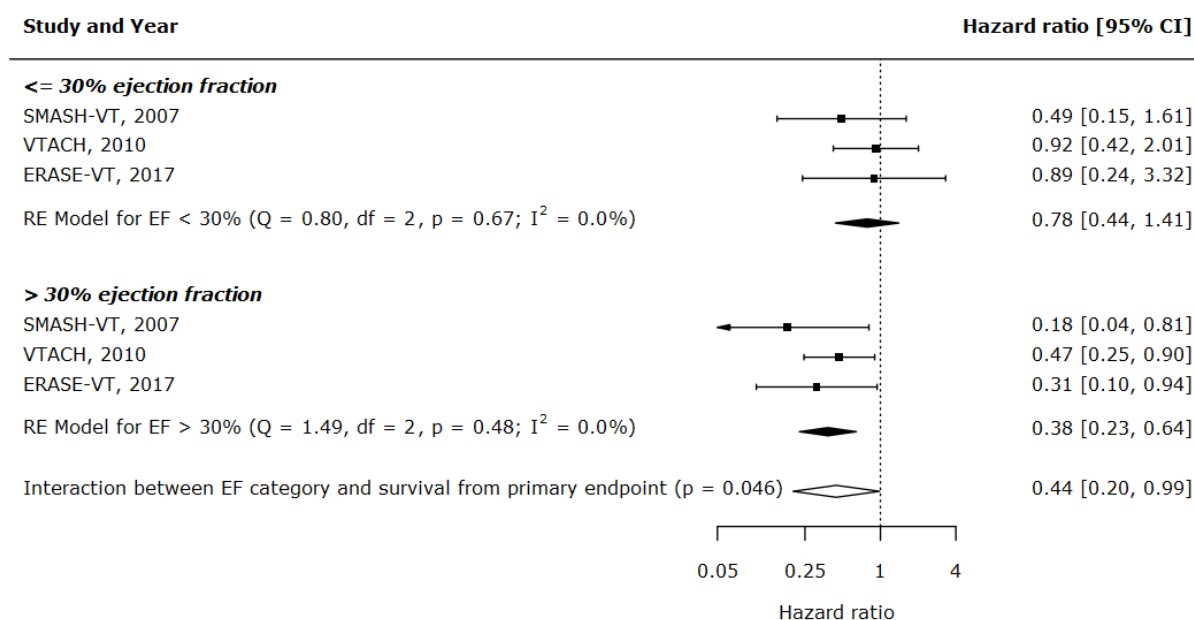


Figure 3-11: Impact of an early ablation strategy on primary endpoint, stratified by ejection fraction.

By performing a mixed-effects meta-analysis across both groups of ejection fraction categories, with both the trial and the ejection fraction category as moderators, there was a significant interaction between ejection fraction category and outcomes ($p = 0.046$). This suggests that this difference was not merely due to under-powering of the $\leq 30\%$ EF subgroup; rather there was a significant difference between responses.

3.3.4 Discussion

This meta-analysis includes four trials assessing the effects of VT ablation in patients with ischaemic cardiomyopathy. The analysis has found an early VT ablation strategy in these patients is associated with increased survival from either VT/VF or ICD therapy.

Furthermore, this meta-analysis has demonstrated that ejection fraction is a key determinant in the effectiveness of a VT ablation strategy. The 'EF hypothesis' for improved outcomes from VT ablation amongst patients with higher ejection fractions was first supported by the oldest trial included in this analysis, SMASH-VT. This trial demonstrated a significant benefit in patients with ejection fractions >30%, but not in those ≤30%. However, the test for interaction was not significant ($p = 0.29$) and so whether ejection fraction was a meaningful predictor of outcomes was unclear. Since then, however two of the three subsequent randomised trials have found similar results, with VT ablation improving survival from ICD therapy or VT/VF only amongst patients with ejection fractions >30%. Only the SMS trial, reported that "no significant difference was found in the primary endpoint" in patients with EF > 30%. Unfortunately, as no survival data is provided for this, the SMS trial was unable to contribute towards this aspect of our meta-analysis. This 'EF hypothesis' is further strengthened by the results of several non-randomised studies with similar findings. Izquierdo *et al.* demonstrated no overall benefit to ablation in those with electrical storm, except in those specifically with EF >25%.¹⁸⁵ Colella *et al.* showed that in patients where the clinical VT was ablated, VT recurrence was avoided in those with EF >35%, whereas almost half had recurrence in those with EF ≤35%.¹⁸⁶ Acosta *et al.* described that the benefit of ablation was driven largely by those with EF >35%, with no differences in VT recurrence with or without ablation with EF <35%.¹⁸⁷ The most recent guidance on VT ablation suggests early catheter ablation should be considered in post infarct patients with an ICD.¹⁶² On the basis of this meta-analysis, we recommend that this consideration, specifically for early ablation, be based on the patients underlying EF%.

This meta-analysis has not demonstrated any mortality benefit to VT ablation. Large sample sizes are required to determine a mortality benefit of VT catheter ablation. Recognizing the challenges in patient recruitment in prospective studies, 12 of the most experienced tertiary centres around the world came together between 2002 and 2013 to develop a shared database for retrospective analysis, forming the International VT Ablation Center Collaborative group. The data from this group offers the largest of any

study addressing outcomes of VT ablation from multiple centres.¹⁷⁵ Whilst this is of importance, the authors themselves recognize the limitations of their analysis, being retrospective, observational and non-randomised, in particular the inherent potential biases and inaccurate or incomplete data sets.

3.3.5 Study limitations

Any systematic review of VT ablation studies is limited by heterogeneity in the study designs that reduce the external validity of a meta-analysis. There were some differences between each trial (Table 3-9). Firstly, whilst ERASE-VT and SMASH-VT recruited patients with any ventricular arrhythmia, VTACH only recruited patients with stable VT and SMS only recruited patients with unstable VT. Secondly, in addition to substrate ablation, VTACH and SMS ablated in VT where possible. Thirdly, the ablation protocol in VTACH may have been more extensive as it targeted non-inducibility of any VT, as opposed to just the clinical VT.

3.3.6 Conclusion

In patients with ischaemic heart disease, early catheter ablation of VT improves survival free from ICD therapy or VT/VF. Ejection fraction is a significant predictor of success from VT ablation, with patients with ejection fractions >30% demonstrating improved survival from ICD events or VT/VF when compared to those with ejection fractions $\leq$ 30%.

Chapter 4

4 Increasing mapping resolution within myocardial scar

Despite the use of robotic catheter navigation to increase ablation tip stability, the recurrence rate post VT ablation was still high, and comparable to other studies. We believe an important reason for this could be inadequate characterization of the arrhythmic substrate, where only 200 data points were collected within the LV cavity, and where the scar was broadly characterized with widely spaced catheters using a voltage amplitude of <1.5mV. This chapter explores whether increased resolution offered by an ultra-high density mapping system within low voltage areas can more accurately define the activation patterns within scar.

4.1 Activation mapping within myocardial scar using ultra-high density

4.1.1 Introduction

A multi-electrode basket catheter has been developed which comprises 64 mini-electrodes with narrow inter-electrode spacing (Orion, Boston Scientific, Cambridge, MA) paired to a 3D mapping system (Rhythmia, Boston Scientific).¹²⁰ The system offers “ultra-high” electro-anatomical point density (often in excess of 10,000 points per map) and improved EGM resolution for activation mapping.^{188, 121, 189}

We aimed to test this system in mapping activation within scar. The opportunity to map reentrant activation within ventricular scar in clinical practice is rare, as VTs are often non-sustained or poorly tolerated. Similar complex patterns of activation have also been described within iatrogenic atrial scar following previous AF ablation, and were considered a more stable substrate to study.^{70, 85, 190} In this study, we tested the effectiveness of optimising EGM resolution using the Rhythmia system to delineate the activation in scar related ATs as a guide to ablation.

4.1.2 Methods

4.1.2.1 Procedural details

Patients with symptomatic ATs post previous AF ablation referred to our centre and mapped with Rhythmia were studied. The pre-procedural setup was as documented in Chapter 2.1.

4.1.2.2 Activation Mapping

The geometry of the cardiac chambers was acquired based on the location of the outer-most electrodes of the basket using in-built magnetic and impedance sensing. Mapping was performed in tachycardia, seen either from the start, or induced with atrial burst pacing. Beats were automatically and continuously collected, and were only accepted for display on the map having passed through a series of beat acceptance criteria: a stable cycle length within 10ms of the target TCL; relative timing deviation of 5ms between 2 coronary sinus reference electrodes; respiration gating in expiration phase; stable catheter location within 1mm; and stability of the mapping catheter signal morphology of at least 75% from beat to beat. Only EGMs within 2mm of the surface geometry were displayed and used for map computation.

The system displayed activation around the cardiac chamber by measuring the LAT at different sites in relation to a stable reference, presenting this information on a colour coded map. Details of the method of LAT assignment and WOI setup are presented in the general methodology (section 2.4). Each EGM displayed on the map was highlighted as a “dot” at its corresponding anatomical location, and each dot was coloured according to its LAT in relation to the WOI. The system compared the LATs of neighbouring dots, and assigned a background colour to the map only where it was “confident” that the LATs of all neighbouring dots were relatively consistent. Regions with inconsistent timing appeared in grey. A “confidence mask” within the system could be adjusted to increase or lower the threshold at which the system determined whether the LATs were consistent. The less stringent the desired consistency, the more background colour was filled in the map, akin to the colour threshold in the CARTO systems. The default confidence mask threshold of 0.03mV was used in this study, and areas below this threshold were displayed in grey and defined as scar. Reducing this value below <0.03mV reduced the grey zone size. No manual re-annotation of activation time was performed.

4.1.2.3 AT diagnosis

All AT mechanisms were studied to determine their underlying reentrant mechanism (localised or macro-reentrant). A “focal” AT demonstrated centrifugal activation away from a discrete region, and a “macro-reentrant” AT demonstrated progressive activation around the cardiac chamber covering the full color spectrum of the color coded map once the complete cycle length has been mapped.^{61, 63} Localised reentry (LR) was considered where continuous rotational activation around a small area of scar <2cm in diameter was evident, with each rotation encompassing one full TCL.^{78, 79}

4.1.2.4 Ablation

Entrainment manoeuvres were generally avoided owing to the risk of transforming or terminating the tachycardia, and because local capture within low voltage areas may have proved difficult. In a macro-reentrant circuit, the narrowest region of conduction supporting activation around the cardiac chamber was ablated. In a focal tachycardia, the site of origin according to the map was ablated. In a localised reentrant circuit, a long duration fractionated EGM within the circuit was ablated. Power controlled (25–35W) RF energy was delivered (Stockert 70 RF generator, Biosense Webster) through an irrigated ablation catheter (17mL/min) with a target temperature of 40 °C

4.1.2.5 Statistics

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median (interquartile range) for non-parametric data.

4.1.3 Results

A total of 23 left ATs were fully mapped in 15 patients (age 64 ± 11 yrs) using ultra-high density ($16,253 \pm 9,192$ points displayed per map). Each patient had undergone previous atrial fibrillation (AF) ablation (pulmonary venous isolation (100%), roof line 8/15 (53%) mitral isthmus line 5/15 (33%), EGM defragmentation 5/15 (33%)), and 11/15 (73%) patients had undergone 2 or more ablation procedures including 5/15 (33%) for a previous AT. The mean AT cycle length mapped was 279 ± 76 ms, 8 of which were induced (either initially or post termination of a different AT). The mean LA volume was 133 ± 37 cc, collected from 2197 ± 1649 beats over an average mapping time of 26 ± 14 mins.

Activation maps were studied to determine the AT mechanism and a putative strategy for ablation. Remarkably, upon first review, we were struck by the number of small rotational activations seen on the map suggestive to us as representing localised reentry. We labelled this rotational activation appearance as a “carousel”. These rotations contained the full rainbow colour spectrum, with an early (red) meets late (purple) site. An example is illustrated in figure 4-1 and video 4-1.

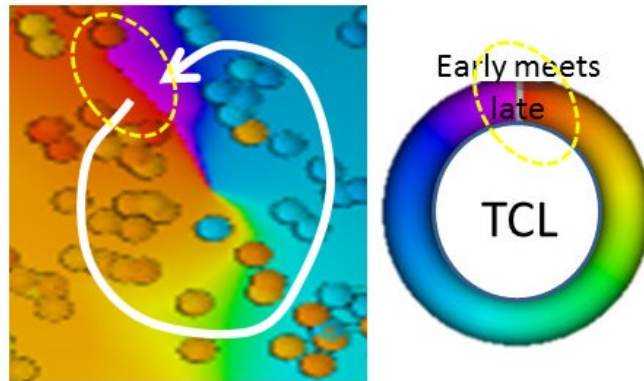


Figure 4-1 (see also video 4-1): Carousel activation

Putative sites of LR were identified as continuous rotational activations where each rotation encompassed one full TCL. This pattern of activation was labelled a “carousel”. On the static LAT map, carousels were identified as sites that spanned the full rainbow spectrum (per the colours of the rainbow), running from red to purple, where the site of earliest activation (red) met the site of latest activation (purple).

Unexpectedly, we observed carousels in most maps collected (20/23 maps, implying a LR mechanism in the majority of these cases. Furthermore, we observed >1 carousel in 9/23 maps collected, suggesting that many of these carousels denoted something other than LR. We eventually identified n=50 carousels

(median 2, range 0-13 per map) in these 23 maps. Table 4-1 summarizes the clinical details, the patient procedural history and the number of carousels per patient.

Pt no	Age	Sex	Prior ablations	Previous Ablation Hx	Volume/ cc ³	AT maps	Carousels
1	72	M	1	PVI + Roof + MI	111	1	0
2	77	F	3	PVI + CFAE + Roof	124	1	3
3	55	F	2	PVI + CFAE + MI	132	1	1
4	70	M	2	PVI	128	2	13
5	77	F	3	PVI + Roof + Anterior MI + anterior isthmus	120	1	2
6	43	M	4	PVI + CFAE + Floor + Septum + GPs	69	1	2
7	71	M	3	Surgical AF (Epicor) + LAA + RPV	156	1	0
8	76	F	2	PVI + CFAE	99	2	4
9	65	M	2	PVI + Anterior isthmus + Roof	162	1	2
10	71	M	1	PVI + MI	134	3	6
11	47	M	1	Roof line	178	3	6
12	52	M	1	Roof line + LLPV isolation	203	1	1
13	57	M	2	PVI + Roof + CFAE	148	1	0
14	68	M	1	PVI	117	3	9
15	53	M	2	PVI + MI + Roof	228	1	1

Table 4-1: clinical details, past procedure history and the number of carousels per patient.

Ablation was delivered to several of these carousels, assuming they represented LR driving the AT. In only n=7/50 (14%) carousels did ablation terminate the AT - we labelled these as type I carousels and true localised reentry. EGMs tracked around these circuits encompassed the full TCL, and activation in the wider area around the carousel moved away in all directions. Ablation had been delivered at most fractionated EGM along the carousel (117±18ms; 44±13% of TCL). Rotation appeared to occur around probable scar, coloured grey in the map, defined by a peak amplitude <0.03mV or inconsistent activation timing between neighbouring points, of a size smaller than previous studies have suggested (max. diameter 12±6mm; median surface area 44mm² (IQR=31-55)). Examples are presented in figures 4-2 & 4-3 and videos 4-2 & 4-3. The EGMs sampled around the circuit were clear and sharp with low background noise, a function of smaller recording electrodes with narrow spacing.

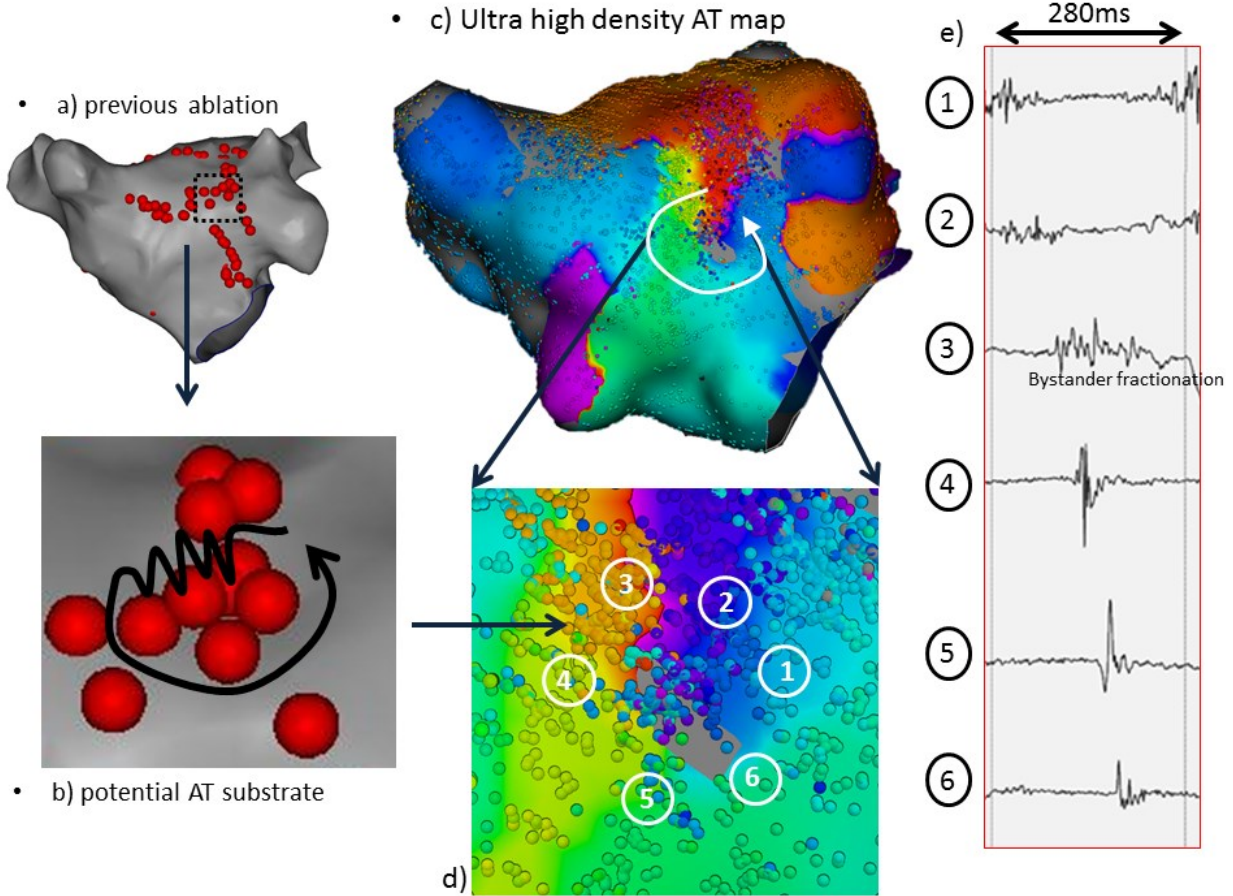


Figure 4-2 (see also video 4-2): Type I Carousel - localised reentry directly attributable to gaps in a previous ablation line

A patient with previous pulmonary venous isolation and EGM defragmentation for PsAF, as well as linear lesions for both peri-mitral and roof dependent ATs underwent redo atrial tachycardia (CL 280ms) ablation. The previous peri-mitral AT was treated with 2 lines (LLPV - posterior mitral annulus, RSPV - anterior mitral annulus), and the roof dependent AT with an anterior roof line. (a) The original roof line appeared incomplete as suggested by the ablation tags, (b) with the potential to set up LR. (c) 28,365 electro-anatomical points were collected in 41mins. (d) The activation map showed the full colour spectrum rotating counter-clockwise around a small island of scar (12mm, 55mm²) on the anterior wall, akin to a carousel. (e) EGMs sampled around this small circuit (1-6) contained very low voltage (0.05mV-0.15mV) and fractionated signals, and EGMs could be tracked around the circuit covering the full cycle length. Ablation delivered within the circuit terminated AT. Notably, some of the fractionation in EGM 3 is likely bystander, as it extends beyond local signal at EGM 4 and 5.

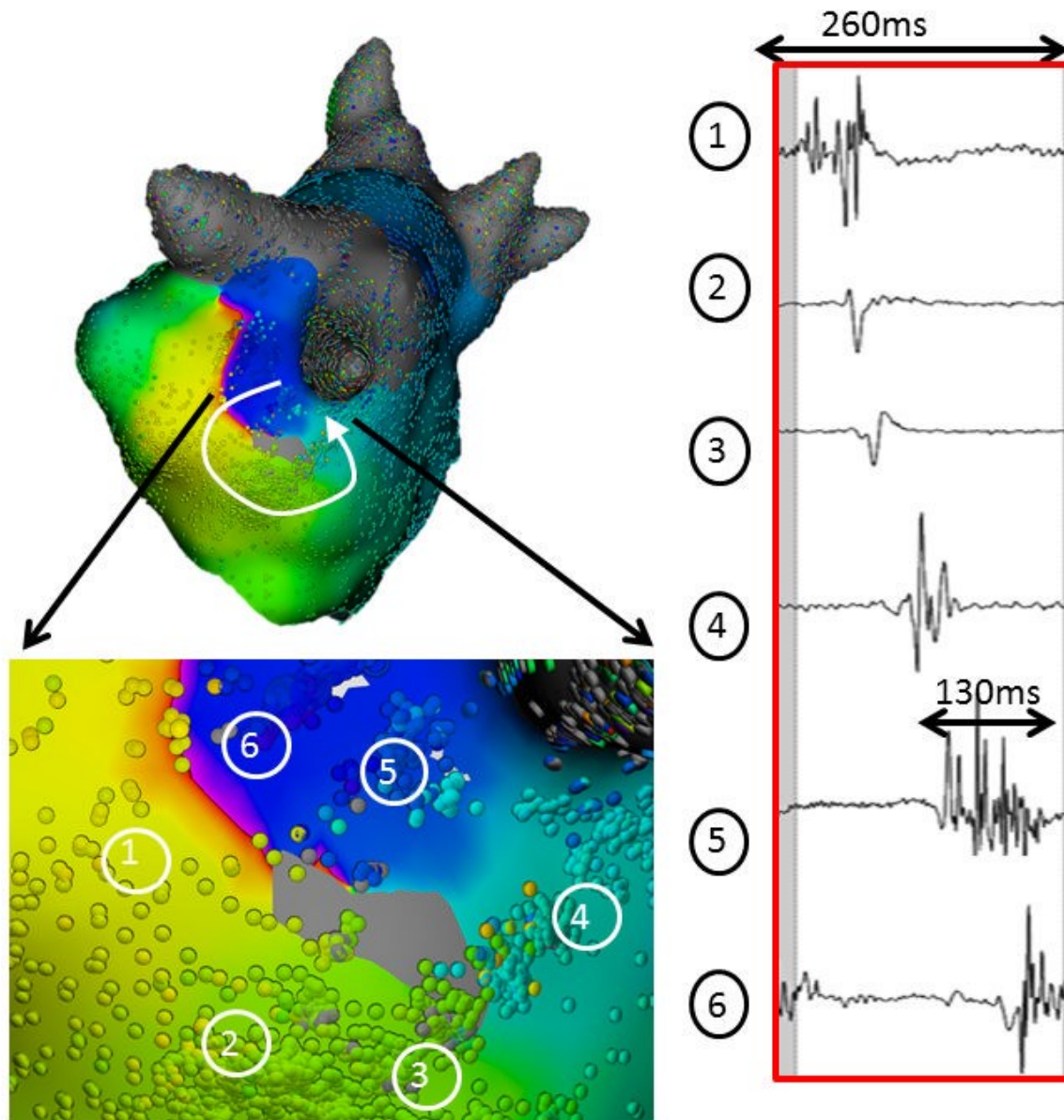


Figure 4-3 (see also video 4-3): Type I carousel - localised reentry inferior to the left PVs

A further example of type I localised reentrant AT (263ms) from a patient with previous pulmonary venous isolation, roof line and anterior mitral isthmus line. 26,978 electro-anatomical points were collected in 51mins. The activation map showed the full colour spectrum rotating counter-clockwise around an island of scar (9mm, 29mm²) beneath the left sided veins. EGMs sampled around this small circuit (1-6) covered the full cycle length. Fractionation within the circuit spanned 50% of the TCL. Ablation delivered within the circuit terminated AT.

The remaining n=43 carousels represented something other than LR. Upon careful analysis of EGMs and activation patterns with these cases, we discovered that these carousel patterns were pseudo-reentrant, and occurred for two reasons, which we described as either a type II or type III carousel. In a type II carousel, as the head of an activation wavefront entered a region of low voltage, it slowed and curved around this site. A secondary wavefront was seen to enter this region from elsewhere, colliding with the head of the primary wavefront and advancing activation around it. This complex wavefront interaction created a false visual impression of rotation. This carousel was characterized by overlapping regions of split or fractionated potentials coinciding with wavefront collision, highlighted by the colour heterogeneity of the points annotated within this region (indicative of adjacent EGMs with different activation timings). EGMs could not be tracked around the full TCL, owing to the unaccounted for isoelectric period between the split potentials. These type II pseudo-reentrant carousels were observed in n=21/50 (42%) carousels (median 0.5, range 0-8 per map, identified in 8/23 AT maps. Examples are presented in figures 4-4 & 4-5 and videos 4-4 & 4-5. Ablation was inappropriately delivered within n=5 of these type II carousels, where we had been fooled into thinking they represented LR.

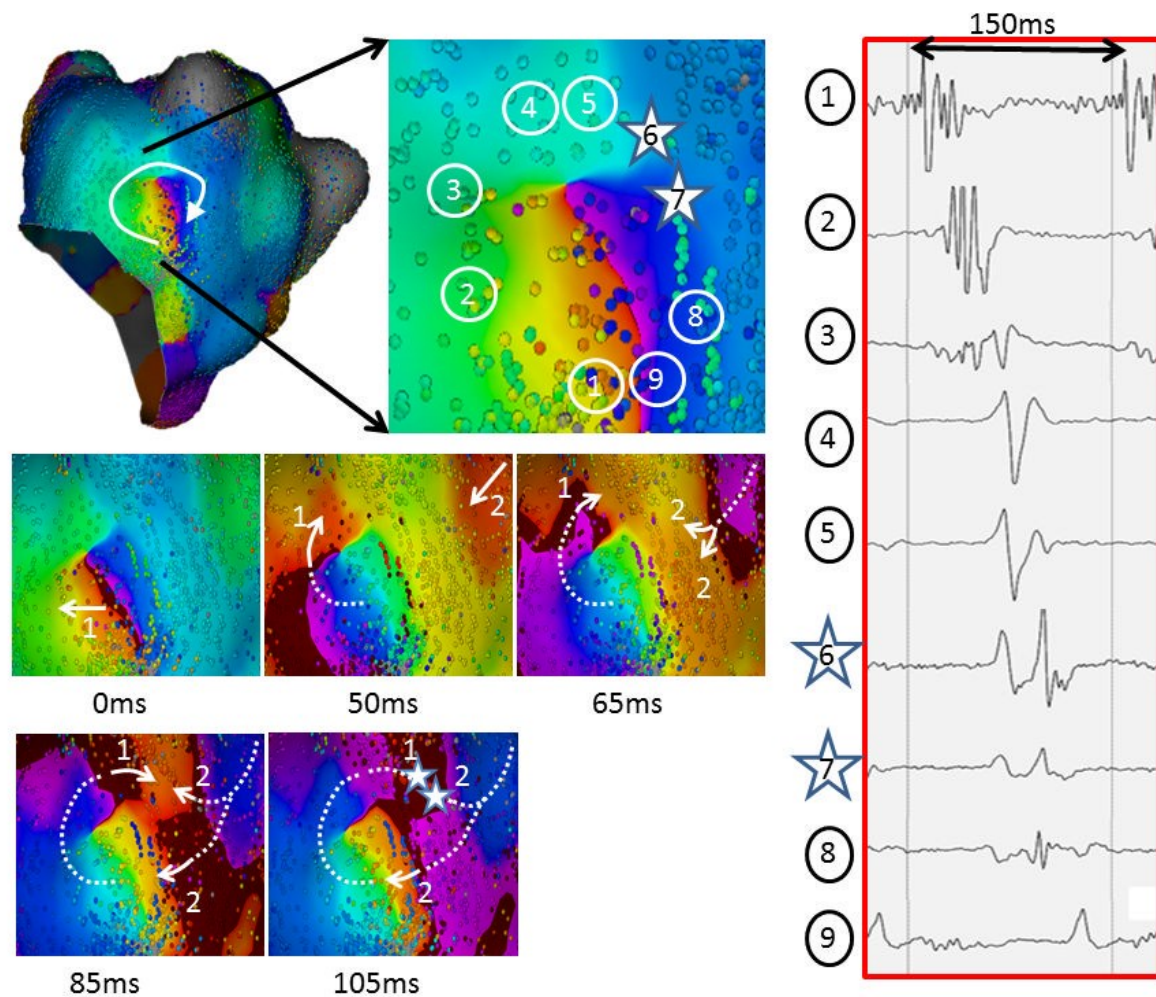


Figure 4-4 (see also video 4-4): Type II Carousel – pseudo reentry on the posterior mitral isthmus

A patient with previous pulmonary venous isolation underwent mapping for a rapid AT (CL 150ms). 34,524 electro-anatomical points were collected in 56mins. A carousel was evident on the posterior mitral annulus with a pinwheel present at the centre of rotation. This is captured in the static LAT map (top left) and magnified (top centre). Upon closer inspection, the true nature of the carousel became apparent. This has been illustrated in the timing panels of propagation, which preserves the colour coded display and demonstrates the leading edge of the activation wavefront in maroon. The dotted arrow represents where activation has been in the preceding timing panels. At time 0ms-65ms, a primary activation wavefront (labelled 1) travelling leftwards towards the mitral annulus turned clockwise through an area of slow conduction (sites 1-3) characterized by EGM fractionation (right panel). A secondary wavefront (labelled 2) travelled in from the roof and collided with the head of the primary wavefront (starred, characterized by a region of split potentials on one end - sites 6-7), and advanced activation around (site 9) creating the impression of complete rotation. EGMs could not be tracked around the full TCL, owing to the unaccounted for isoelectric period between the split potentials. The presence of this incoming wavefront allows the operator to immediately discount this carousel as an active circuit.

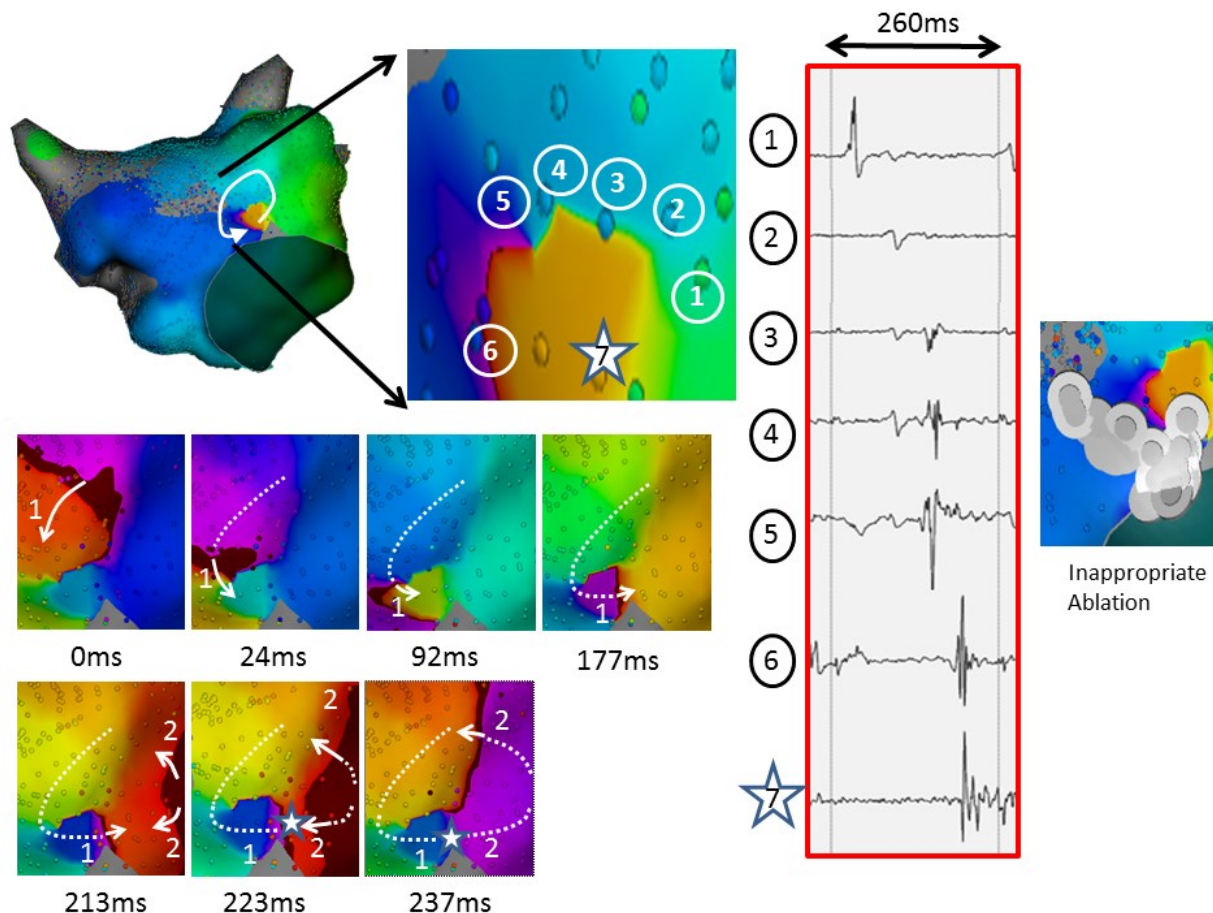


Figure 4-5 (see also video 4-5): Type II Carousel – pseudo reentry on the posterior mitral isthmus

A further example of pseudo-reentry from a patient with multiple previous ablations and stable AT (CL 260ms). Carousel activation was seen on the anterior wall near an area of low voltage tissue, rotating around a pinwheel. This is captured in the static LAT map (top left) and magnified (top centre). This was misdiagnosed as LR and extensively ablated without change in tachycardia activation (far right). An explanation for pseudo-reentry has been illustrated in the timing panels of propagation, which preserves the colour coded display and demonstrates the leading edge of the activation wavefront in maroon. The dotted arrow represent where activation has been in the preceding timing panels. Between time 0ms-92ms, a primary wavefront of activation (labelled 1) travelling towards the mitral annulus encountered a line of block (sites 3-5), characterized by a regions of split potentials (EGM panel). The wavefront turned counter-clockwise around this line into a cul-de-sac (site 6). A secondary wavefront (labelled 2) travelling towards this area of low voltage collided with the head of the primary wavefront (starred – site 7), and advanced activation around (site 1-2) creating the impression of reentry.

The remaining n=22/50 (44%) carousels were considered type III, as they occurred secondary to mis-annotation of artefact signal and interpolation in areas of lower sampling density from incomplete mapping (often adjacent to the mitral annulus and PVs). This was observed in (median 1, range 0-5 per map, identified in 10/23 AT maps). As illustrated in figure 4-6 and video 4-6, just 3 points with different local activation times across the WOI can create the appearance of continuous rotation owing to interpolation of activation between these sites.

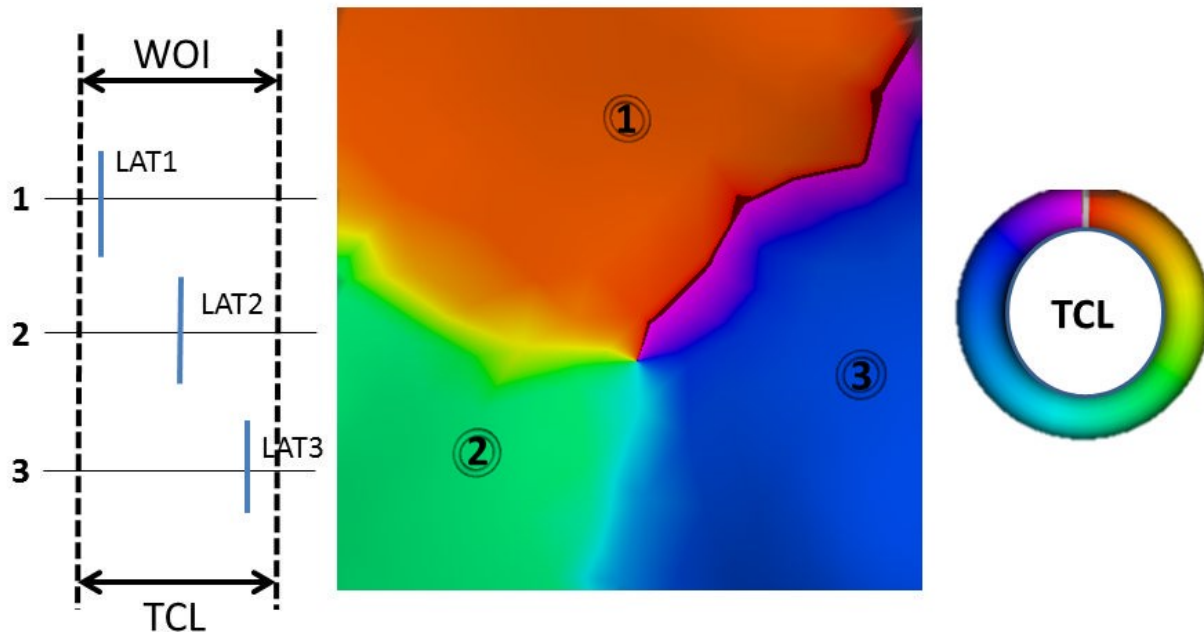


Figure 4-6 (see also video 4-6): Type III Carousel – a function of interpolation

Carousel activation can be seen from just 3 closely spaced points with different annotation of activation timing across the WOI owing to interpolation between these three timings.

Figure 4-7 and video 4-7 illustrates how annotation of noise was able to create carousel activation near the mitral annulus. Real EGMs could not be tracked around the full TCL. Carousel activation was inconsistent between unipolar and bipolar activation maps. Another example is presented in figure 4-8 and video 4.8. These carousels were easily recognizable as an interpolation error, given the presence of a pinwheel at the centre of rotation and colour heterogeneity between the dots and background colour.

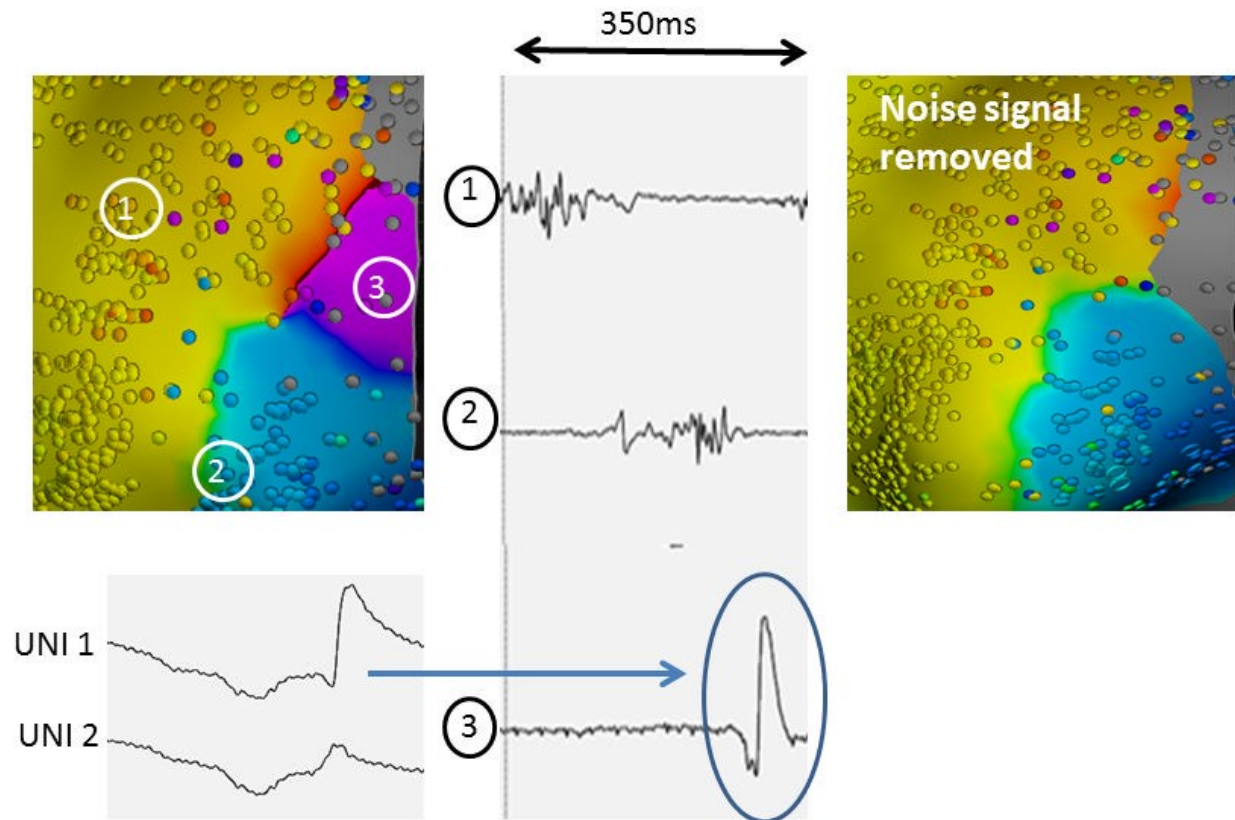


Figure 4-7 (see also video 4-7): Type III Carousel - Artefact

(a) A carousel was seen within an area of low voltage signal rotating around a pinwheel. (b) Bipolar EGMs 1-3 cover the tachycardia cycle length. However, site 3 signal was erroneous, as evident by the broad and blunt appearance in comparison to the other fractionated signals, and this was confirmed upon analysis of the unipolar signals from which it was derived. It was incorporated into the activation map owing to interpolation in an area of incomplete mapping near the mitral annulus. (c) By removing the noise signal, carousel activation was no longer evident.

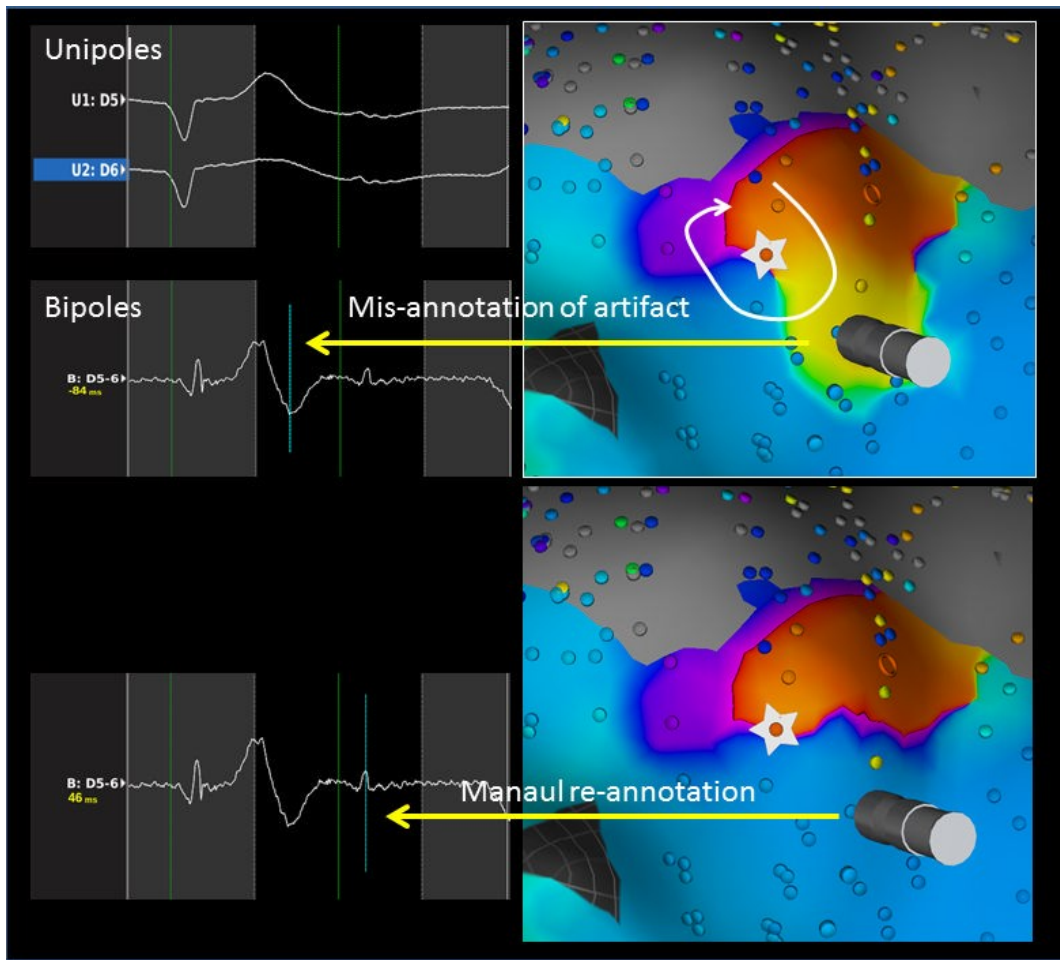


Figure 4-8 (see also video 4-8): A further example of type III carousel.

Annotation of artefact on the bipolar EGM and interpolation in areas of low sampling density create a carousel. Re-annotation to the smaller local signal eliminates the carousel.

A summary of the distinguishable features of each carousel is presented in table 4-2, categorized into three distinct types.

Category	<u>Type I – Localised reentry</u>	<u>Type II – pseudo-reentry</u>	<u>Type III – artefact</u>
Macroscopic activation	Moves away in all directions	Incoming wavefront from elsewhere observed to head into the carousel, and advance activation around it	Interpolation in areas of low density.
Core (Scar threshold <0.03mV)	Area of grey ~1cm.	Pinwheel, or area of grey	Pinwheel
CL mapped	EGMs around carousel encompass full TCL	EGMs can not be tracked around TCL owing to unaccounted isoelectric period between split potentials	Annotation encompasses TCL by chance
EGMs	Fractionation within carousel usually critical site for ablation	Overlapping regions of split or fractionated potentials coinciding with wavefront collision.	Unipolar/bipolar EGMs suggestive of poor catheter contact, noise or movement artefact.
Map annotation display	Consistent pattern on bipolar and unipolar display	Consistent pattern on bipolar and unipolar display.	Inconsistent pattern on bipolar and unipolar annotation display.
Trouble-shooting		Careful interpretation of collision point and appreciation of split potentials	Can be removed by adjusting the confidence mask.

Table 4-2: A summary of the different carousel types and their distinguishing features

Using the Rhythmia system, macro-reentrant tachycardia was eventually diagnosed in n=10/23 AT maps (43%), localised reentry in n=7/23 (30%), and focal tachycardia with centrifugal activation in n=3/23 (13%). Ablation delivered in each of these ATs eventually resulted in a change in tachycardia activation or termination to sinus rhythm. The tachycardia mechanism from the remaining n=3/23 (13%) activation maps was unclear, owing to alternating tachycardia cycle lengths and widespread very low voltage, requiring remapping and multiple attempts at entrainment.

4.1.4 Discussion

In chapter 3, ablation delivery within ventricular scar was guided by 3D maps with very low point density and widely spaced catheters, which was insufficient to accurately identify the arrhythmic substrate. In this study, we used ultra-high density mapping in combination with catheters with small tip and narrowly spaced catheters to improve mapping resolution. As post-infarct VTs are often poorly tolerated for mapping, post ablation ATs were used as a surrogate for studying activation within scar as they are also based on reentrant mechanisms between scar and healthy tissue..^{61, 63, 191} As within ventricular scar, mapping local activation within regions of slow conduction has been limited by the resolution of EGM signals recorded by conventional mapping catheters. Furthermore, limited point density on prior mapping systems resulted in large areas of activation interpolation..^{85-87, 192}

The Rhythmia mapping system offers ultra-high density mapping with increased EGM resolution..¹⁰⁴ Combining 64 very small electrodes with narrow inter-electrode spacing (0.4 mm²; 2.5 mm centre-to-centre spacing), as well as a point density >10 fold that of conventional maps, allowed us to identify regions of conductive tissue with voltage 5-10 times lower than previous studies had defined as non-conductive..^{121, 189, 193}

This study is the first to fully delineate the activation of localised reentry within scar. These circuits appeared as small rotatory activations around scars approximately 1cm in diameter. We termed this type of activation a “carousel.” LR is known to involve slow conduction and reentry around a small area of scar characterized by long duration and fractionated EGMs within the circuit spanning approximately 50% of the TCL..^{78, 79} Prior studies with multi-spline catheters suggested that LR involves reentry around an area of scar around 2cm in diameter, corresponding to the mapping field of the specific catheters used at the time. The EGMs sampled around the carousels with the small electrodes in this study were clear and sharp with low background noise. The very high sampling density collected around the circuit, facilitated the automated decision making of timing annotation of each multicomponent EGM. EGMs could be followed around the circuit and encompassed the full TCL, and ablation at sites of EGM fractionation within these carousels interrupted the tachycardia in each case.

Unexpectedly, we observed carousels in most maps, implying a localised reentrant mechanism in the majority of cases in this study. However, ablation of some of these other carousels did not change the

AT, suggesting an incorrect AT diagnosis. Furthermore, we observed >1 carousel in several maps collected, suggesting that many of these carousels denoted something other than LR. The majority of carousels were in-fact pseudo-reentrant. In what was eventually labelled as a type II carousel, where an activation wavefront curved around an area of non-uniform anisotropy, a critically timed secondary wavefront entering from the opposite direction collided and extinguished the primary wavefront, and advanced activation around it, creating the visual impression of rotational activation. Upon closer inspection, the exact nature of these wavefront interactions was understood, akin to recurrent reset seen during entrainment, an observation facilitated by ultra-high density.^{194, 195} These areas of collision contained overlapping regions of split or fractionated potentials. This appearance was distinct from LR where activation moved away in all directions. Without careful recognition of this phenomenon, operators may be misled to deliver ablation at these pseudo-reentrant sites irrelevant to the clinical tachycardia.

Despite the multiple advances in activation mapping associated with the Rhythmia system, it is still restricted by some of the fundamental limitations inherent with mapping activation using local activation time, particularly within regions of low voltage. This was evident by the frequent occurrence of false (type III) carousels, which we observed from mis-annotation of artefact signal and interpolation in areas of incomplete mapping. All LAT maps employ an interpolation algorithm that assigns the average activation time between mapped points in order to display an interpretable propagation pattern on the assumption that activation is uniform. A minimum of three closely spaced points is sufficient for the system to interpolate rotational activation, where annotation happens to span the majority of the WOI. Such an occurrence might be seen in areas of inconsistent timing, secondary to EGM fractionation (where the system must assign a single activation time to a multi-component signal), in areas with poor catheter contact or motion artefact, and in areas with a low signal to noise ratio. To highlight the operator to regions of incorrect interpolation, Rhythmia displays the LAT of each collected electro-anatomical point as a coloured “dot” on the map, and regions of colour heterogeneity between these dots and the background activation map is indicative of areas with inconsistent LAT. We observed large regions of colour heterogeneity on all the collected maps within the ablated atria, as evident in most of the figures presented. Ideally, the assignment of LAT of each highlighted inconsistent point should be evaluated, and manually readjusted as needed. However, this is both time consuming and subjective, and completely impractical when many thousands of points have been collected. Figure 4.9

illustrates an example where, even with high density, the annotation of artefact on the map was incorporated into the LAT display causing a chaotic activation pattern.

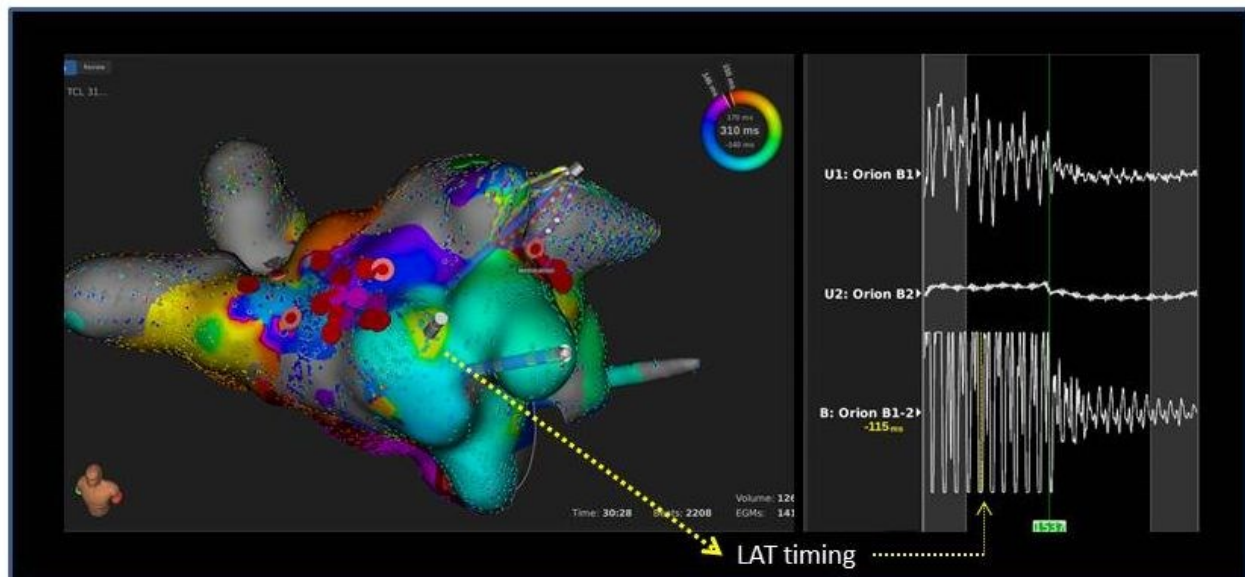


Figure 4-9: Noise artefact

In order to increase mapping time, the catheter stability beat acceptance criteria was intermittently withheld. In doing so, a clear noise artefact was incorporated and annotated within the map (which happened to be towards the onset of the WOI), creating a chaotic activation pattern.

To help overcome this issue, the degree of interpolation can be adjusted using a “confidence mask” which “greys out” areas of the map with significant timing inconsistency. This is often seen in areas of extremely low voltage. In this study, we applied the default confidence mask setting of 0.03mV, and labelled this as scar. However, this confidence mask threshold, or as some studies have labelled a “scar threshold”, is completely arbitrary, as there exists no current voltage value that differentiates scar from conducting tissue within the atrium. Importantly, recent studies have shown that the appearance of propagation changes considerably with adjustment of this setting.¹⁹⁶ By reducing the threshold, we saw that the grey core at the centre of LR carousels became filled with interpolated colour, giving the false appearance of rotation anchored around an artificial “pinwheel”, which operators might erroneously target.

Recent other studies using the Rhythmia mapping system within the atrium have also reported on the presence of “visual reentry” where two opposing wavefronts cross near a line of block, akin to our carousels.¹⁹⁷ Studies within ventricular scar have not reported on the presence of carousel type

activation, but it seems likely to be prevalent owing to the widespread areas of slow conduction and non-uniform anisotropy within ventricular scar.¹⁸⁹ One might even postulate that figure of 8 reentry, commonly described with 3D activation mapping in VT is in fact one limb of true localised reentry, and one limb of pseudo-reentry. Close inspection of published figures using the Rhythmia system in VT also demonstrate areas of colour inconsistency between the collected dots and background activation map, just as we observed in this study in atrial scar, and indicative of areas with inconsistent LAT (figure 4-10). Furthermore, close inspection of these published figures demonstrates significantly manual re-annotation, as evident by the rings replacing the dots on the map. Thus the interpretation of these activation patterns should be interpreted with caution.

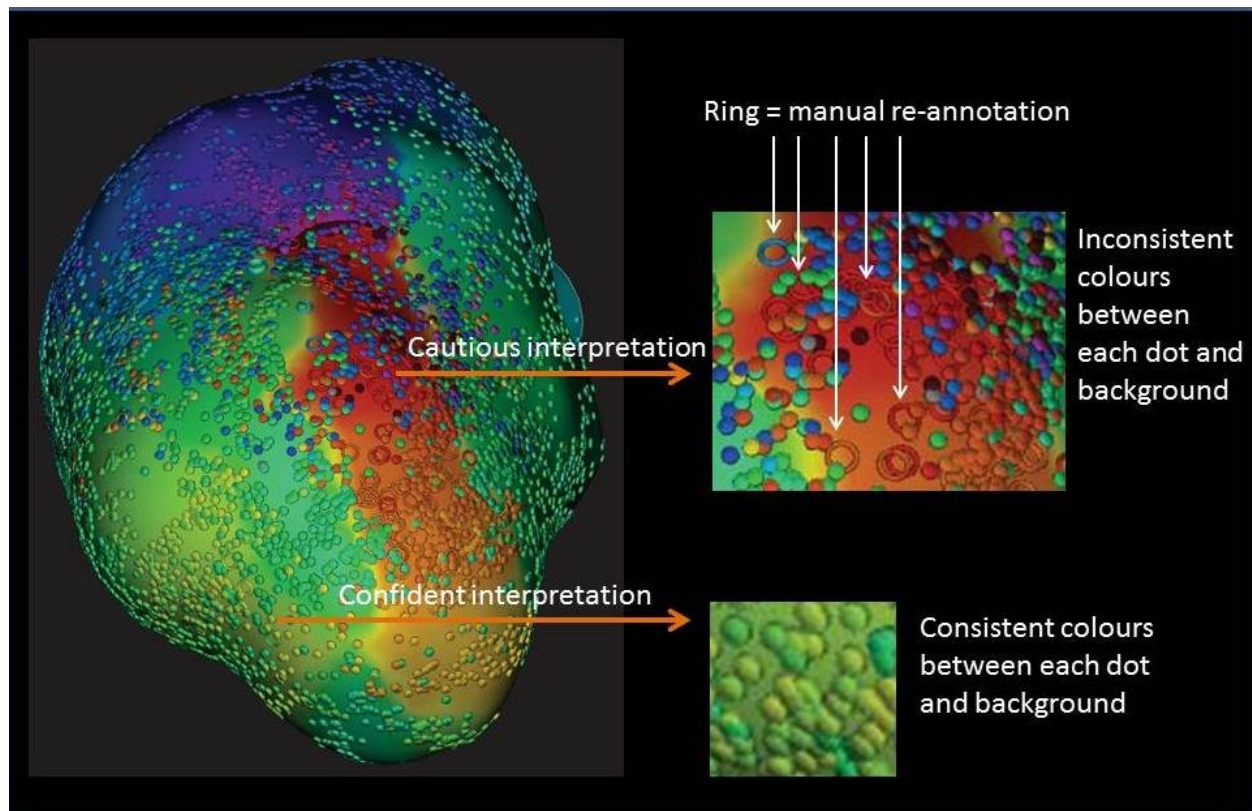


Figure 4-10 VT activation map

The activation map of reentrant VT in the anterior-septum of the left ventricle. The static LAT map suggests a common channel of activation bounded by two lateral lines of block. Upon closer inspection, we note ample heterogeneity between the colouring of the dots within the channel, and the background colour. We also note evidence of manual re-annotation, evident by the replacement of the dots with rings. Adapted from Anter et al, Circulation 2016.¹⁸⁹

4.1.5 Limitations

We did not perform entrainment manoeuvres within the carousels owing to this risk of transforming or terminating the clinical tachycardia and because local capture within these low voltage areas may have proved difficult. A comparison of the response to entrainment within the carousel types would have offered greater understanding of their electrophysiological characteristics.

We used the conventional bipolar voltage metric to define scar, though changes in amplitude of a bipolar signal can occur according to the electrode orientation, wavefront direction, wavefront collision and atrial rate. Furthermore, there is no practical lower bound on voltage that defines a lack of conduction.

4.1.6 Conclusions

The use of ultra-high density mapping in combination with increased EGM resolution within atrial scar is effective in delineating the arrhythmogenic substrate, specifically in this study in localised reentrant circuits involving slow conduction around small scars. Here, activation appeared as a stable and continuous rotation around a small island of scar (approximately 1cm in diameter) that encompassed the full TCL. However, this pattern of activation had poor specificity, and more commonly occurred in areas of wavefront turning and collision or due to annotation of artefact or interpolation in areas of incomplete mapping, a result of mapping activation within regions of low voltage using local activation time and presenting this information using a colour coded scheme. We believe a mapping system which avoids the need for annotation of LAT and the setting of WOI is imperative to more accurately understand the activation pattern within scar.

Chapter 5

5 Ripple Mapping: an alternative method of activation visualisation

Whilst the Rhythmia system offered ultra-high density and improved EGM resolution for mapping, we found that it was still restricted by some of the fundamental limitations inherent with mapping activation using local activation time – mis-annotation and interpolation. Furthermore, whilst it effectively demonstrated activation within regions of extremely low voltage, the assignment of a voltage threshold that defined scar was completely arbitrary. Ripple Mapping was developed specifically to overcome the difficulties of mapping low amplitude and fractionated EGMs found in scar. In this chapter, we describe the prospective application of RM in our institution and across other centres, mapping tachycardia within atrial scar (where the circuits are more stable than within ventricular scar), as a novel approach to defining scar and overcoming the limitations of LAT mapping. This was the first time RM was used clinically during ablation procedures.

5.1 An algorithm to optimize data collection and interpretation of Ripple Maps

RM is a novel and unique method of activation visualisation that is not reliant upon annotation of activation time or setting a WOI, and avoids interpolation within unmapped sites. It has been described in detail in section 2.5. Offline retrospective studies in our institute demonstrated the feasibility of mapping both AT and VT substrates using RM.^{124, 125, 128} At the start of this thesis, RM was integrated into a research module in CARTO3v4 for prospective testing. As this was the first time the clinical system was being used in patients, a mapping algorithm that considered how to optimize the use of RM within CARTO3v4 was developed and is summarised below.

CARTO offer two types of geometric displays – “Fast Anatomical Maps” (FAM) or “point by point” displays. Figure 5-1 illustrates a “point by point” geometric display of precisely where the mapping catheter has acquired a data point. FAM smoothens out the geometric shell making it easier on the eye when studying RM. The degree of smoothing is adjustable, defined by the system using an arbitrary range from 0-20. The lower this value, the greater the degree of smoothing. We adopted a standard value of 10 as this supported clear visualisation of the ripple activation wavefront on the endocardial surface without falsely distorting the anatomy.

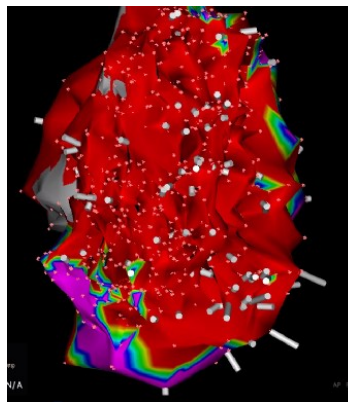


Figure 5-1: Point by Point map projection

The endocardial surface of the LV has been mapped. Ripple bars are played over a bipolar voltage map. With point by point projection, the geometry is interconnected precisely between the exact anatomical location that the EGM signal was acquired. In doing so, the display has a rough contour with multiple sharp ends. This makes the visual interpretation of Ripple bars very difficult to interpret, and was avoided.

A “colour threshold” function limits the degree of background colour interpolation on the acquired geometry, defined by the system again using an arbitrary range from 0-20. The lower this value, the less interpolation of colour is evident between data points. Figure 5-2 illustrates the appearance of identical maps displayed with different colour thresholds. RM is most effective with raw data collected evenly throughout the whole chamber-of-interest so that activation can be visualised globally during the whole cycle length. We found that applying a high background colour threshold, operators were mis-lead in assuming all regions within the map contained data points. We subsequently collected maps with a colour threshold of 5, highlighting areas on the map without point acquisition in a grey background to help the operator fill in all the areas.

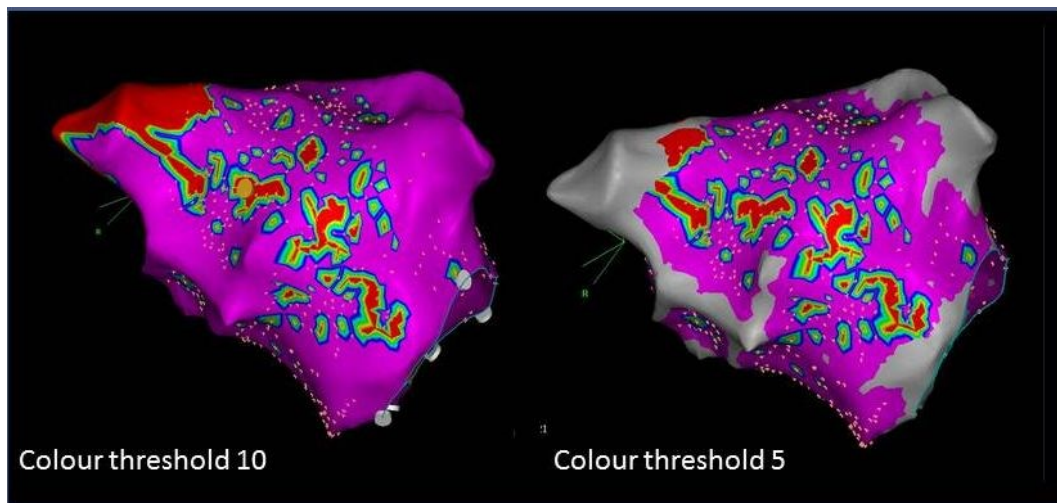


Figure 5-2: Colour threshold.

The lower the colour threshold, the less colour interpolation between data points occurs. At high colour threshold operators may miss collection of data points.

During LAT and voltage mapping, the CARTO system automatically hides the display of EGM signals below an arbitrary voltage value, typically 0.05mV, tagging the point in grey, assuming that it is scar and therefore not involved in the activation sequence. This function, known as “scar auto tagging” was turned off, as we aimed to map the EGMs throughout the entire chamber evenly throughout, especially within low voltage areas.

Rapid catheter movement led to noise artefact on the intra-cardiac EGM that would appear on the Ripple map as a rogue signal independent of the activation wave. The ‘show bars above’ dialog box within the map preference tool was used to enter the minimum voltage at which the Ripple bars

became visible, and we found in our Lab that '0.03mV' was effective in hiding noise signal. The "Clip bars above" feature was used to control the height of the bars. We found that if the bars were too small, it limited visualisation of the Ripple wavefront. However, if the bars were too tall, they overcrowded the geometry and overlapped each other, hiding activation within regions of low voltage. The 'Clip bars above' option was assigned at 0.25mV to limit the height of the bars at this assigned voltage.

For each point collected, 2.5seconds of intra-cardiac data was stored. The duration of intracardiac signal that was played as a Ripple Map could be adjusted using the "Ripple Viewer function" on the workstation. We set the viewer to display two complete cycle lengths of the tachycardia, ensuring an entire cycle is displayed smoothly without interruption or jump.

CARTO3v4 also incorporates the ConfiDENSE module, a feature designed to improve EGM signal quality. This has been described in detail in section 2.3.1. Our institute was invited to test the ConfiDENSE module as part of Biosense Webster's early evaluation phase with this system. Given that there were no specific recommended values for these filters offered by Biosense, we aimed to determine the most effective filter settings to reduce noise acquisition on a Ripple map without significant compromise to mapping speed. The LASSO Nav catheter was used in a series of simple experiments to this cause: several maps of the posterior wall of the left atrium were repeatedly collected, targeting 200 data points, to determine the individual influence of each filter on noise level and mapping time, whilst controlling all others. Noise was graded between 1-4 (1 – no noise, 4 – max noise).

We started with "high stringency", including TPI as "on," Position Stability of 2mm, and LAT Stability of 3ms. Mapping time was slowed by temporary system stalls as TPI was calculated (mapping time of 216ms), but when studying the Ripple Map within this localised region, there was grade 1 noise (negligible) detected. Switching off TPI accelerated mapping time (58ms) though with grade 4 noise, which was deemed an unacceptable level. Keeping TPI on and relaxing the position stability to 6mm resulted in grade 2 noise with only marginal reduction in mapping times (153ms) as compared to "high stringency", and at 12mm resulted in grade 3 noise. Extending the LAT stability to 10ms had no influence on mapping time or noise signal, likely as the posterior wall mapped in this study consisted of normal healthy tissue where local LAT inconsistencies were infrequent. This is summarized below.

Setting	Time to 200 points	Noise
High stringency	216	1
TPI off	58	4
Pos. stab. 6mm	153	2
Pos. stab. 12mm	128	3
LAT stab. 10ms	208	1

On the basis of these findings, we proposed that TPI is always applied when using multi-polar catheters, with “Position Stability” set at 2mm, and LAT stability set at 3ms. We defined “density” as at least 1mm, as this value seemed the ideal balance between a dense map and one that avoided an uneven point distribution and overcrowding of Ripple bars in a given area.

During the ConfiDENSE early evaluation phase, we tested some of these CARTO ConfiDENSE EGM filters settings in a case of outflow tract VT using conventional LAT mapping (figure 5-3), and found it effective in limiting erroneous and poor contact point acquisition.¹⁹⁸

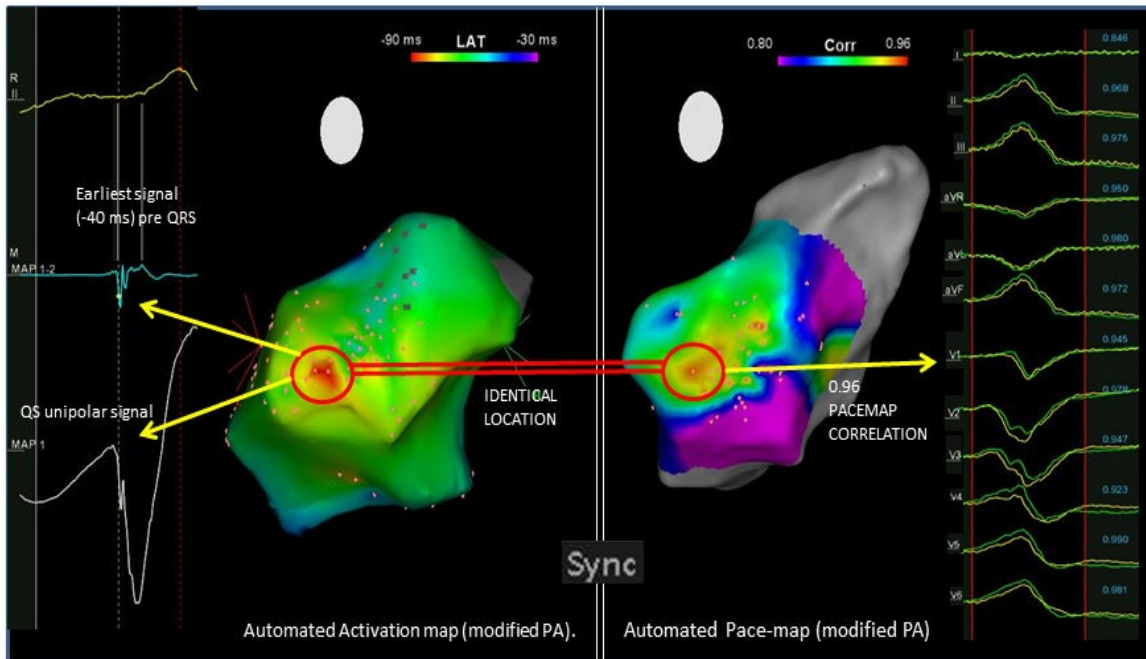


Figure 5-3: ConfIDENSE EGM filters

A 78 year old male underwent radiofrequency ablation for symptomatic Outflow Tract Ventricular Tachycardia (CL 440ms, LBBB morphology, inferior axis, precordial transition between V3-V4). Endocardial mapping was performed using a Smart Touch ablation catheter (Biosense Webster). An automated CARTO LAT map was collected (187points) within the RVOT. Each electro-anatomical point passed through our pre-assigned filter settings (CL within 5% of the TCL; catheter position stable within 2mm; assigned LAT stable within 3ms). Without operator adjustment, the activation map (left hand panel) revealed centrifugal activation away from the septum (-40ms pre-QRS, QS unipolar signal). The VT terminated at this site with mechanical pressure prior to ablation delivery.

Re-induction resulted in an unstable, non-clinical rhythm requiring immediate electrical cardioversion and a map shift due to patient movement. An automated isochronal pace-map was subsequently collected (PaSo). 20 bipolar pace-maps (10mA, pacing drive=600ms) were analysed. The ECG waveform of each paced signal was compared to the VT waveform, and correlation was scored between 0-1 (right panel). The site with the best pace-map (0.96) overlapped the site of earliest activation. 10mins of RF were clustered around this area (25-30W, 37°C, 20-30ml flow) until non-capture. Post ablation, the VT was non inducible with aggressive programmed stimulation down to 3 extra-stimuli.

Table 5-1 summarizes our approach towards the integration of RM with CARTO, and was used in all future prospective testing within AT procedures.¹²⁵

CARTO3 MAPPING SETTINGS • Scar auto-tagging: OFF. Map acquired in Fast Anatomic Mapping mode with resolution of 10 • Colour threshold set at 5 – aim to fully cover the chamber such that no part of the geometry is left unmapped (gray) • ConfiDense Continuous Mapping point collection: - o Cycle Length range/stability: Select a CL range (+/-5% of TCL). - o Position Stability: 2mm - o LAT Stability: 3ms - o Density (1-4mm): 1mm. • MEM: Tissue Proximity Indicator applied Respiratory gating applied Internal points filter set at 6mm. RIPPLE MAP VIEWING PREFERENCES • Adjust the Ripple viewer to display 2CL of the tachycardia - 1 TCL before the reference to 1 TCL after the reference. • ‘Show bars above’ to 0.03mV. • ‘Clip bars above’ to 0.25mV.
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Table 5-1: CARTO Ripple Map algorithm.

5.2 A Prospective Study of Ripple Mapping in scar related Atrial Tachycardia

5.2.1 Introduction

RM is the only mapping system that can present activation without assignment of LAT, interpolation, or setting a WOI. Furthermore, it is unique in presenting both activation and voltage information on the same display. Displaying activation wavefronts on a voltage map enables a novel approach to differentiating electrically active myocardium from scar. In this study we applied the RM algorithm developed in section 5.1 to determine the path of AT wavefronts through scar, as an approach to AT diagnosis and a guide to ablation.

In chapter 4, we described how the Rhythmia mapping system was able help guide ablation delivery towards AT termination, despite the presence of pseudo-reentrant carousel activation initially misleading the operator to erroneous sites for ablation. In order to standardise the assessment of RM, outcomes were based on AT termination only following the first ablation set, and an operator grade of mapping confidence.

5.2.2 Methods

5.2.2.1 Study Population

The study population consisted of consecutive patients with symptomatic sustained ATs more than 3 months after AF ablation. Patients with cavo-tricuspid isthmus dependent atrial flutter or with variable AT cycle lengths were excluded. Local ethical approval was granted for this study. Details of the procedural setup is described in section 2.1.2.

5.2.2.2 Settings for data collection

RM is part of the mapping module in CARTO3v4 (Biosense Webster). During map acquisition, the bipolar voltage map was displayed and the LAT map remained hidden to all lab staff. Settings for data collection followed the algorithm presented in section 5.1, designed to optimise data collection and interpretation of Ripple Maps in ATs. CARTO3v4 also includes the ConfiDENSE module, designed to improve EGM fidelity of the map – the application this feature was at the discretion of the operator. Mapping was performed predominantly using multi-electrode catheters (Lasso or PentaRay, Biosense Webster), and

the remaining cases with a linear catheter (SmartTouch Thermocool, Biosense Webster). A “tissue proximity” filter was used for multi-electrode mapping based on catheter location and impedance measurements.

5.2.2.3 Ripple Map Interpretation

As described in table 5.1, after all points were collected, bipolar EGM data was played as a Ripple map. Deflections less than 0.03mV were considered to be noise and not shown. The bars were clipped above 0.25mV to allow low voltage bars to be seen without being obscured by large bars from areas of healthy tissue. The Ripple map was played as a continuous loop displaying two complete cycle lengths of the tachycardia. During this study, we developed a novel technique for studying activation over a voltage map, known as “scar thresholding.”

Scar Thresholding: The ripple map was played over a display of bipolar voltage. At the start of the case, the underlying voltage map was displayed as a single arbitrary value (e.g. 1mV-1mV), with purple highlighting tissue above this value, and red highlighting tissue below it. When the Ripple map was played over the voltage display, the voltage scale was manually reduced to identify the lowest voltage supporting wavefronts of Ripple bars (e.g. 0.2mV-0.2mV). In doing so, only those areas that did not support activation wavefronts were displayed as red, and these regions of non-conductive tissue were labelled as “scar”. Whilst not necessarily defining “scar,” but rather non-active tissue for a given tachycardia (including functional block), we found that this term was more intuitive and familiar.

This approach was used to characterize every potential ripple activation wavefront around scar, to determine where it began and ended and whether there was any possibility of reentry. If reentry could not be demonstrated, each wavefront was studied to identify a site of activation breakout from a localised area. In complex cases, it was helpful to mark out the route using the ‘design line’ tool. In macro-reentrant circuits, the narrowest isthmus was defined as the ‘critical isthmus.’ If more than one wavefront shared the same critical isthmus, the primary circuit was defined as the one penetrating the common isthmus first (the CARTO Ripple Viewer tool enabled multiple EGMs to be selected around the isthmus site for analysis of timing). If reentry could not be demonstrated, each wavefront was studied for a breakout pattern from a localised area. Once the left atrial activation mechanism was fully characterized, the bipolar voltage was measured at either the source of activation breakout or the narrowest isthmus of the primary macro-reentrant circuit.

5.2.2.4 Categorization of Ripple Maps

During each case, the Ripple Map was graded for diagnostic confidence. Cases where the operator proceeded directly to ablation based on the Ripple map were classified as Grade I. Moderate diagnostic confidence (Grade II) was defined when the operator performed a set of entrainment before ablation but this did not result in a change in the diagnosis. An entrainment set included all entrainment attempts required to prove the diagnosis. Finally, low diagnostic confidence (Grade III) was where the operator elected to remap the tachycardia, or entrainment manoeuvres disproved the diagnosis.

Termination of tachycardia or change to a different activation pattern with an associated change in cycle length during the first ablation set was considered a successful endpoint. (The first ablation set encompassed all the ablation lesions delivered to target the AT diagnosis based on the Ripple Map). The study protocol was applied only to the first map collected and first ablation set delivered. If the tachycardia changed to a new circuit, operators were allowed to adopt any mapping approach.

5.2.2.5 Radiofrequency Ablation

Power controlled (25–35W) RF energy was delivered (Stockert 70 RF generator, Biosense Webster) through an irrigated ablation catheter (SmartTouch Thermocool). All PVs were evaluated and any reconnection was re-isolated after AT ablation or as part of the ablation strategy.

5.2.2.6 Independent Assessors analysis

The Ripple Map and corresponding LAT map for each case was retrospectively reviewed by two independent experienced trainee operators to enable fair comparison between the mapping systems and minimize the bias of ‘LAT mapping experience’. These assessors had previously received formal training and were familiar with LAT interpretation but with <100 case experience. They were trained de-novo on the RM bar settings and “scar thresholding” technique. The LAT maps and RMs were reviewed without the patients’ clinical and electrophysiological data. Maps were presented on the workstation in a random unpaired sequence. Maps were reviewed without manual adjustment, exactly as the operator saw during the cases immediately after finishing point collection. LAT maps had been auto-annotated using either the most negative gradient of the unipolar signal within the bipolar EGM window or to the maximum bipolar peak (assigned from the start of the case). The WOI was set to be equal to the tachycardia cycle length, with the reference EGM at the centre of this window. No manual re-annotation was allowed. The same scale based on whether the assessors would have been prepared to ablate without entrainment (Grade I), after a single confirmatory entrainment (Grade II), or needed

further mapping to make a diagnosis (Grade III) was applied. In the event of an incorrect diagnosis, the map was denoted a grade 3 map as remapping/multiple entrainments would have been needed.

5.2.2.7 Statistical analysis

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median (lower quartile – upper quartile) for non-parametric data. Paired data were analysed using the Wilcoxon Signed Ranks test for non-parametric data. Unpaired data were analysed using a Student's T-test for parametric data and Mann-Whitney U-Test for non-parametric data. McNemar's test was used for paired categorical data. A two sided p value was determined where applicable and a value of $p \leq 0.05$ was considered significant. R (version 3.1.0) was used for statistical analysis.

5.2.3 Results

5.2.3.1 Patient Characteristics and Previous Ablations

20 patients were studied (65 ± 9 yrs), all with previous AF ablation (percutaneous PVI in 90%, surgical AF ablation as part of concomitant mitral valve surgery in 10%). Additional lesions sets included a combination of roof (35%) and mitral isthmus ablation (45%) and EGM defragmentation (35%). 11/20 (55%) of patients had undergone 2 or more ablation procedures including 5 patients who had been treated for an AT after AF ablation. Patient demographics and ablation history are summarized in Table 5-2. Left atrial size was 4.3 ± 0.5 cm in diameter. LV systolic function was documented as normal in 90% of patients. All patients were on long-term anticoagulation and (50%) patients were on anti-arrhythmic drugs (flecainide, sotalol, amiodarone).

Pt	Age	Sex	Previous Ablation history	Mapping catheter	Mapping		
					ConfIDENSE	Points	Mins
1	65	M	1. PVI + MI	Smartouch	No	182	37
2	43	M	1. PVI; 2. Redo PVI	Smartouch	Applied	807	42
3	71	F	1. PVI	Smartouch	Applied	1143	38
4	67	M	1. Surg AF abl. (with MVR)	LassoNAV	Applied	2426	16
5	76	F	1. PVI; 2. Redo PVI + Roof + CFAE	Smartouch	No	214	33
6	50	M	1. PVI + CTI	Lasso NAV	Applied	2973	18
7	77	F	1. PVI; 2. Roof + Anterior MI	Lasso NAV	Applied	1202	26
8	72	M	1. PVI, 2. Redo PVI + MI, 3. Roof	Lasso NAV	Applied	1050	22
9	58	M	1. PVI + CFAE + CTI. 2. Roof	Lasso NAV	Applied	1045	15
10	70	M	1. PVI; 2. Redo PVI + MI + CTI	Lasso NAV	Applied	918	29
11	70	M	1. PVI, Anterior MI	Lasso NAV	No	613	24
12	68	M	1. Surg AF abl. (with MVR); 2. Roof + MI	Pentaray	Applied	1761	33
13	60	M	1. PVI + Roof + MI + CFAE	Lasso NAV	Applied	1148	27
14	70	M	1. PVI; 2. Redo PVI + CTI	Lasso NAV	Applied	2823	33
15	58	M	1. PVI; 2. Redo PVI + Roof	Smartouch	No	363	35
16	77	M	1. PVI + MI + CFAE	Lasso NAV	Applied	1683	25
17	65	M	1. PVI + CFAE	Lasso NAV	No	700	22
18	60	M	1. PVI + CFAE	Lasso NAV	Applied	1719	27
19	54	M	1. PVI + CTI 2. Redo PVI + MI	Lasso NAV	Applied	1212	20
20	77	M	1. PVI; 2. Redo PVI + Roof + CFAE	Lasso NAV	Applied	1224	33

Table 5-2: Baseline Demographics and Mapping data

5.2.3.2 Procedural data

Left atrial geometry (area $208 \pm 36 \text{ cm}^2$) and electrical data were collected simultaneously. The automated point collection facility (ConfiDENSE) was applied in 15 cases with the remaining 5 cases collected point-by-point. Point density was significantly greater using the automated system (median 1212 (1097-1740) vs. 363 (214-613) points per map; $p=0.001$), with similar mapping times using both approaches (ConfiDENSE 29 ± 9 mins vs point-by-point 35 ± 3 mins; $p=0.40$).

5.2.3.3 Ripple Map Interpretation

Scar thresholding

The voltage threshold on the bipolar voltage map was adjusted to display non-conducting tissue, presumed scar, where wavefronts of Ripple bars could not be identified as red (figure 5-4 and video 5-4). The median scar threshold was 0.3 mV ($0.19\text{-}0.33 \text{ mV}$). Scar occupied $33 \pm 9\%$ of the voltage map.

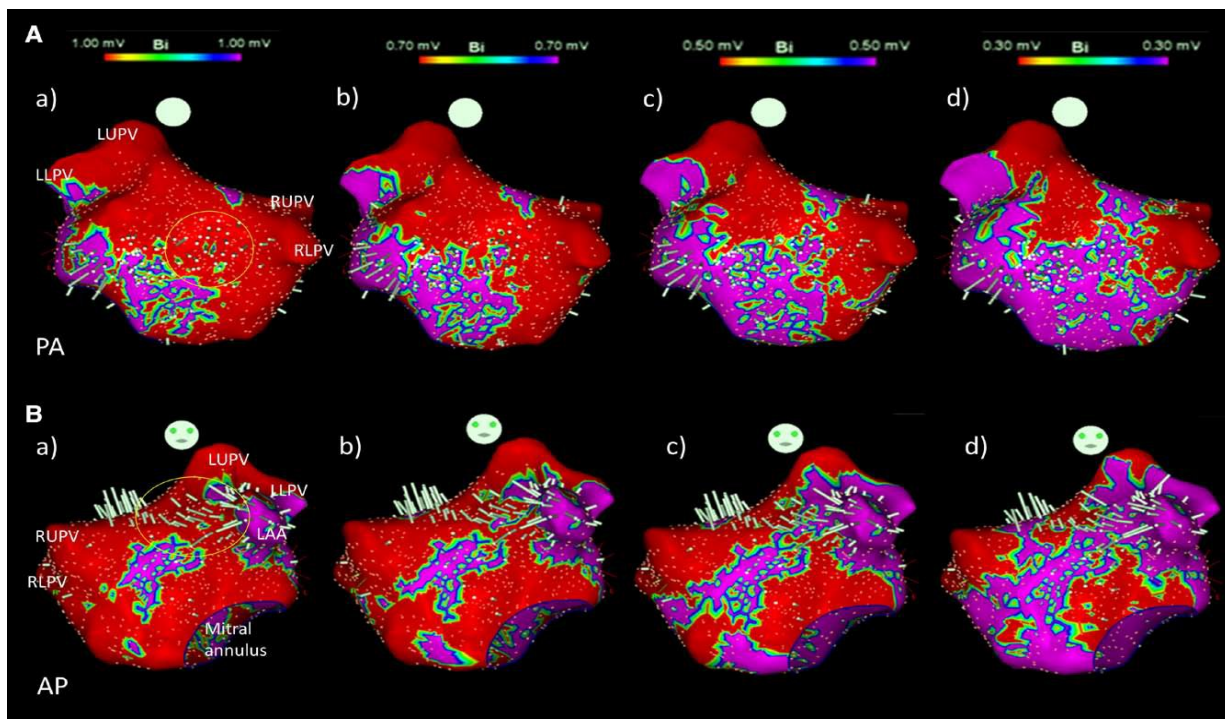


Figure 5-4: (see also video 5-4) Scar Thresholding

Panel (A): A patient with previous CPVI, roof line and anterior mitral isthmus line. The bipolar voltage map is displayed in PA. The voltage threshold is set arbitrarily at 1 mV (a), with red representing voltage below 1 mV and purple representing voltage above 1 mV . When the Ripple Map is played, bars are seen to propagate towards the roof within areas of red on the map (yellow circle). The scar threshold is progressively reduced (b - 0.7 mV ; c - 0.5 mV ; d - 0.3 mV) until only those areas with propagating ripple bars appear as purple, representing active tissue. This was achieved at 0.3 mV (scar threshold) and $<0.3 \text{ mV}$ was defined as non-conductive and shown as red for this map.

Panel (B): For illustrative purposes the effect of reducing the scar threshold in the AP view is shown. Bars are seen to travel from the left atrial appendage (LAA) towards the roof (a) within red voltage map display (yellow circle). The process of scar thresholding is again displayed (b-d). At 0.3mV, an isthmus of active tissue is seen bordered by non-conductive site between the roof and mitral annulus (“non-conducting-non-conducting” isthmus) confirming that for this chamber this level is appropriate.

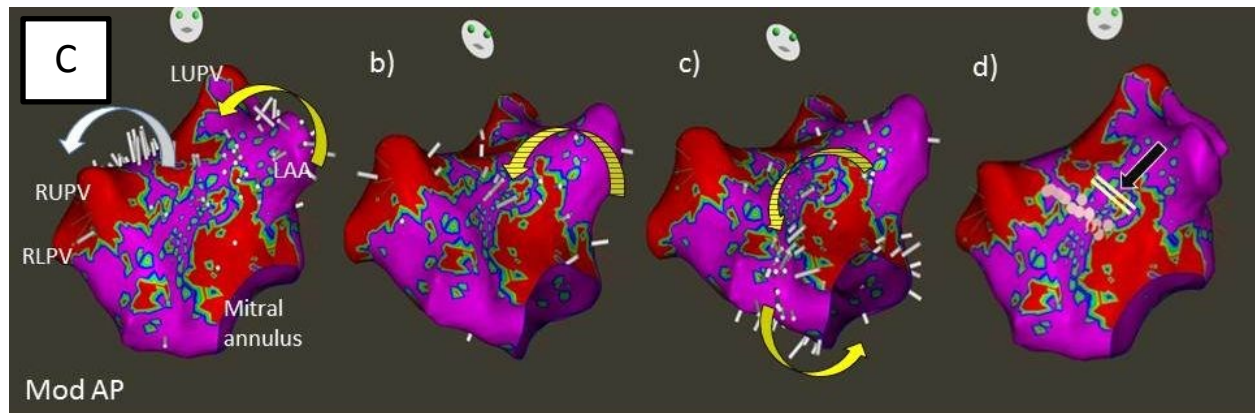


Fig 5-4 cont...Panel (C): A modified AP projection (a) is displayed. A wavefront of bars ascends towards the roof (white arrow). A further wavefront travels towards the isthmus (yellow arrow). The ripple bars percolate through the isthmus (b-c) and exit near the septum, continuing counter-clockwise around the mitral annulus. Transecting this critical isthmus terminated tachycardia with bidirectional block eventually achieved.

Isthmus dependent circuits

Following review of the Ripple Map, 14/20 (70%) cases were diagnosed as an isthmus dependent circuit. The isthmuses were bordered on either side by non-conducting tissue (considered scar), or non-conducting tissue on one side and an anatomical border on the other. Isthmuses within non-conducting tissue were seen in 9/14pts and “non-conducting - anatomical” isthmuses in the remaining 5/14pts. The median isthmus width of the primary circuit was 14mm (11-18mm) and the median EGM amplitude was 0.52mV (0.34-0.82mV). The total circuit length was a median of 186mm (154–201mm). A summary of these isthmus dependent circuits is seen in Table 5-3. Oscillating Ripple bars, due to fractionated EGMs, were seen to percolate slowly through the isthmus in 6 circuits, secondary to either an idiopathic area of slow conduction, or a gap in a previous line of ablation. As activation travelled away from the isthmus, it was seen to split around regions of non-conducting tissue or anatomical structures (valve annuli, PVs) in 9/14 maps, resulting in bystander circuits. The bystanders were supported by their own isthmus (“non-conducting - non-conducting” isthmuses seen in 70%, median isthmus width of 13mm (10 – 21mm)). The bystander circuit length was a median of 197mm (176-217mm). All bystander circuits re-joined the primary circuit, forming a dual or multi-loop circuit. The narrowest isthmus supporting the primary circuit and shared by all circuits was deemed the “critical isthmus” (figure 5-5 and video 5-5).

Pt	ATCL (ms)	Chamber area (cm ²)	Activation Threshold (mV)	NC %	Primary circuit				Bystander Circuit			
					Length (mm)	Critical isthmus			Length (mm)	Isthmus		
						Width (mm)	Voltage /mV	NC - NC Anat		Width (mm)	Voltage /mV	NC - NC Anat
1	260	185	0.40	32	152	8	0.54	X		24	1.67	X
3	254	130	0.08	35	87	11	0.15			11	0.15	
4	260	185	0.06	30	280	21	0.50	X		8	0.18	X
5	320	233	0.14	47	205	41	0.87	X		9	0.27	X
7	280	187	0.30	35	221	18	0.67	X		12	0.14	X
8	270	248	0.25	48	149	9	0.33	X				
9	230	220	0.40	48	180	23	1.61					
10	280	233	0.40	45	155	12	0.37	X				
13	260	141	0.15	31	197	9	0.29	X				
14	260	200	0.30	31	187	17	1.19					
15	260	216	0.30	35	190	20	1.57					
17	250	260	0.20	25	185	11	0.38					
18	260	232	0.30	30	202	14	0.63	X				
19	220	202	0.15	20	153	7	0.13	X				
Median	260	209	0.28	34	186	13	0.52					
LQ	256	186	0.15	30	154	10	0.34					
UQ	267	233	0.30	43	201	20	0.82					

Anat. Indicates anatomic structure; ATCL, atrial tachycardia cycle length; LA, left atrium; and NC, nonconducting

Table 5-3: Isthmus dependent Circuits (note: activation threshold = scar threshold)

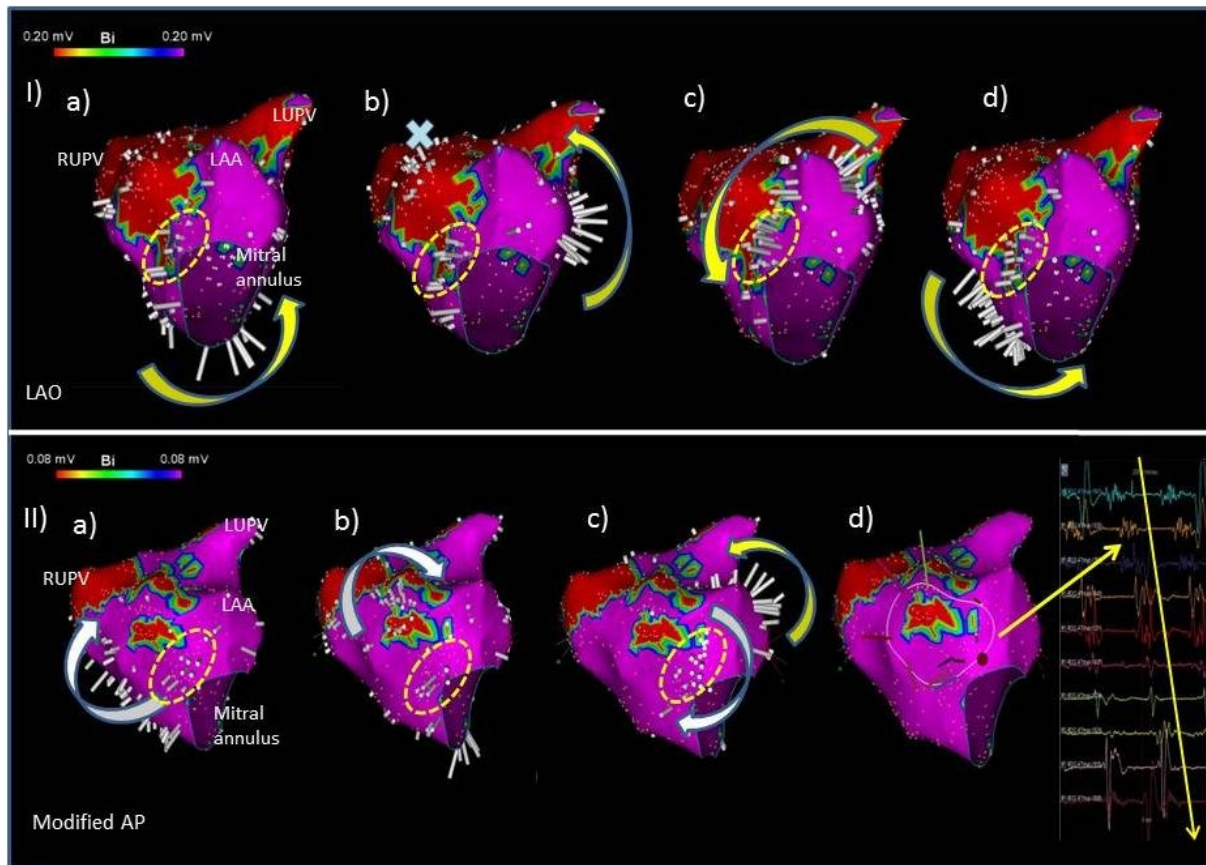


Figure 5-5: (see also video 5-5) Circuit around a small island of scar
A patient with previous CPVI alone. The Scar threshold was 0.2mV.

Panel (I): The voltage map is displayed in LAO, and a counter-clockwise circuit of Ripple bars (yellow arrow) travels around the mitral annulus (a-d). A small circuit of Ripple bars (b) is also seen on the anterior wall within an area of red displayed on the voltage map ("X").

Panel (II): The map is displayed in AP. Non-conductive tissue is redefined to 0.08mV taking into consideration this activation on the anterior wall. This reveals a small island of idiopathic non-conductive tissue on the anterior surface. This small circuit navigates clockwise around this island (a-c) and returns towards the anterior mitral annulus ahead of the peri-mitral circuit. Sampled EGMs around this circuit include the full tachycardia cycle length (d). A slowly conducting isthmus (notched yellow circles) common to both the small circuit and peri-annular circuit have been identified. This area contains frequently oscillating ripple bars due to EGM fractionation. Ablation (red tag) within this isthmus terminated tachycardia within 40 seconds of RF.

Breakout Activation

In the remaining 6/20 (30%) cases, a breakout of activation away from an area of non-conducting tissue was evident (figure 5-6 and video 5-6). It was not possible to determine whether these were related to localised reentry within this apparent area of non-conducting tissue. The median EGM amplitude at the breakout was 0.35mV. The breakout wavefront split around regions of non-conducting tissue or anatomical structures, forming individual paths of activation travelling through their own channels. A total of 11 wavefronts were seen in these 6 maps, navigating through 7 “non-conducting - non-conducting” isthmuses, and 4 “non-conducting - anatomical” isthmuses respectively, before terminating post collision with a sister wavefront (5 wavefronts) or non-conducting tissue (6 wavefronts). A summary of these breakout activations is seen in table 5-4.

Patient	ATCL (ms)	Chamber area (cm ²)	Activation Threshold (mV)	NC (%)	Active Breakout site	Break-Out Voltage /mV	Incomplete wavefronts	Additional Isthmuses			Termination	
								NC- NC	NC- Anat.	Location	Wavefront collision	NC site
2	270	242	0.50,	24	LSPV	0.48	2	N/A			2	
6	240	262	0.50,	23	RSPV	0.37	2	N/A			2	
11	230	192	0.30	46	Posterior R WACA	0.15	3	1	2	Scar on roof, anterior and posterior LA	1	2
12	240	234	0.10	34	Mid posterior wall	0.14	4	3	1	Scar on roof, anterior and septal LA	2	2
16	250	188	0.20	47	MI line	0.32	2	0	2	Scar on roof, anterior and posterior LA	0	2
20	240	173	0.20	32	Lower posterior wall	0.39	2	2	0	Scar on posterior wall, previous WACA site and roof	2	0
Median	240	213	0.25	33		0.35	2	1.5	1.5		2	2
Lower Quartile	240	189	0.2	26		0.19	2	1	1		1	1.5
Upper Quartile	248	240	0.45	43		0.39	3	2.5	2		2	2

ATCL – Atrial Tachycardia cycle length; NC: Non-conducting; Anat – Anatomical structure, WACA – wide-area circumferential ablation

Table 5-4 Breakout activation (note: activation threshold = scar threshold)

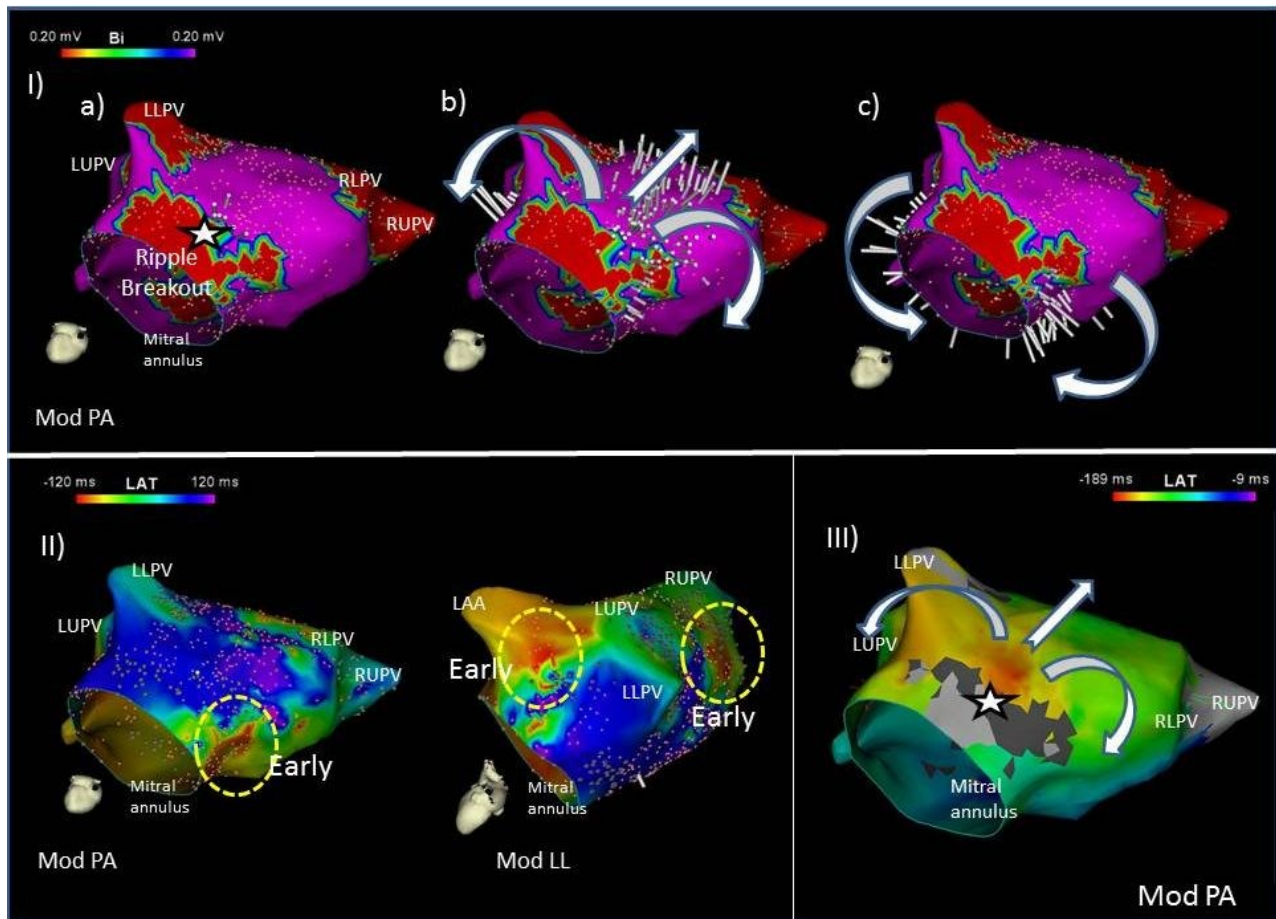


Figure 5-6: (see also video 5-6) Breakout circuit

A patient with previous CPVI, roof line and CFAE ablation. The scar threshold was 0.2mV.

Panel (I): The voltage map is displayed in modified PA. Breakout of Ripple bars (a) from a region of non-conduction (starred label) on the posterior wall close to the mitral annulus is evident. This travels passively around the atrial chamber (b, c), with one wavefront ascending towards the roof, and two further wavefront travelling in opposite directions around the mitral annulus. Ablation clustered around the area of breakout terminated tachycardia.

Panel (II): The unadjusted LAT map is displayed with the WOI set equally either side of the reference. A chaotic pattern of activation is seen with multiple areas denoted as early.

Panel (III): The WOI has been manually adjusted to identify the earliest site of activation. Only then is the correct pattern of activation seen.

LAT mapping assumes that the inter-atrial conduction time (IACT) is less than or equal to the WOI (WOI) and can mis-annotate very late activation outside the WOI as early points. However, the RM was able to show that these areas were out-of-sequence with the rest of the activation when more than one cycle was viewed (figure 5-7 and video 5-7).

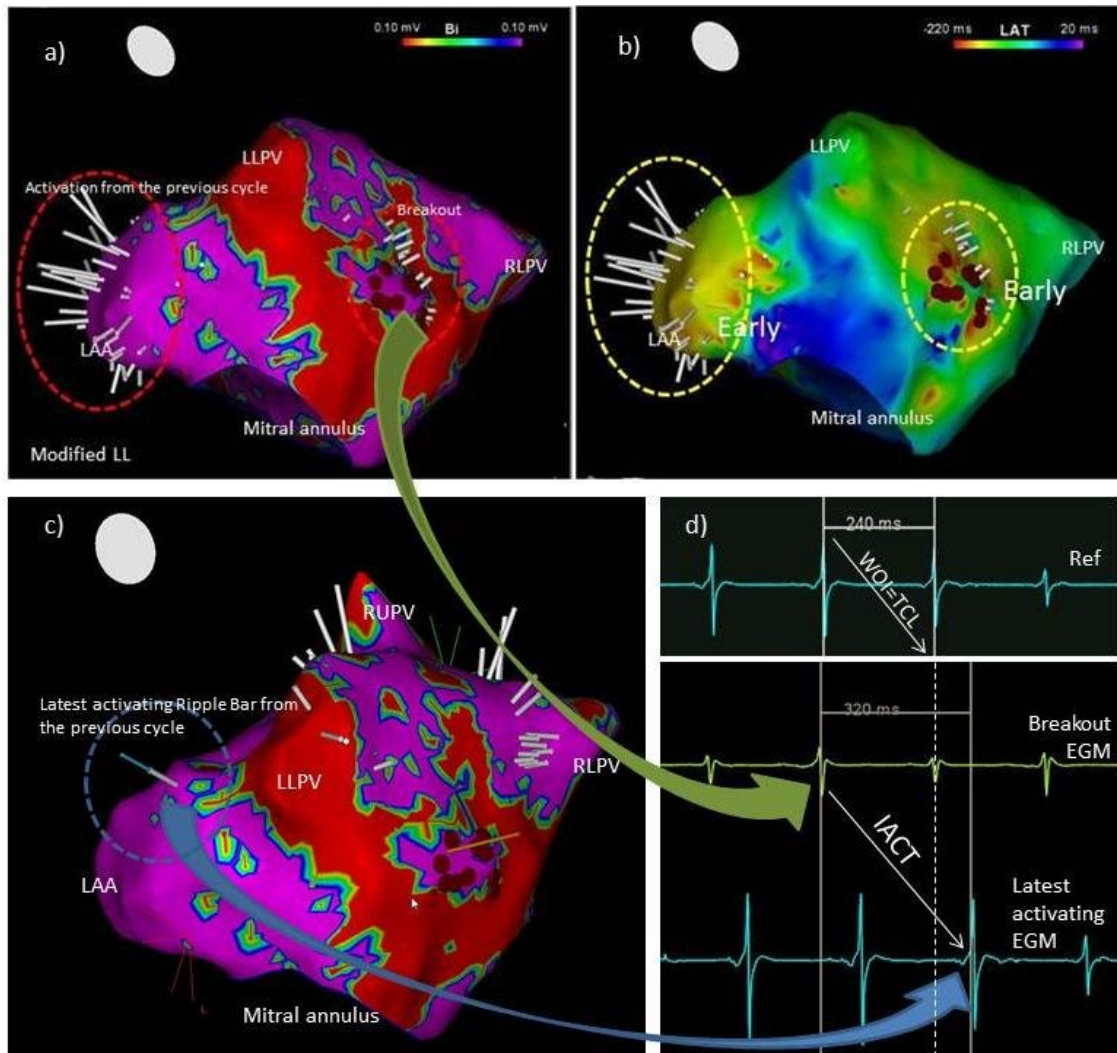


Figure 5-7: (see also video 5-7) Break-out circuit with $IACT > WOI$

A patient with previous extensive AF ablation (surgical/percutaneous PVI + roof and MI lines) presented in stable AT (TCL 240ms). (a) The scar threshold was 0.1mV. A breakout circuit from an area of apparent non-conductive low voltage on the posterior wall was diagnosed and ablation clustered at this site terminated AT. (b) The LAT WOI was adjusted (-220)-(+20) around the CS signal in order to demonstrate the correct pattern of earliest activation (red isochrones) on the posterior wall. Despite the correct WOI adjustment, an additional early activating site was seen at the LAA. The ripple map confirmed simultaneous activation from the breakout site and the LAA, though viewing more the one cycle revealed LAA activation from the previous cycle. (c) The latest activating Ripple bar within the cycle was highlighted with a blue ripple marking and displayed in the Ripple Viewer (d), along with a single component EGM (green EGM) sampled close to the breakout site, for ease of display. The interval between the EGM from the breakout site and the latest activating site (intra-atrial conduction time) was 320ms. The latest activating bar was outside the set WOI (displayed in the figure by manually aligning the Reference EGM with the EGM from the breakout site). As the inter-atrial conduction time on the LAT map is assumed to be the same as the WOI, the LAA has been incorrectly assigned on the LAT map as early. However, the RM was able to show that the LAA was being activated very late through a narrow slow conducting isthmus.

5.2.3.4 Diagnostic Confidence

Grade I confidence was documented in 15/20 (75%) cases. The operator performed a single set of entrainment prior to ablation in the remaining 5/20 (25%) cases (Grade II confidence) all of which confirmed what was already suspected from the Ripple map. The LAT map was not reviewed during any case.

5.2.3.5 Ablation Outcome

The outcome of ablation is summarized in table 5-5. ATs changed or terminated in 19/20 cases with the first planned ablation set. A median of 22:56mins (12:58-31:10mins) of ablation were delivered to transect isthmus dependent wavefronts without previous ablation. Isthmuses of slow conduction required only a median of 58secs (29secs - 5:04min) of ablation. Breakout circuits received a median of 2:50mins (=52secs - 5:35mins) of ablation.

In isthmus dependent circuits, a line of ablation transecting the critical isthmus was delivered. In breakout circuits, ablation was clustered around the region of earliest breakout. In patient 17, the critical isthmus was shared by two circuits and was located at the septum, the operator elected to avoid this isthmus, and transect an isthmus for each circuit. In patient 13, an isthmus dependent circuit navigating clockwise around the mitral annulus was diagnosed, which also passed through a narrower “non-conducting - non-conducting” isthmus at the septum. This septal site was chosen for ablation but termination could not be achieved at this isthmus, whereas ablation in the mitral isthmus terminated tachycardia. Entrainment showed the septal isthmus was part of the circuit. Failure to achieve block at the septum was confirmed by remapping the tachycardia post ablation with ongoing conduction through the septal isthmus seen. This was the only case where the first lesion set did not alter the tachycardia.

Pt	Ripple Map		
	Map Grade	Ablation time (mins:secs)	Outcome of first ablation set
1	1	0.20	Termination
2	1	0.34	Termination
3	2	0.59	Termination
4	2	5.32	Change
5	2	31.60	Termination
6	1	0.39	Termination
7	1	0.56	Termination
8	2	0.02	Termination
9	1	14.46	Termination
10	1	6.25	Termination
11	2	1.30	Termination
12	1	5.31	Termination
13	1	40.56	Failed termination with 1 st set
14	1	31.14	Termination
15	1	22.56	Termination
16	1	4.09	Change
17	1	20.50	Change
18	1	11.10	Termination
19	1	21.10	Termination
20	1	6.04	Change

Table 5-5: Outcome of ablation

5.2.3.6 Independent assessor review

The diagnosis and diagnostic confidence from two independent assessors for each LAT and Ripple map were compared (table 2). The correct diagnosis was offered more with RM than LAT maps; using RM, the correct diagnosis was offered by both assessors in 14/20 maps (70%), by one assessor alone in 4/20 (20%) and by neither assessor in 2/20 (10%); using unadjusted LAT Maps, the correct diagnosis was offered by both assessors in only 4/20 maps (20%), by one assessor alone in 9/20 (45%) and by neither assessor in 7/20 (35%) ($p < 0.001$). Where at least 1 assessor was correct, the time to correct diagnosis was lower with RM (median 56secs (31secs-1:54mins) vs. LAT maps (median 1:38mins (1:25mins-

2:35mins) ($p=0.45$). The assessors would have been confident to proceed to ablation without entrainment confirmation (Grade I) in 12/20 (60%) Ripple maps vs. 3/20 (15%) LAT maps ($p<0.001$). The assessors would have remapped or proceeded to multiple entrainments (Grade III) in 6/20 (30%) LAT maps vs. 0/20 (0%) Ripple maps ($p=0.003$).

	Diagnostic Accuracy		Mean Time to correct diagnosis (s)		Average Map Grading	
	2= Both assessors correct 1= One assessor correct 0=Neither assessor correct Ripple better LAT better		Ripple better LAT better		1= Both would ablate without entrainment 1.5= One would ablate without entrainment 2= Both would ablate after entrainment check 2.5=One would ablate after entrainment check 3= neither confident of diagnosis/incorrect diagnosis Ripple better LAT better	
	Ripple	LAT	Ripple	LAT	Ripple	LAT
1	2	1	34	105	1	2.5
2	2	2	67	49	1.5	1
3	1	0	67	N/A	1.5	2
4	1	2	259	208	2	2
5	1	1	256	85	2	2
6	2	2	55	89	1	2
7	2	0	86	N/A	1	3
8	0	0	N/A	N/A	2	2.5
9	2	1	22	153	1	2
10	2	1	34	42	1	2
11	0	1	N/A	146	2	2.5
12	2	0	277	N/A	2	2
13	2	0	49	N/A	1	2
14	2	1	22	162	1	2.5
15	2	2	58	109	1	2
16	1	1	380	91	2	2
17	2	0	39	N/A	1	2.5
18	2	1	19	85	1	1.5
19	2	1	57	191	1	2
20	2	0	67	N/A	1	3

Table 5-6: Independent assessor review

5.2.4 Discussion

This prospective series demonstrates that RM is a highly effective technique for visualising arrhythmic activation within ablation related scar. The high success rate for ablation was the combined effect of reducing errors related to WOI assignment and activation time annotation, as well as a new method to help define activation through low voltage functional tissue.

Post-ablation atrial tachycardias (AT) are increasingly common and present challenges to conventional mapping methods due to widespread areas of slow conduction and low voltage.⁶¹ The relationship between myocardial scar and the tachycardia circuit is well established, but without a consensus on defining a voltage parameter to help differentiate between active and non-conducting tissue using endocardial mapping. For a specifically mapped tachycardia, non-conducting tissue can be identified in areas of endocardial scar from previous ablation or in areas of functional block. Atrial “scar” has previously been identified by a bipolar voltage of $\leq 0.05\text{--}0.1\text{mV}$ ¹¹² - this threshold originates from the baseline noise in early electro-anatomic mapping systems. Points below this threshold were hidden behind grey “scar” tags when LAT mapping was used. Alternatively, defining scar as locations without pace capture (at 10mA/2ms) led to a suggestion of 0.15mV.¹¹³ Rather than defining non-conducting tissue using a generic value, Ripple Map scar thresholding provides an individualized voltage threshold to help differentiate electrically active from inactive tissue for a specifically mapped tachycardia. RM was able to distinguish between low amplitude fractionated signals that formed the critical parts of slowly conducting isthmuses as opposed to non-conducting tissue. In this study, the median scar threshold was 0.3mV but varied from 0.06mV to 0.5mV. The median active isthmus level was 0.52mV, ranging from 0.13mV to 1.61mV. This is in keeping with other studies that identified isthmuses supporting macro-reentrant circuits as low as 0.05mV to 0.1mV.^{67, 85} Breakout sources had a median voltage of 0.35mV with a range from 0.14mV to 0.48mV. This overlap between non-conductive and active tissue critical to the tachycardia illustrates the challenge in defining the location of non-conductive tissue and potential error from low-voltage active tissue being tagged as scar.

The majority of ATs seen after AF ablation are either macro-reentrant or due to localised reentry.¹⁹⁹ In this study, RM demonstrated tachycardias meeting the definition of peri-mitral or roof dependent reentry and reflecting prior ablation sites. However, in some cases RM enabled a smaller lesion set at an appropriate isthmus, rather than completing linear lesions in the conventional locations. RM enabled a

more precise description of an AT, defining reentrant tachycardia by the width and location of the critical isthmus, the path-length, and a description of each segment of the circuit and number of bystander circuits. Similarly breakout activation was described by the location of origin, evidence of reentry into the scar and any period of electrical quiescence.

Previous extensive atrial ablation for atrial fibrillation can lead to multiple zones of slow conduction or conduction block within the atria. Importantly, it is possible for the intra-atrial conduction time, measured from the earliest to the latest bars on the ripple map, to be longer than the WOI. An accurate WOI can no longer be determined as the timing of the true latest activation site will be displayed early in the WOI with respect to the next cycle of activation.²⁰⁰ RM is not dependent on a WOI and therefore there is no concept of 'early' or 'late.' This represents an important advantage of RM in enabling higher diagnostic accuracy. Even the most recent data describing success rates in ablating scar related left atrial tachycardias using activation and entrainment mapping ranges from 77% - 86% depending on left atrial location.¹⁹⁰ This highlights the need for an improved mapping approach or improved ablation efficacy/lesion assessment in about 20% of cases.

It is important to emphasise that these impressive outcomes of RM guided ablation were based on the first lesion set delivered. Other studies may quote similar success rates, though whether their success rates were based on such a strict criteria is unknown. Conventionally, most operators only define failure to successfully ablate an AT when they resort to an electrical cardioversion to restore sinus rhythm, and by this definition, cases which eventually achieve AT termination following ablation at multiple incorrect sites are still considered successful. This success would have been achieved even though the operator was initially uncertain of the diagnosis after mapping. In chapter 4, we described how the Rhythmia mapping system was able to eventually help guide ablation delivery towards AT termination, despite the presence of pseudo-reentrant carousel activation initially misleading the operator to erroneous sites for ablation.

The independent trainee assessors reached the correct diagnosis more often with RM. The assessors were naïve to RM and scar-thresholding techniques so there were some errors related to this lack of experience. It was also apparent that the assessors were not used to seeing multiple circuits and trying to identify which was the primary circuit. Whether RM is easy to adopt by new users during clinical procedures requires further study.

5.2.5 Limitations

As the study protocol was applied only to the first map collected and first ablation set delivered, only acute results are presented, without long-term follow-up. This study did not attempt to perform prospective direct comparison between RM and LAT mapping.

The absolute value of the scar threshold determined by this method of identifying conducting tissue is dependent on the recording technique and noise threshold of the recording system which will influence the resolution and quality of the EGMs that are used for the Ripple maps. We suspect that some of the breakout activation away from low voltage areas actually represents some localised reentry within this area, but mapping resolution was not sufficient to elucidate these.

5.2.6 Conclusions

RM can be used to guide ablation in scar related AT with high diagnostic confidence and acute success rates. This is a combined effect of avoiding errors related to WOI assignment and activation time annotation as well as a new method to help define activation through low voltage areas, hence particularly effective in mapping within the scarred atria. The reproducibility of these findings in other centres is now required.

5.3 Initial multi-centre experience of Ripple Mapping in atrial scar

5.3.1 Introduction

RM is a novel approach to activation mapping in areas of low voltage, that avoids the need for EGM annotation, setting a WOI and interpolation.¹²³ However, RM looks very different to conventional 3D activation mapping which uses a colour spectrum to define local activation time. It also has a modified approach to use as operators are encouraged to collect more points than they would routinely, and study activation over a display of bipolar voltage.^{180, 191} A mapping technique must be easily adopted by new operators to be able to deliver improved outcomes. We studied the outcomes of electrophysiologists from 5 independent sites, experienced in CARTO mapping, using RM for the first time to guide ablation in scar related ATs. Operators reviewed the LAT maps post ablation, and we compared the diagnosis and diagnostic confidence of both mapping modalities for each AT.

5.3.2 Methods

5.3.2.1 Study sites

Centres with extensive experience of 3D mapping of ATs that were using the CARTO Confidence™ module for multi-electrode mapping were selected. All operators received off-line training in the use of RM, individually reviewing 10-15 AT cases of increasing complexity.

These centres included:

- Hospital de Santa Maria, Lisbon, Portugal;
- Royal Bournemouth & Christchurch Hospital, Bournemouth, UK;
- Essex Cardiothoracic Centre, Basildon, UK;
- Barts Heart Centre, London, UK;
- Papworth Hospital, Cambridge, UK.

Patients with documented AT post previous left atrial ablation were included in the study. The procedures were performed with informed consent and local approval at each site was granted for this study.

The process of map acquisition and Ripple Map analysis has already been described. The LAT display was hidden from the operator until ablation had been delivered based on the Ripple map. All LAT maps were studied as “unadjusted” without any change in WOI or manual re-annotation of activation time.

5.3.2.2 Map Grading

A diagnosis was made on the basis of the Ripple and LAT map, and these were classified as Grade 1 diagnostic confidence if the map offered sufficient information to deliver ablation; Grade 2 diagnostic confidence if the diagnosis was suspected but not certain, and further diagnostic information such as entrainment was required; Grade 3 diagnostic confidence if a diagnosis could not be made, or if ablation failed to interrupt the tachycardia circuit and entrainment disproved the tachycardia mechanism.

Power controlled (25–35W) RF energy was delivered (Stockert 70 RF generator, Biosense Webster) through an irrigated ablation catheter (SmartTouch, Thermocool). All ablation lesions were delivered exclusively on the basis of the Ripple map. The site of termination/change of tachycardia was compared with the diagnosis from each mapping method and the grade of diagnostic confidence. If the tachycardia changed to a new circuit, operators were allowed to adopt any mapping approach.

5.3.2.3 Statistics

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median (lower quartile – upper quartile) for non-parametric data. SPSS version 23 was used for statistical analysis.

5.3.3 Results

To specifically capture the initial experience of RM use, the first 20 cases across 5 centres performed by operators naïve to RM are reported in this study. Table 5-7 summarises the patient demographics from these first 20 cases using this approach. All patients (age 64 ± 9 yrs, male $n=13$ (65%)) had undergone at least 1 previous left atrial ablation (median $n=2$; PVI $n=19$ (95%); linear lesions $n=10$ (50%); EGM defragmentation $n=3$ (15%); left lateral accessory pathway $n=1$). Chamber geometry ($212\pm 45\text{cm}^2$; LA $n=18$; RA $n=2$) and high density maps (2935 ± 1328 points) were collected in AT (cycle length $296\pm 95\text{ms}$) over a mapping time of (30 ± 13) minutes. The Ripple Map scar threshold was determined in each case ($0.23\pm 0.12\text{mV}$). Isthmus dependent macro-reentrant tachycardia bordered by scar or anatomical boundaries were identified in $n=12$ (60%), of which $n=4$ (20%) navigated through a residual narrow gap from a previous ablation line. Breakout activation was identified in $n=5$ (25%), which arose from regions of scar in 3/5. Small rotatory circuits around islands of scar within the atrial body were identified in the remaining $n=3$ (15%).

No.	Age	Sex	Previous ablation history	ATCL (ms)	Catheter	Points	Mapping time (mins)	Area /cm ²	Scar threshold (mV)
1	53	M	1.PVI	245	Lasso	4665	36	210	0.4
2	72	F	1.PVI + roof line + left atrial appendage occlusion	450	Lasso	3105	46	217	0.04
3	69	M	1. PVAC. 2. redo PVI	215	Lasso	4956	20	163	0.3
4	71	F	1. PVI, Roof, CFAE	220	Pentaray	4268	18	191	0.2
5	65	M	1.Surgical MAZE. 2. redo PVI	340	Pentaray	1667	14	194	0.15
6	56	M	1. PVI. 2. Redo PVI. 3 Redo PVI, Roof, MI, CTI	290	Pentaray	2681	12	222	0.2
7	50	M	1. PVI. 2. Roof. 3. MI	220	Pentaray	1432	21	260	0.5
8	56	M	1. PVI, 2. CTI	260	Pentaray	3551	41	248	0.5
9	66	M	1. PVI 2. Redo PVI and mitral and CFAE 3. Roof	240	Pentaray	3504	17	272	0.2
10	65	M	1. PVI, roof	250	Pentaray	1963	18	190	0.2
11	66	M	1. CTI, 2. RA flutter. 3. Left AVRT	200	Lasso	1725	17	270	0.15
12	74	M	1. Surgical PVI + RA focal	550	Pentaray	429	35	93	0.3
13	69	F	1. PVI, Surgical ASD repair, 2. Redo PVI, MI, Roof	200	Pentaray	3915	47	281	0.15
14	65	F	1. PVI, Roof, CFAE	290	Lasso	1479	45	226	0.2
15	65	M	1. PVI, Roof, 2. LAA focal, CTI	250	Lasso	2405	30	210	0.2
16	75	F	1. PVI and Roof line	252	Lasso	3946	47	217	0.1
17	39	F	1. PVI, 2. MI, 3. LAA	430	Lasso	2476	46	140	0.3
18	69	F	1. PVI 2. Redo PVI	233	Lasso	4656	42	231	0.15
19	65	M	1. PVAC 2. PVI	410	Lasso	4593	31	235	0.1
20	71	M	1. PVI + CTI	370	Pentaray	1278	17	172	0.3
Av	64			296		2935	30	212	0.23
SD	9			95		1328	13	45	0.12

Table 5-7: Patient Demographics and Mapping data

As illustrated in figure 5-8 (and video 5-8), a higher density map (4665points) than would usually be used for 'interpolated activation' was collected to ensure that 'real electro-anatomical data' was available throughout the complete shell without any unmapped areas. The Ripple bars were played over a surface anatomy displaying bipolar voltage so that non-functional tissue could be assigned as scar. In this case, breakout of activation between the left sided veins was diagnosed in a patient with previous pulmonary venous isolation. The AT was terminated with RF energy at this site within 5 seconds.

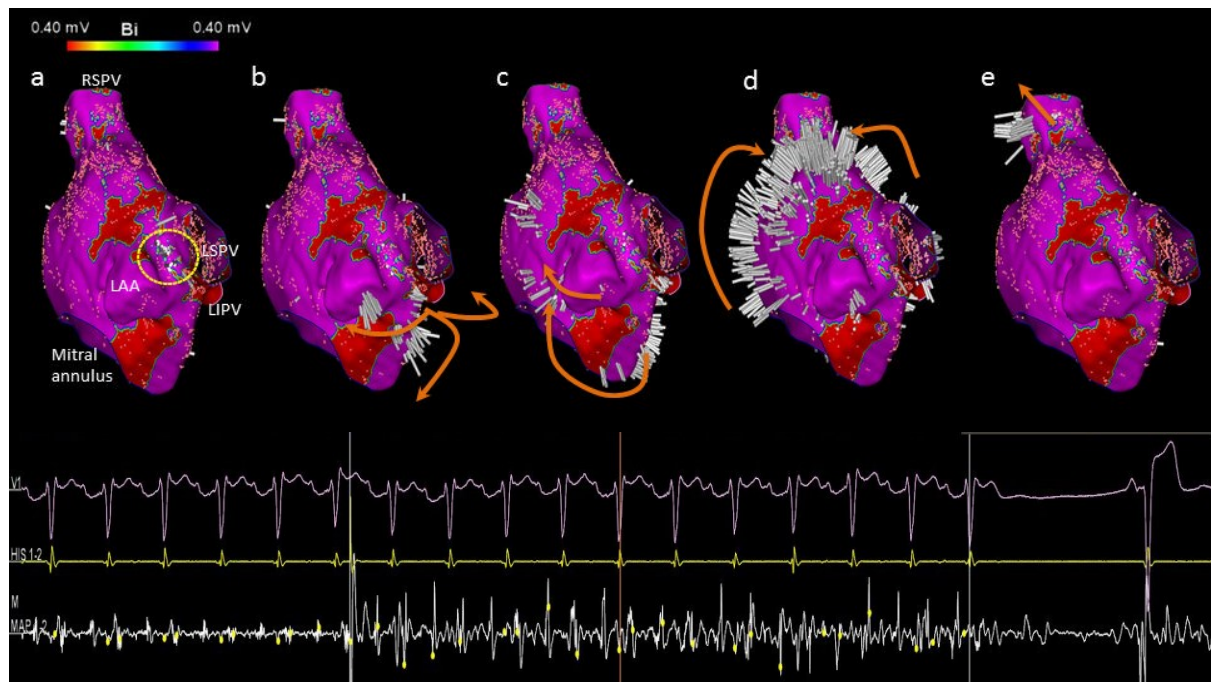


Figure 5-8:(see also video 5-8) RM guided AT ablation

The LA is presented in a modified left lateral orientation. The underlying voltage map is displayed at 0.2mV, below which no wavefront of ripple activation appears. (a) A breakout of ripple bars occurred between the left sided PVs, adjacent to a line of block from previous pulmonary venous isolation (red) at the roof. (b) The wavefront travelled towards the mitral annulus, (c) and around the anterior and posterior walls respectively, (d) before colliding at the roof. (e) The latest site of activation occurred is a non-isolated RSPV. A single ablation lesion at a fractionated signal at the site of breakout terminated tachycardia in 5.3secs.

‘Scar-thresholding’ was a new concept for operators and involved adjusting the bipolar voltage map so that areas deemed ‘scar’ did not have any propagating Ripple wavefronts. Figure 5-9 (and video 5-9) illustrates this process in a case where the Ripple maps suggested counter-clockwise peri-mitral activation. However, using scar-thresholding, the Ripple map demonstrated that this circuit travelled through a narrow isthmus of slow conduction on the anterior wall bordered on either side by scar. Rather than ablating the conventional mitral isthmus, which can be challenging, this alternative isthmus was targeted, terminating tachycardia.

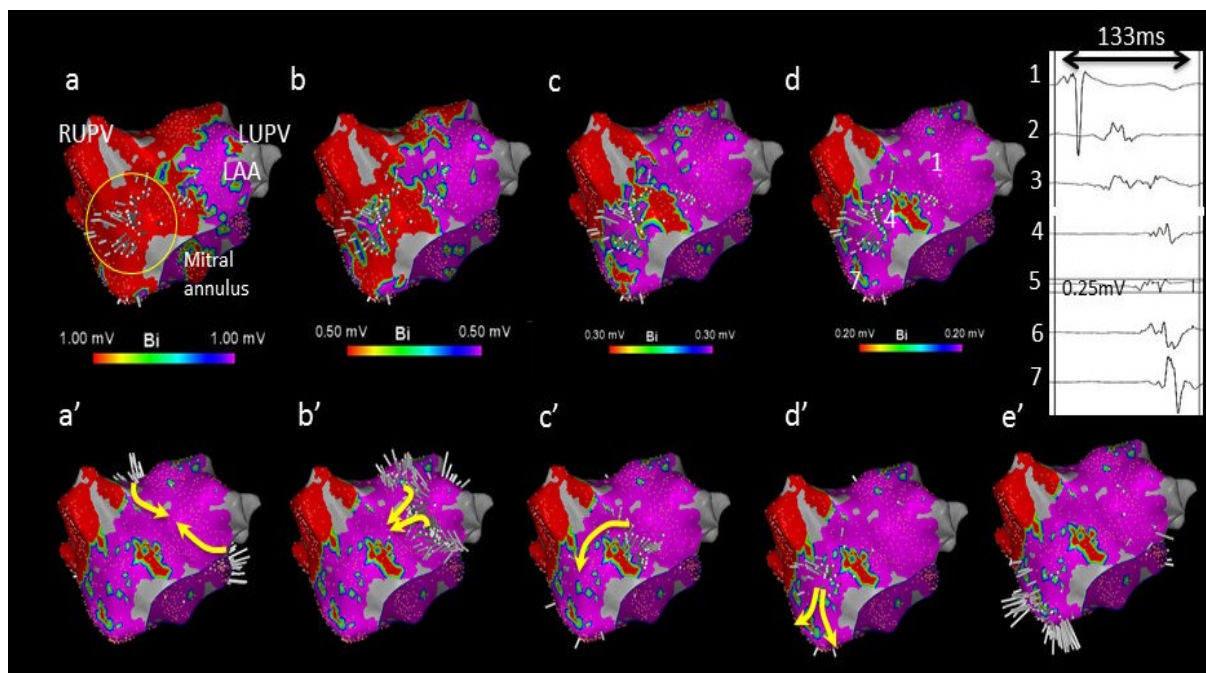


Figure 5-9: (see also video 5.9) Scar thresholding reveals a narrow isthmus of slow conduction

(a-d) The LA bipolar voltage map is displayed in AP. (a) The voltage threshold is set arbitrarily at 1mV with red representing voltage below 1mV and purple representing voltage above 1mV. Ripple bars were seen to propagate within areas of red on the map (yellow circle) and the threshold was progressively reduced (b - 0.5mV; c - 0.3mV; d - 0.2mV) until only those areas with propagating Ripple bars appear as purple. This was achieved at 0.2mV, and demonstrated a narrow isthmus of active tissue bordered on either side by scar. (e) Conduction across this isthmus was slow (133ms, and incorporated (133/250ms) 53% of the tachycardia cycle length, associated with fractionated signals measuring 0.25mV. (a'–e') With the map played at 0.2mV, wavefronts of Ripple activation from the roof and mitral annulus were seen to adjoin on the anterior wall and navigate slowly through this narrow isthmus on the anterior wall, exit near the septum, and continue counter-clockwise around the mitral annulus. Targeting this area of fractionation within the isthmus terminated tachycardia, and avoided the conventional mitral isthmus line.

With RM, grade 1 diagnostic confidence was recorded in n=13 (65%), where the operator felt there was sufficient information offered by the map alone to proceed directly to ablation without entrainment. RM offered the correct diagnosis in n=18 (90%) as determined by termination to sinus rhythm (n=15) or change of AT activation (n=3) post the first planned ablation set. In the 2 patients where the first ablation set guided by RM failed, patient 1 suggested a small circuit around an ASD repair septostomy scar, though ablation adjoining scar-scar sites was unsuccessful. This patient was undergoing their fourth ablation procedure, with extensive low voltage seen throughout both atrial chambers and where entrainment attempts failed to capture in multiple sites. RM in patient 2 directed the operator to a critical site at the roof which entrainment confirmed was part of the circuit, though failed to terminate with a roof line. Further analysis of the Ripple map revealed a small loop circuit around an island of scar immediately adjacent to the roof, which was successfully ablated.

The LAT maps of each case were retrospectively reviewed. LAT maps were considered of Grade 1 diagnostic confidence in only n=6 (30%) and ablation at the site suggested by the LAT map would have been successful in only n=13 (65%).

Table 5-8 summarises the RM and LAT mapping outcomes.

No	Ripple Map		Entrainment Performed *	LAT Map	
	Proposed AT Mechanism  -incorrect/did not terminate	RIPPLE Diagnostic Confidence Grade		LAT Diagnostic Confidence Grade	Proposed AT Mechanism  incorrect/did not terminate
1	1 - Breakout from carina	1		1	1 - earliest activation from carina
2	1 - Complex macro-reentry through scar isthmus on anterior wall	2		3	0 - x2 sites of early activation
3	1 - Dual loop (MI and roof) critical at MI	1		1	1 - Dual loop (MI and roof) critical at MI
4	1 - Mitral isthmus dependent	1		2	1 - MI circuit apparent, though x2 sites of early activation (near LLPV and anterior wall)
5	1 - Small loop around posterior scar	2	*	3	0 - x2 sites of early activation anterior and posterior wall
6	1 - Gap in Roof line	1		3	0 - x2 sites of early activation (near LAA and RPV)
7	1 - Gap in Roof line	2	*	2	1 - Gap in Roof line, though backward wavefront apparent
8	1 - Gap in CTI line	1		2	1 - CTI dependent, though backward wavefront on RA lateral wall
9	1 - Dual loop (roof and mitral) critical in gap at MI	2	*	2	1 - Dual loop (roof and mitral), though backward wavefront at the roof
10	1 - Dual loop (MI and roof) critical at MI	2	*	2	1 - Dual loop (MI and roof) critical at MI
11	1 - Breakout from post. mitral ann.	1		3	0 - x2 sites of early activation (near LLPV and anterior wall)
12	1. Breakout from SVC	1		1	1- Focal from SVC
13	0 - Small loop around septostomy scar	3	*	3	0 - chaotic - widespread low voltage
14	0 - Roof dependence - unable to terminate. Subsequently diagnosed small loop around scar near roof - AT terminated	3	*	3	0 - focal from roof
15	1 - Mitral isthmus dependent	1		2	1 - Mitral isthmus dependent
16	1 - Mitral isthmus dependent	1		2	1 - Mitral isthmus dependent (backward wavefront at early meets late)
17	1 - Breakout from LAA	1		1	1 - Focal from LAA
18	1 - Mitral isthmus dependent	1		1	1 - Mitral isthmus dependent
19	1 - Complex macro-reentry through isthmus near the roof	1		3	0 - Chaotic - multiple early-meets late site
20	1. Breakout from RSPV	1		1	1. Focal from RSPV
Total	Correct: 18/20	G1: 13/20		G1: 6/20	Correct: 13/20

Table 5-8: Proposed AT Mechanism, diagnostic confidence

Operators noted potential sources for diagnostic error with these LAT maps. Figure 5-10 (and video 5-10) illustrates breakout activation near the posterior mitral annulus in which the LAT propagation map incorrectly demonstrated activation moving towards the posterior wall. This was a WOI error whereby the usual practice of selecting the window around the reference signal led to more than one area being incorrectly assigned as ‘early.’ This was only corrected retrospectively once the correct diagnosis from the Ripple map was evident. The operator did not encounter this problem with the Ripple map as it is not dependent on setting a WOI.

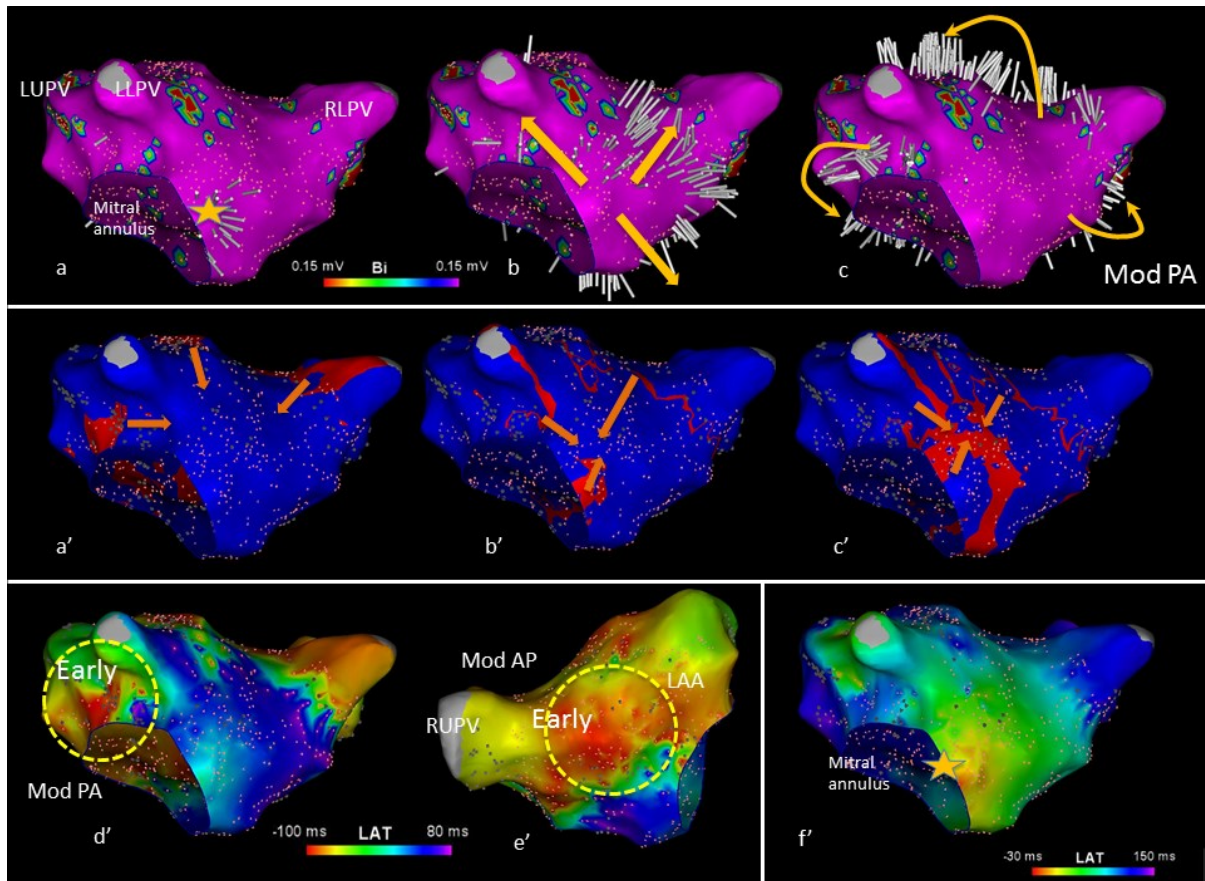


Figure 5-10: (see also video 5-10) RM overcomes LAT WOI errors

(a-c) A modified view of the posterior left atrium is presented. The Ripple Map demonstrates breakout of activation near 3 o'clock on the mitral annulus with wavefronts moving away in all directions. Ablation at the site of breakout changed tachycardia activation. (a'-c') The LAT propagation map incorrectly shows activation (red bands) converging on the posterior wall from all directions. This activation pattern is a consequence of a WOI selection error. (e') This was set around the reference signal (-100ms to +80ms), and several "early" sites are seen on the map. Post procedure, (f') the WOI was adjusted (-30 to 150ms) to display the correct pattern of activation.

An example of a 'backward wavefront' causing error with LAT mapping is shown in figure 5-11 (and video 5-11). In this roof dependent AT circuit, the propagation map appeared to demonstrate 2 wavefronts – the correct roof dependent circuit and a second wavefront moving slowly in reverse. This “backward wavefront” was an interpolation error that occurred at the site where “early meets late” was expected on the LAT display, but where the apparent early and latest activating sites did not actually meet, and interpolation of colours across the rainbow spectrum occurring in between. The Ripple map does not interpolate into unmapped areas so this phenomenon does not occur.

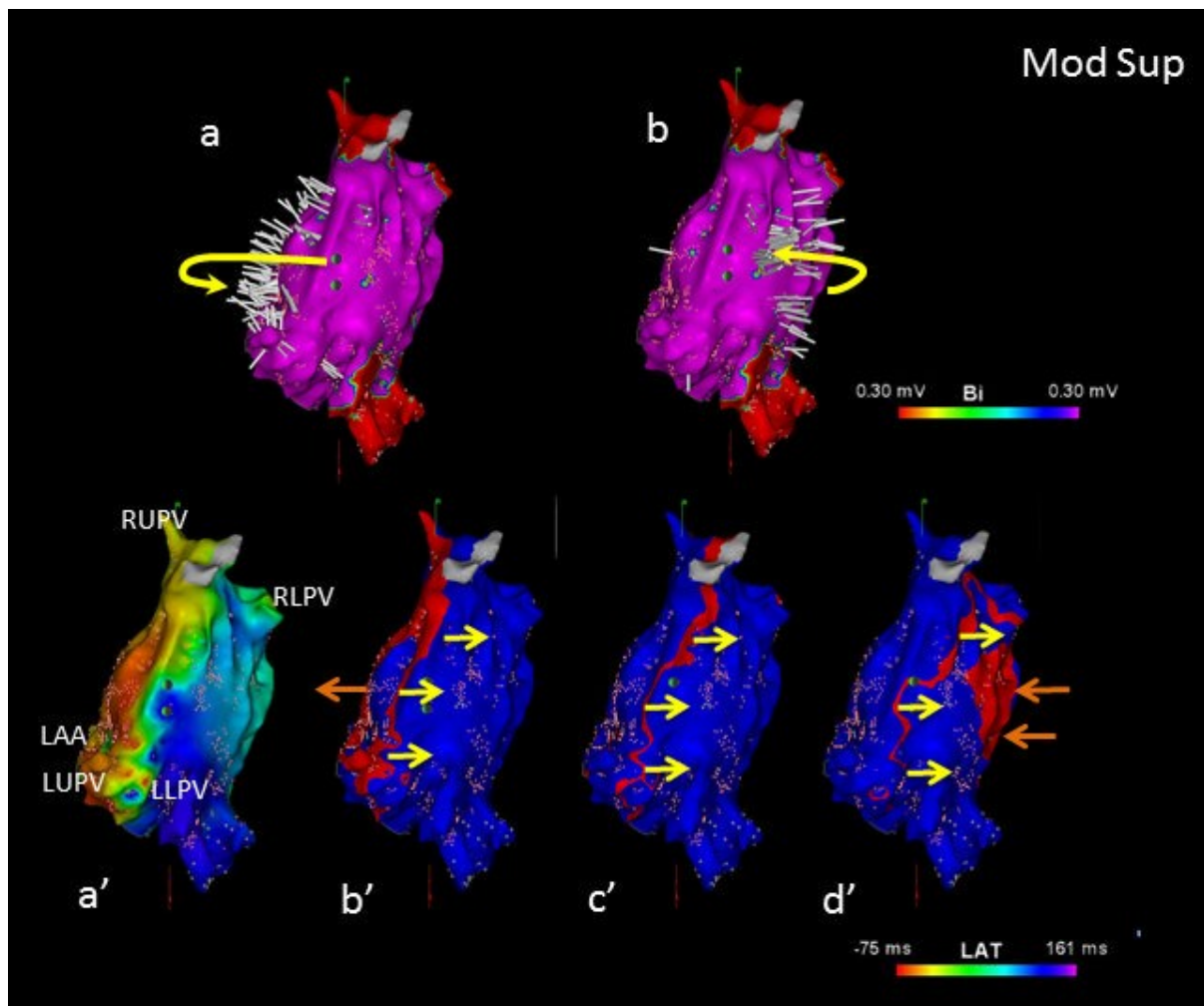


Figure 5-11: (see also video 5-11) Backward wavefront – interpolation error with LAT mapping

The left atrium is presented in a modified superior view with roof enface. (a-b) The ripple map in AT demonstrated a roof dependent macro-reentrant circuit (travelling right-left) between previously ablated PVs. (a') The LAT map showed a large early red patch at the roof with colours moving along the spectrum away from this site in both direction - suggesting focal activation from this roof. (b'-d'). However, the LAT was misleading, as the full cycle length was incompletely mapped, and “early meets late” did not meet. Colour interpolation between the apparent early and latest sites of activation resulted in this backward wavefront on the LAT propagation map.

The voltage map in figure 5-12 (and video 5-12) illustrates considerable low voltage signal along the roof, in a patient with prior roof line ablation. The Ripple Map suggests a roof dependent circuit, and scar thresholding allowed the operator to find an isthmus of recovered conduction with peak bipolar signal of only 0.04mV. This was successfully ablated. The vast low voltage substrate resulted in widespread areas where the system was challenged to annotate LAT, producing LAT propagation maps that were difficult to interpret. As RM displays activation without annotation of activation time, this represents an important advantage of RM in achieving greater diagnostic accuracy.

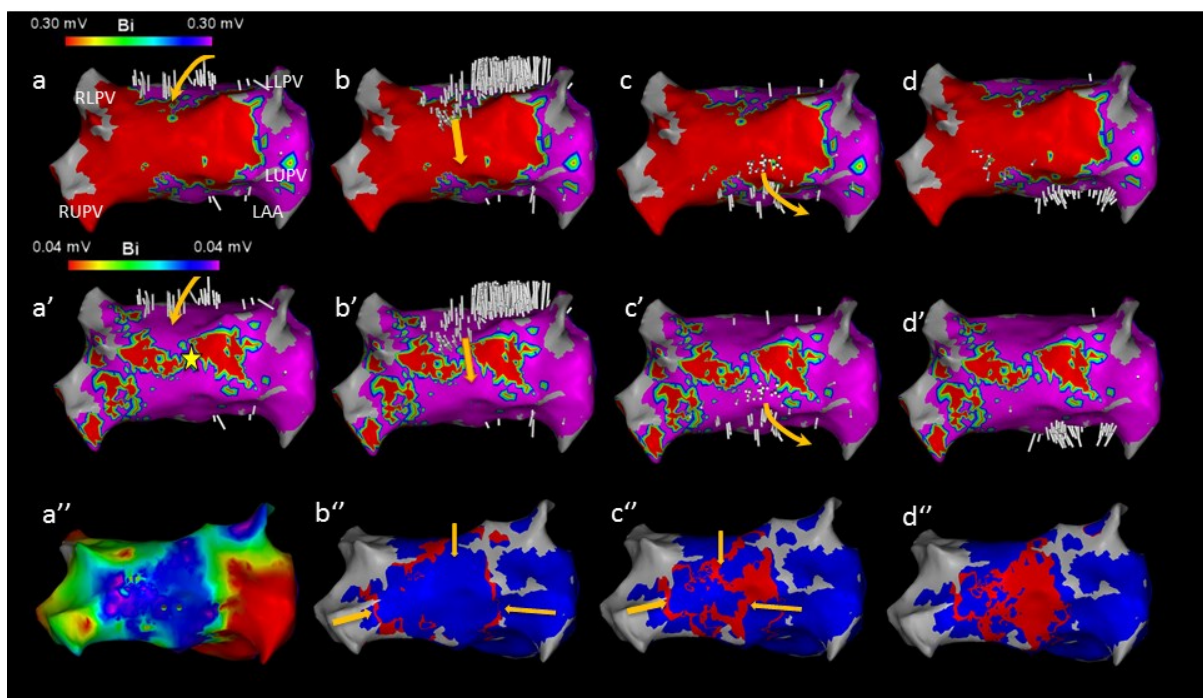


Figure 5-12: (see also video 5-12) RM identified a recovered isthmus of slow conduction at 0.04mV

The superior view of the left atrium is displayed in a patient with previous PV isolation and roof line. (a-d) present the voltage map at 0.3mV. The Ripple map displays a wavefront of tachycardia that ascends the posterior wall, converges within the centre of the roof, and descends the anterior wall. (a'-d') present the same map in the same orientation with voltage at 0.04mV. A gap is seen within the roof line where the ripple bars escape and corresponds to the site of termination of tachycardia post ablation. Owing to the extensive low voltage at the roof, the LAT map appears chaotic (a'') with several early sites on the map and propagation (b''-d'') shows activation converging on the roof.

5.3.4 Discussion

This study demonstrates that RM is an easily adopted and effective mapping technique in scar related AT ablations, and overcomes common limitations of LAT mapping.

RM at a first glance appears very different to conventional mapping methods. Every other mapping system takes the information from an EGM and reduces it, either manually or via an automated algorithm, to a single LAT time or voltage. This transformation may well present an easier dataset to the operator, but also has the risk of misleading the operator. By displaying every EGM deflection at each mapped point, the operator might be overwhelmed by far more visual information. Furthermore, studying propagation over a bipolar voltage map is quite different to conventional practice. In this study, operators experienced in conventional activation mapping and naive to RM were able to adopt an RM guided approach to AT ablation very quickly, accurately, and with high diagnostic confidence.

Adopting any new approach can be challenging, but these centres did not appear to have issues using RM. Whilst high-density point collection might prolong mapping duration, increasing the chance the arrhythmia might change or become unstable, it was performed fairly rapidly in most cases and operators were not unduly affected by collecting data with the map colour-threshold reduced to 5mm. Rapid catheter movement lead to noise artefact on the intra-cardiac EGM that appeared as rogue signals on the ripple map. Generally, operators were able to differentiate these rogue signals from the dominant ripple wavefront. Occasionally, two wavefronts of ripple activation within the same cycle length were observed near the mitral annulus due to atrial activation and far-field ventricular signals, though operators were able to adjust the Ripple Viewer to play a cycle that avoided ventricular signal when AV conduction was 2:1 in tachycardia. In low voltage atria, passive bystander circuits were often observed which did not pose a distraction to following the dominant wavefront. In all cases, by simply being aware of these challenges was enough to avoid diagnostic uncertainty and error.

LAT maps require precise annotation of local activation times within an assigned WOI.²⁰¹ There are inherent limitations in this approach which can lead to error.^{29, 202, 203} Even in this small series of patients, there were cases where the limitations of LAT mapping were evident. Changes in the timing WOI can sometimes completely change the activation pattern, especially when the conduction time is slow across scarred atria. The process of setting this window at the onset of the case is arbitrary, and varies

between centres. RM is not dependent on a WOI so avoids the dilemmas raised by using the concept of 'early' and 'late.'

Interpolation algorithms enable conventional 3D mapping to be used effectively when there are <100 points within a chamber. However, interpolation assumes that activation is uniform between collected points with minimal scar. Multi-electrode point collection reduces the risk of errors from insufficient points, but requires the operator to validate more points and lengthen the analysis time. In propagation maps, interpolation leads to the 'backward wavefront' at sites where "early meets late" do not quite meet, due to interpolation of colours occur between the apparent early and latest sites on the map resulting in a wavefront moving slowly in reverse to the true direction of activation. RM does not interpolate between unmapped sites so is not susceptible to this error.

Complex EGMs within areas of slow conduction can contain a significant portion of the TCL. Incorrect annotation of local activation time, or inappropriate tagging of these EGMs as scar can lead to failure to account for the entire cycle length and mis-diagnosis. LAT annotation algorithms continue to improve and the effect of mis-annotation is minimised in high-density point collection. However, manually checking several thousand points also becomes difficult. RM displays all EGM components on the map and no points need deletion or re-annotation because they don't "fit the diagnosis".

Despite the limitations illustrated with LAT mapping, published data report high success rates in AT ablation.^{63, 85, 190, 204} These were however a combination of combining LAT mapping with entrainment. Activation mapping without entrainment is an ideal, to avoid the chance of pace-termination or degeneration to fibrillation. De Ponti et al developed an approach to LAT mapping alone with high success rates – they described a mathematical formula which set the onset of the WOI in mid-diastole, and covered 90-95% of the TCL.²⁰¹ The interface between early and late identified the correct target site for ablation. However, this formula is only applicable in macro-reentry, something which is unknown to the operator at the start of a clinical case. Where signal was seen outside the limits of the constructed window, manual re-annotation was performed to ensure all signal was contained within the assigned window. In doing so, operators avoided error from the "backward wavefront" as we have seen. Whilst this was feasible in their study with only 100 mapping points collected, it is impractical and time consuming in high density mapping used by current systems.

5.3.5 Limitations

The analysis of LAT maps used in this study was retrospective and unadjusted. Conventionally, operators adjust the annotation of activation time or modify the WOI whilst mapping in areas of uncertainty during a case to make more sense of propagation, hence the clinical benefit of the RM approach over LAT mapping can only be identified during a larger prospective and randomised study. This is described in the next section. Ripple Maps are also unadjusted as they present raw EGM data without the requirement to assign a timing annotation or set a WOI (scar thresholding involves adjustment of the background voltage map, not the Ripple Map), we feel allowing for fair comparison in this study.

5.3.6 Conclusions

Despite presenting activation in an alternative way of visualisation, new users found it easy to apply in post-ablation ATs with high diagnostic accuracy and acute procedural success.

5.4 A randomised multi-centre study comparing Ripple Mapping against Activation Time mapping in Atrial Tachycardia ablation (RIPPLE-AT)

5.4.1 Introduction

The comparative analysis between RM with LAT mapping has been retrospective, using “unadjusted” LAT maps. Conventionally, operators adjust the annotation of activation time or modify the WOI during a case to make more sense of propagation. To more accurately determine the effectiveness of RM in scar related tachycardia over conventional mapping, a randomised and prospective study was planned. To avoid bias from single centre expertise, the study was conducted as a multi-centre trial (RIPPLE AT). This study tested the hypothesis that RM is superior to LAT mapping in diagnosing the mechanism of scar related AT and guiding the delivery of RF ablation.

5.4.2 Methods

5.4.2.1 Endpoints

This study aimed to compare the effectiveness of RM against conventional activation time mapping as determined by:

- The operator’s confidence in the diagnosis of the mechanism of atrial tachycardia from their first map collected.
- The percentage of cases where the tachycardia changed/terminates with first ablation set after map categorisation.
- The dependence on entrainment mapping to make a diagnosis.

The primary endpoint for the study was the % of correct diagnosis, as determined by tachycardia change/termination with the first ablation set, and the operator diagnostic confidence. The first ablation set encompassed all the ablation lesions delivered to target the AT diagnosis based on the studied activation map.

5.4.2.2 Approvals

This study was open to the same centres involved in the initial prospective studies, each with extensive experience of 3D mapping of ATs, and using the CARTO Confidense™ module for multi-electrode mapping, and now experienced in RM in AT (see section 5.3.2.1). The Study Coordination Centre obtained Ethical approval to conduct the study in the United Kingdom. Sponsorship was granted from Imperial College Healthcare. Peer review of the protocol from 2 independent experts in the field was obtained prior to commencements. Site Specific Assessment (SSA) was obtained for each participating UK NHS Trust site. Independent local ethical approval was granted for the Portuguese site. The study was registered on clinicaltrials.gov (NCT02451995) before recruiting the first patient.

As before, patients with documented AT post previous left atrial ablation were recruited in the study. Patients were block randomised into an unblinded 1:1 mapping design of either RM or LAT mapping to guide ablation. Randomisation was performed via a sealed envelope and block of 20. Patients with typical flutter, a contraindication to catheter ablation or those who might be unable to give informed consent were excluded. The procedural setup and settings for data collection/Ripple Map analysis are as described previously. As patient recruitment was proving slow, inclusion criteria was broadened to include patients with previous cardiac surgery, advanced valvular disease or structural heart disease where low voltage substrate was likely to be seen.

5.4.2.3 Prospective LAT mapping approach

The WOI was set from the start, spanning between 90%-100% the tachycardia cycle length and either around the reference signal or the surface p wave as per operator preference. In order to avoid bias from differences in sampling density between the different mapping approaches, the same method for data collection was applied for all patients. Therefore, the colour threshold was consistent at 5mm, and the same automated ConfiDENSE point collection criteria were used including 1) cycle length stability within a 5% range of the tachycardia cycle length, 2) electrode position stability within 2mm, 3) LAT stability of 3ms, 4) and tissue proximity to the endocardial surface. During map acquisition, the LAT and bipolar voltage map was displayed and the Ripple map remained hidden to all lab staff. All the advances to activation time mapping incorporated within the CARTO3V4 ConfiDENSE module were available to operators. Automated annotation of activation timing was assigned using the Wavefront algorithm to the maximal negative distal unipolar derivative contained within the relevant bipolar activation time. In the absence of a sharp negative slope $>0.03\text{mV}$ in unipolar signal, a grey square was projected as the system could not automatically assign LAT. After all points were collected, the static LAT map and

propagation maps were reviewed. The Map consistency filter was used to highlight points with inconsistent timing to its neighbouring points for review and manual re-annotation or deletion as required. Operators were able to adjust the WOI as required using the automated recalculation function.

A diagnosis was made using the mapping arm assigned and these were later classified using the diagnostic confidence grading system previously described in section 5.2.2.4, and a strategy for ablation was planned. Grade 3 diagnostic confidence was considered where a diagnosis could not be made, or if ablation failed to interrupt the tachycardia circuit. Importantly, to differentiate between a failure of mapping from a failure of ablation, if entrainment confirmed the tachycardia mechanism, the mapping diagnosis was considered correct even if the tachycardia failed to terminate with ablation.

Cases where the tachycardia was non-inducible or terminated prior to full map collection were excluded from analysis. Operators were free to continue mapping and performing ablation in the patient's best interests. If the tachycardia changed prior to the first ablation set, or in the event of a grade 3 diagnosis, operators were able to proceed as per individual preference. The study protocol was applied only to the first map collected and first ablation set delivered. If the tachycardia changed to a new circuit, operators were allowed to adopt any mapping approach. No long-term follow up data was collected.

5.4.2.4 Statistics

Sample size: Our initial multi-centre experience demonstrated a diagnostic yield using RM compared to standard CARTO activation maps of 90% vs. 65%. Assuming the same outcome measures, in order to detect a difference between arms with 80% power, at the 5% two-tailed significance level, this would require at least 40 patients in each group. (<https://www.sealedenvelope.com/power/binary-superiority/>).

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median (lower quartile – upper quartile) for non-parametric data. Categorical data were analysed using a fishers exact test. Unpaired data were analysed using a Student's T-test for parametric data. A two sided p value was determined where applicable and a value of $p \leq 0.05$ was considered significant.

5.4.3 Results

An interim data analysis halfway through the study was performed to assess the quality of the study design. All study sites contributed data to the interim analysis.

A total of 40 patients have been studied. Table 5-9 summarises the previous history and mapping data from these cases.

A further 20 patients have been recruited but did not contribute any data to the primary outcome for the following reasons:

- 10 patients presented in sinus rhythm on the day of the procedure and remained non-inducible for regular sustained tachycardia despite burst pacing and programmed atrial stimulation testing.
- Tachycardia terminated during first map collection in a further 5 patients.
- Tachycardia degenerated to AF either during pacing or during map collection in 3 patients.
- A further 2 patients were found to have left atrial appendage thrombus on pre-procedural trans-oesophageal echocardiography despite continuous anticoagulation up until 2 days prior to the procedure.

LAT Mapping					Ripple Mapping				
Pt	Site	Previous ablation Hx	Chamber	Points	Pt	Site	Previous ablation Hx	Chamber	Points
1	1	1. PVI, Roof, CFAE	L	5049	1	1	1. PVI. 2. Redo PVI + MI + CFAE + CTI	L	2877
2	1	1. PVI + MI, 2. Redo PVI, 3. CTI	L	3243	2	1	1. PVI. 2.Redo PVI + Roof + Floor line + CFAE + CTI	L	4302
3	1	1. CTI. 2. PVI. 3. Redo PVI	L	1979	3	2	1. PVI, 2. Redo PVI 3. Redo PVI + Roof + MI + CTI	L	2681
4	1	1. PVI, 2. Roof + MIG	L	4409	4	2	1. CTI 2. PVI + Roof + MI + CFAE	R	3551
5	1	1. PVI + Roof + MI + CFAE	L	3228	5	3	1. CTI, 2. RA flutter. 3. Left AVRT	L	1725
6	1	1. PVI + CTI 2. Ant wall	L	1338	6	1	1. CTI. 2. Left sided PVI + MI	L	1164
7	3	1. PVI, CTI	R	895	7	1	1. PVI + Roof + MI + floor + LA isthmus + CFAE. 2. CTI	L	4304
8	3	Nil	R	2852	8	4	HCM	L	2640
9	1	1. Surgical MV repair, 2. CTI, 3. PVI, 4. PVI + CFAE + MI + LAA	L	1756	9	4	1. PVI + CTI + Roof + LAA	L	2405
10	1	1. ASD patch repair. 2. CTI line	R	4887	10	1	1. PVI + CTI + Roof + MI	L	2068
11	5	1. Nil. Moderate MS	L	3910	11	5	1. PVI + Roof + MI + Posterior	L	2836
12	6	CTI line x2	R	3118	12	3	1. Surgical PVI 2. RA focal	R	429
13	6	PVI, Roof, CFAE	L	3118	13	2	1. PVI 2. PVI and mitral and CFAE 3. Roof	L	3504
14	5	1. PVI and CTI	L	3221	14	6	1. PVI + Roof + Posterior line. 2. Redo PVI + CTI	L	2650
15	5	Nil. Mod AS	L	1312	15	6	1. PVI	L	2630
16	2	1. CTI, 2. PVI, 3. PVI	L	2437	16	2	Nil	R	2201
17	1	1. PVI 2. PVI + Roof	L	5990	17	6	Nil		2640
18	1	1. PVI. 2. Line from LAA to MA	L	3118	18	5	1. PVI (nMARQ)	L	5004
19	6	1. PVI. 2. MI line	L	1879	19	5	CABG	L	1675
20	5	Mitral Valvuloplasty	L	4625	20	2	PVI	L	1560

Table 5-9: Baseline Ablation history and mapping data

Table 5-10 summarises the patient demographics and procedural outcomes from the first 20 patients in the LAT Mapping cohort. Most patients (age 68 ± 7 yrs, male $n=11$) had undergone at least 1 previous left atrial ablation. High density maps (3118 ± 1461 points) were collected in AT (cycle length 254 ± 48 ms). Macro-reentrant tachycardia was identified in $n=12$ (60%). Focal tachycardia was diagnosed in $n=4$ (20%). Small rotatory circuit within the atrial body were identified in the remaining $n=2$ (10%). The mechanism was unclear in $n=2$. Grade 1 diagnostic confidence was recorded in $n=8$ (40%), where the operator felt there was sufficient information offered by the map alone to proceed directly to ablation without entrainment. LAT offered the correct diagnosis in $n=13$ (65%) as determined by termination/change of AT activation post the first planned ablation set. Figure 5-13 illustrates a grade 1 LAT map.

LAT						
Pt	AT mechanism	Ablation site	Grade	Entrained	Correct Dx	Comments
1	Gap reentry - Roof	Roof gap	3	1	0	Crossed over to RM. Also suggested roof dependence. Entrainment unclear. DCCV. Roof not blocked
2	Focal - anterior LA	Earliest activation site	3	1	0	Crossed over to RM. Breakout from anterior LA. Entrainment unclear. DCCV.
3	Macroreentry - Roof	Roof line	1	0	1	Nil
4	Gap reentry - Roof	Roof line	1	0	1	Nil
5	Localised reentry - anterior wall	Fractionated EGM within small loop	1	0	1	Nil
6	Focal - PV	Earliest activation site	2	1	1	Nil
7	Gap reentry - CTI	CTI gap	2	1	1	Nil
8	Focal - TV annulus	Earliest activation site	1	0	1	Nil
9	Unknown	Nil	3	1	0	Crossed over to entrainment. Dx localised reentry from MI line. RM not used
10	Focal - RA free wall	Earliest activation site	3	1	0	Crossed over to RM - gap in previous CTI line, terminated RF
11	Dual loop reentry - Mitral annulus and posterior scar	Isthmus ablation (MI and posterior wall)	1	0	1	Nil
12	Macroreentry - CTI	CTI gap	3	1	0	Crossed over to RM - breakout adjacent to the CTI line, terminated RF
13	Macroreentry - mitral	Mitral line	1	0	1	Nil
14	Macroreentry - Roof	Roof line	1	0	1	Nil
15	Macro-reentrant circuit - RPVs	Critical isthmus inside scar on anterior wall	2	0	1	Nil
16	Unknown	Nil	3	0	0	Crossed over to RM - roof dependent. Terminated with RF
17	Gap reentry - Roof	Roof gap	1	0	1	Nil
18	Gap reentry - anterior line	Gap ablation	2	1	1	Nil
19	Gap reentry - mitral	Gap in MI line	2	1	1	Nil
20	Localised reentry at the posterior wall	Posterior box	3	1	0	?

Table 5-10: LAT outcome data

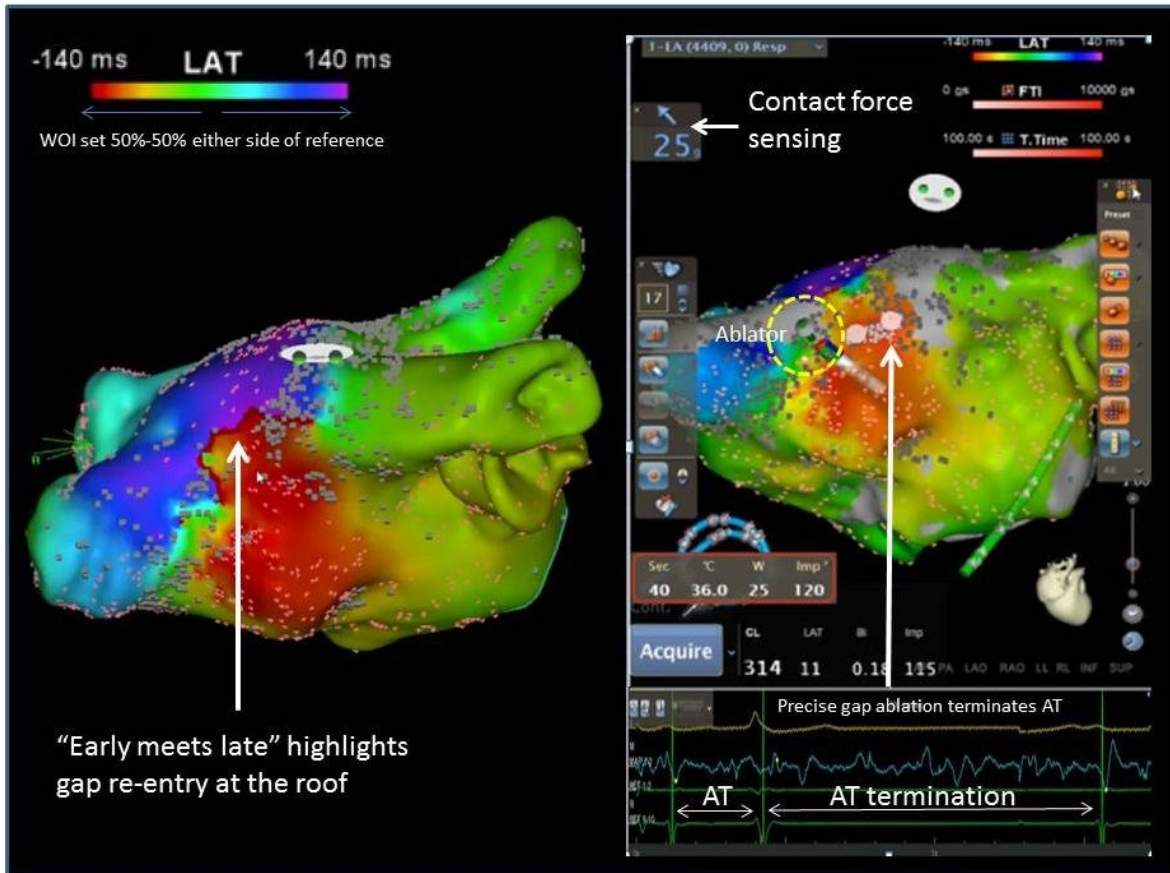


Figure 5-13: Grade 1 LAT map.

LAT map collected in a stable AT (280ms) post Cryo PVI for PAF, roof line and mitral lines of a subsequent AT. A total of 4409 points were collected using the Lasso Nav multipolar catheter in the left atrium. These points were annotated automatically using the Wavefront algorithm which annotates to the maximum unipolar derivative in the bipolar EGM. Small grey squares on the map represent sites of extremely low voltage <0.03mV where no bipolar signal exists for unipolar annotation. Areas with bipolar voltage <0.05mV have been automatically labelled “scar” and greyed on the background colour. The WOI time has been 50% either side of the reference signal. The Map consistency algorithm has identified all inconsistent points which have been either re-annotated manually, if a clear signal is apparent or deleted. The “early meets late” function has highlighted a region where “head meets tail” at the roof, and propagation was consistent with gap reentry through the prior roof line. This was diagnosed with grade 1 confidence. Irrigated contact force ablation (25W) achieving contact force between 10-30g (highlighted on the CARTO workstation) was delivered at the roof just inferior to the “early meets late” line, precisely closing the gap and terminating AT.

There were 7/20 (35%) mapping/ablation failures in the LAT arm. Some of these were a result of interpolation errors from the backward wavefront and assigning annotation in regions of extensive low voltage. Changing to the Ripple Map determined the correct diagnosis in some of these cases resulting in tachycardia termination with ablation. An example of LAT error is presented in figure 5-14.

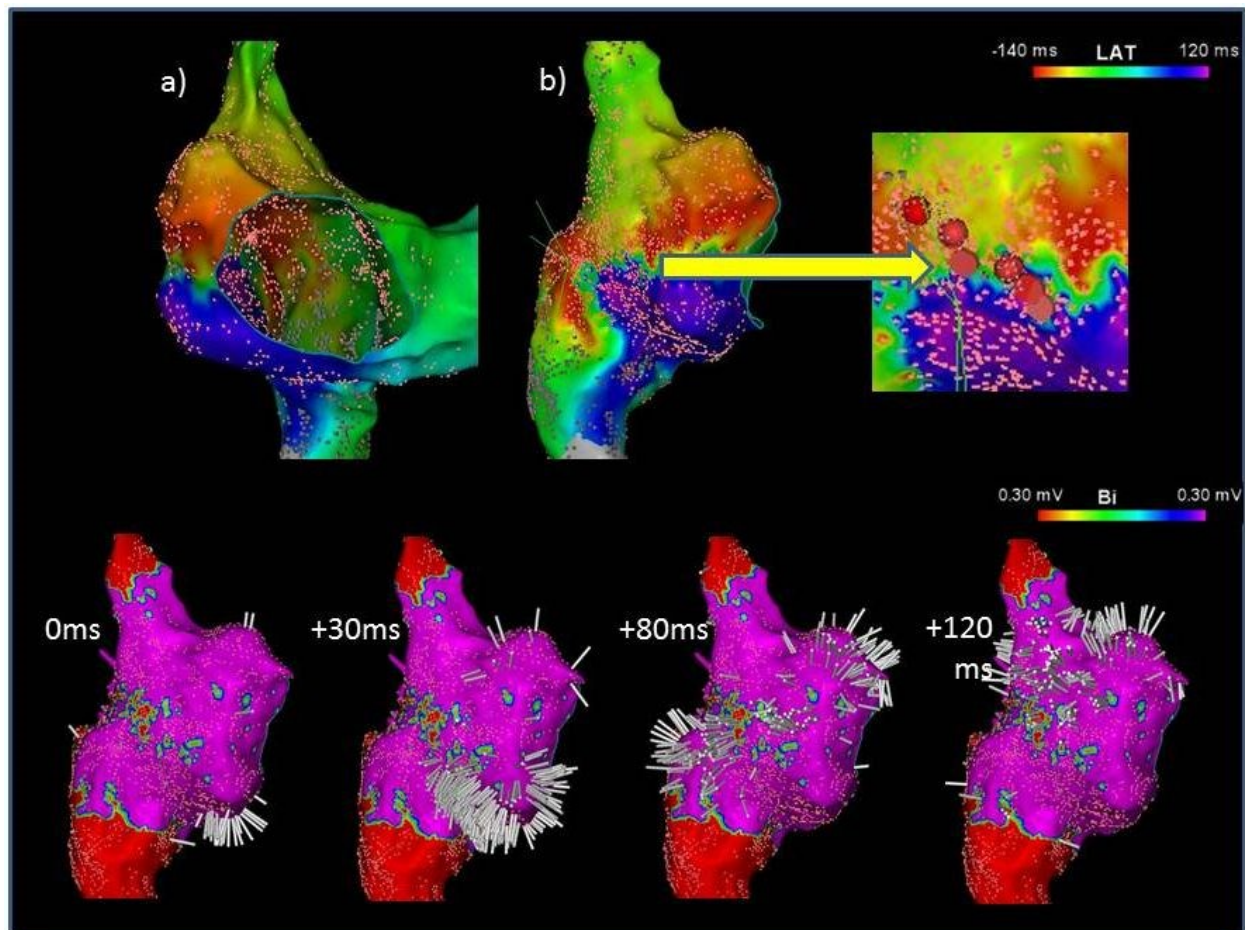


Figure 5-14: Grade 3 LAT map resolved by Ripple map

A patient with persistent left sided SVC and a secondary coronary sinus underwent ablation for sustained AT. He had undergone prior CTI line for typical flutter. The patient was randomised to LAT mapping. A total of 4907 points were collected using ConfiDENSE mapping and annotated using Wavefront algorithm. On the basis of the LAT map (a and b) the operator recognised that conduction was still apparent across the CTI, but diagnosed a focal/localised reentry from the lateral RA wall. This was based on a large area of “red” denoting early activation with colours in according to the rainbow spectrum moving away from this site. Ablation at this site was ineffective. The patient crossed over to RM which demonstrated (0 – 120ms) activation moving progressively up the lateral wall, and overall clockwise flutter. Ablation at a gap within the CTI terminated tachycardia. Misdiagnosis occurred due to the backward wavefront observed within the LAT map due to colour interpolation where early meets late.

Table 5-11 summarises the patient demographics and procedural outcomes from the first 20 patients in the RM cohort. Almost all patients (age 64 ± 8 yrs, male $n=15$ (75%)) had also undergone at least 1 previous left atrial ablation. There was no difference in the number of points collected between the mapping strategies (RM: 2643 ± 1209 points) ($p=0.33$), or the ATCL (278 ± 81 ms) ($p=0.32$). The ripple map scar threshold was determined in each case (0.19 ± 0.09 mV). Isthmus dependent macro-reentrant tachycardia bordered by scar or anatomical boundaries were identified in $n=12$ (60%), of which $n=4$ navigated through a residual narrow gap from a previous ablation line. Breakout activation was identified in $n=4$ (20%), which arose from regions of scar. Small rotatory circuits around islands of scar within the atrial body were identified in $n=3$ (15%). The mechanism was uncertain in $n=1$. Diagnostic confidence using RM was numerically greater than with the LAT map. Grade 1 diagnostic confidence was recorded in $n=13$ (65%) RMs. The correct diagnosis was offered more with RM than the LAT maps ($n=18$, 90%, $p=0.12$). Figure 5-15 illustrates a grade 1 Ripple map of localised reentry.

Ripple Mapping							
Pt	Scar Threshold	AT mechanism	Ablation site	Grade	Entrainment	Correct Dx	Comments
1	0.06	Localised reentry - anterior wall scar	Isthmus between scar and MA	2	1	1	Nil
2	0.08	Localised reentry - posterior wall scar	Narrow scar Isthmus	1	0	1	Nil
3	0.04	Gap reentry - roof	Roof Gap	1	0	1	Nil
4	0.2	Gap reentry - CTI	CTI gap	1	0	1	Nil
5	0.15	Breakout – post MA	Earliest ripple bar	2	1	1	Nil
6	X	Unknown	MI Gap + R PVI	3	1	0	Crossed over to LAT – uninterpretable. Bump terminated where mechanism unclear
7	0.08	Gap reentry - Mitral	Mitral gap	2	1	1	Nil
8	X	Unknown	Nil	3	1	0	Crossed over to LAT - uninterpretable. Entrainment unclear. DCCV
9	0.2	Macro-reentrant - MI	Mitral isthmus line	1	0	1	Nil
10	0.3	Gap reentry - Mitral	Mitral gap	1	0	1	Nil
11	0.2	Localised reentry - posterior wall scar	Narrow scar Isthmus	1	0	1	Nil
12	0.3	Breakout – SVC	Earliest ripple bar	1	0	1	Nil
13	0.2	Dual loop - roof and Mitral	critical isthmus in mitral	2	1	1	Nil
14		Macroreentrant - MI	Anterior MI line	2	1	1	Nil
15		Macroreentrant - roof	Roof line	1	0	1	Nil
16	0.3	Breakout – SVC	Earliest ripple bar	1	0	1	Nil
17		Breakout - tricuspid annulus	Earliest ripple bar	1	0	1	Nil
18	0.3	Atypical macroreentrant	Isthmus line from RSPV to anterior MA	1	0	1	Nil
19	0.3	Gap reentry - Roof	Roof Gap	1	0	1	Nil
20	0.15	Macroreentrant - roof	Roof line	1	0	1	Nil

Table 5-11: Ripple Mapping outcome

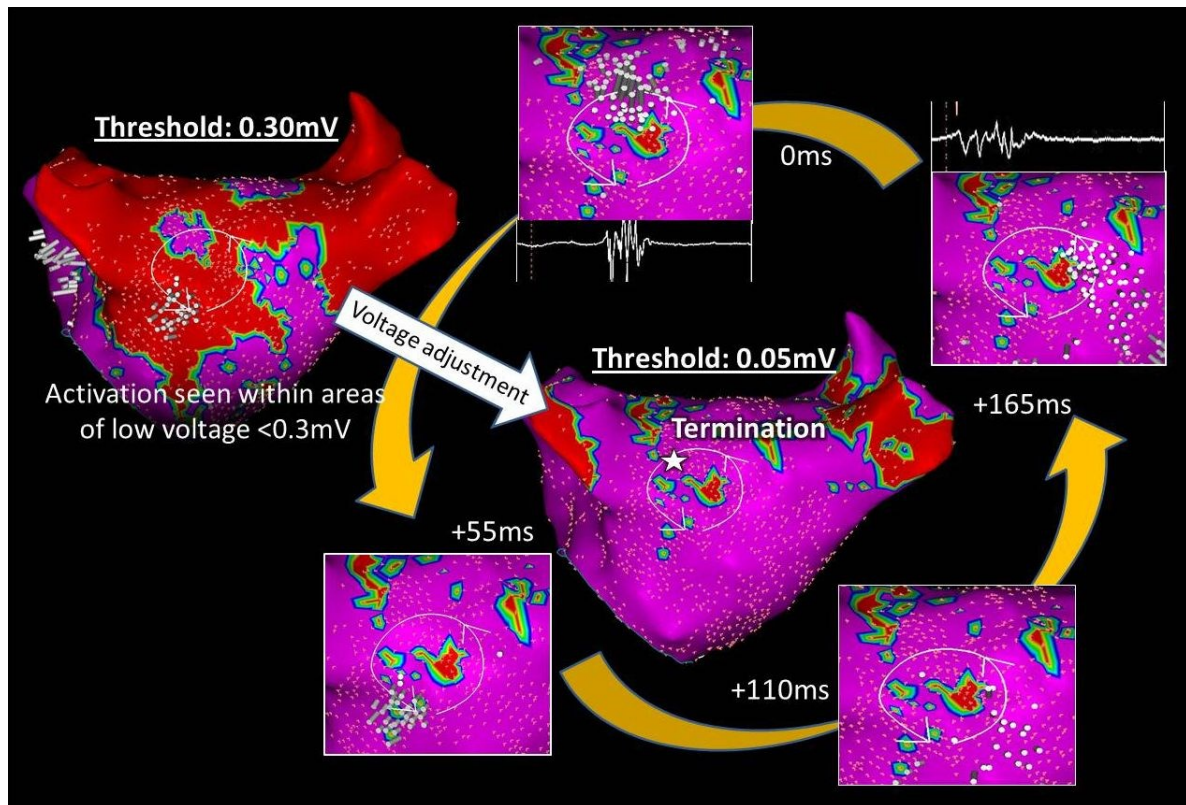


*Figure 5-15: Grade 1 Ripple Map – localised reentry
Adjusting voltage threshold reveals counter-clockwise activation around an island of tissue <0.05mV supporting the full TCL (220ms).*

The 2 failures of RM occurred in cases of patient with extensive low voltage substrate, where the LAT map was interpretable and entrainment failed to capture in multiple sites.

Finally, there was a case of a patient originally randomised to the LAT arm, who crossed over to RM, where both mapping modalities were unable to guide the operator to determine the AT diagnosis (figure 5-16). This was consequent to the limited resolution inherent within the catheters and CARTO system whilst mapping within areas of very low voltage.

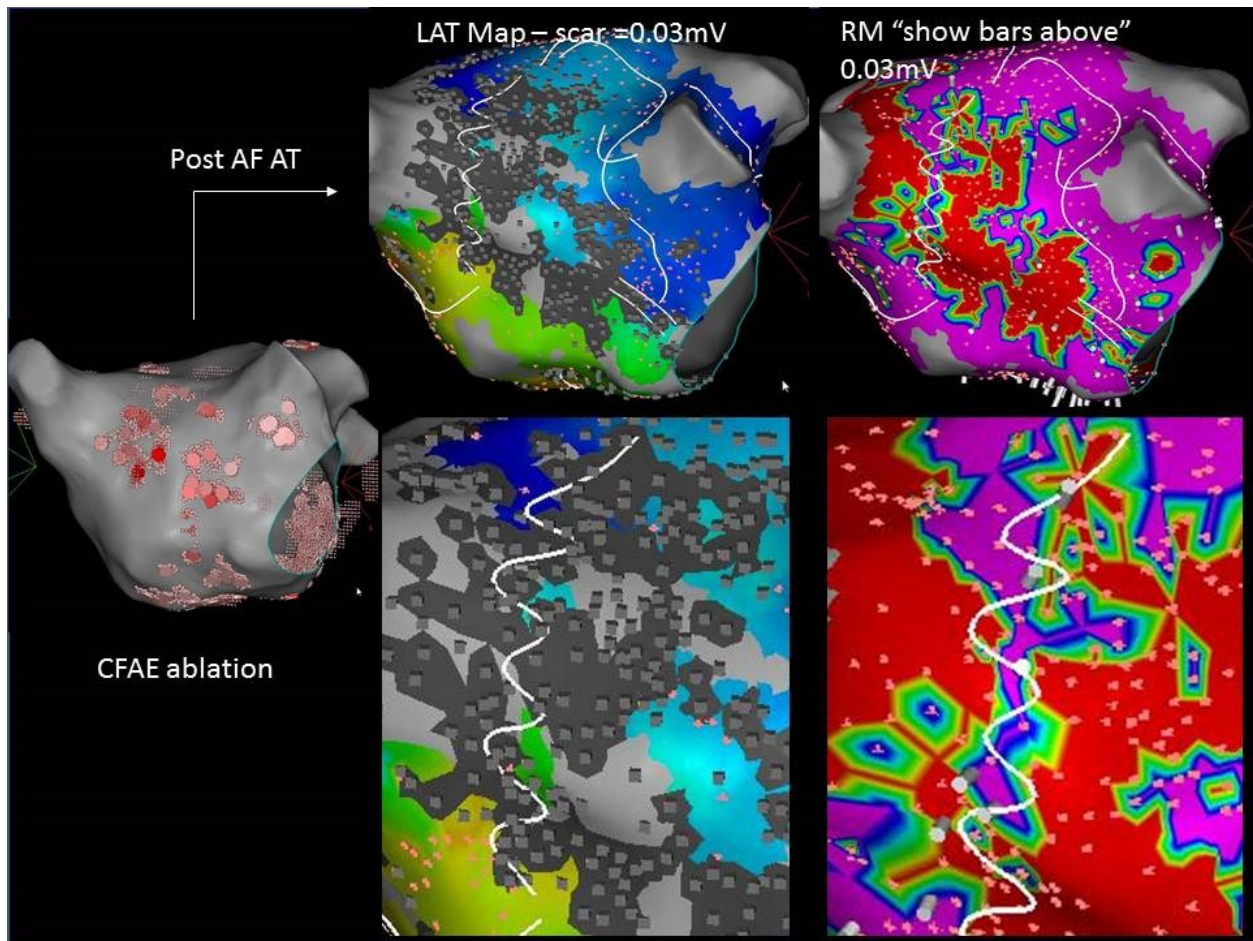


Figure 5-16: Limitation of CARTO mapping resolution

A patient with prior PVI and CFAE ablation underwent mapping for a stable AT. Prior CFAE ablation had been delivered extensively on the anterior wall (displayed on a grey anatomical geometry as red disks), leading to extensive area of very low voltage tissue on the anterior wall. Despite 2600 points collected with a multipolar (Lasso) catheter, both LAT mapping and RM failed to guide the operators to determine the correct mechanism of the mapped AT. The correct diagnosis was eventually diagnosed as roof dependent following extensive entrainment manoeuvres around both left atrial chamber. The pattern of AT activation in light of all mapping modalities is illustrated with design lines. The LAT map had been manually adequately adjusted, including re-annotation at areas of inconsistent timings and resetting the WOI where local signals spanned the border of early meets late. Both maps demonstrated activation moving up the anterior wall from the septum, colliding with an area of scar from previous CFAE ablation. Owing to insufficient mapping resolution associated with low point density and EGM amplitude, it was unclear whether activation conducted through the scar around the roof or was blocked. The LAT map demonstrated scar as grey set below 0.03mV. The Ripple Map shows bars only above 0.03mV. Tachycardia terminated with a conventional roof line – in retrospect, Ripple activation could be seen travelling through the scar (bottom right), though operators had considered this signal as noise.

5.4.4 Discussion

This study describes the interim analysis of Ripple-AT, a randomised multi-centre comparative study between RM and LAT mapping mostly in scar related AT. Performed halfway through recruitment, the study design, randomization process, and data entry appears effective to draw early conclusions between the mapping modalities. Although the numbers in each arm of the study are currently small, the proposed powering for superiority appears reasonable.

Our earlier studies that compared the two mapping modalities, including our offline studies on the CARTO XP, and the initial prospective studies on CARTO3v4 demonstrated statistical superiority with RM, which has yet to be observed in this randomised study.^{124, 191} Whilst this may be due to the current sample size, this is more likely secondary to the prospective nature of this study, where operators can adjust the LAT maps to avoid potential sources of error during the mapping process. Our prior comparisons used unadjusted LAT maps, under the premise that Ripple Maps are not adjusted during the mapping procedure either. Whilst this may be true, the process of adjustment within the CARTO system has been made extremely efficient, including rapid adjustment of the WOI, and the ability to highlight outlier points that appear inconsistent in timing to its neighbouring points. As evident in this study, this has improved the diagnostic yield and accuracy with LAT mapping compared to what we had observed previously. Nevertheless, the success rate of 90% in the RM cohort compared with 65% in the LAT cohort already highlights the potential superiority with RM.

Ripple AT is the first randomised study comparing two different mapping modalities based on the outcome of the first ablation set delivery. Even at this stage of the study, ineffective ablation has been delivered by operators who mis-diagnosed the backward wavefront as a source of focal activation. Importantly, having failed conventional mapping, the protocol allowed cross-over to RM, where the correct diagnosis was made.

The resolution of a mapping system is dependent upon the electrode size and inter-electrode spacing of the recording catheter, and the sampling density allowable within the mapping system. There were cases where both local activation time mapping and RM were unable to guide the operator to determine the tachycardia mechanism, and this was likely a failure of the resolution available within the CARTO system itself. In chapter 4, we described the use of the Rhythmia ultra high density mapping system.

Whilst effective in optimising EGM resolution, it was still limited by many of the limitations inherent within LAT mapping. The integration of ultra-high density and increased EGM resolution with RM into future versions of the CARTO system may overcome this challenge.

5.4.5 Limitations

No firm conclusion can yet be drawn from this study owing to the current small sample size. This study gives an insight into the surprisingly high frequency of elective ATs listed for ablation that are either non-inducible or terminate during map collection, both of which prohibited analysis in the study.

5.4.6 Conclusions

In this early interim analysis, RM has demonstrated potential for superiority in mapping scar related ATs when compared to LAT mapping.

5.4.7 Summary

This chapter describes a mapping algorithm to integrate Ripple Mapping into CARTO3v4, and prospectively tested it in post ablation ATs. We found that RM was able to overcome some of the limitations of activation mapping using local activation time. This chapter also describes a novel method of differentiating scar from conductive tissue during tachycardia and this helped guide AT ablation delivery with high diagnostic success, reproducible in a multicentre study. Halfway through a randomised study comparing RM with LAT mapping in AT, RM has already been able to determine the AT mechanism and optimal site of ablation in cases where AT has failed. Using these experiences and skills learned from Ripple Mapping within atrial scar, we moved on to prospectively study the use of RM in ventricular scar.

Chapter 6

6 Ripple Mapping within ventricular scar

In chapter 3, the arrhythmic substrate within ventricular scar was broadly characterised within regions of the map with EGMs <1.5mV. Ablation was delivered around the borderzones of these low voltage regions, and at any fractionated or late potential sites. However, despite robotic support to increase catheter stability during ablation, recurrence rates were high and comparable to other studies, suggesting that our ablation targets needed to be refined.

The arrhythmic substrate is known to be organized within slowly conducting channels travelling between islands of unexcitable myocardium, and detailed studies of EGMs within ventricular scar have demonstrated how slow conduction is inter-connected within channels of late potentials with increasing conduction delay. These channels are considered a more specific target for substrate ablation.¹²⁶ This chapter describes the application of RM to define these channels as a guide to ablation.^{126, 127}

6.1 A Prospective Study of Ripple Mapping the Post-Infarct Ventricular Scar to guide Substrate Ablation

6.1.1 Introduction

We had previously described how RM can be used to identify slow conduction channels within ventricular scar in a retrospective offline Matlab study.¹²⁸ In this prior study, we defined a channel by the presence of 4 features:

- (1) Sequential movement of 3 evenly spaced ripple bars entering the scar from the scar border zone with progressive LAT.
- (2) Presence of fractionated signals/ double potentials.
- (3) A higher bipolar voltage within the channel bordered by lower voltage in the surrounding tissue
- (4) Onset of EGM activation late within the QRS and spanning beyond the QRS.

RM was subsequently integrated into a research module in CARTO3v4 for prospective testing. On the basis of our experiences during the first few prospective cases, it became apparent that our previous definition of a channel was inaccurate. This was considered for the following reasons:

- 1) The maps had been collected with a colour threshold of 10mm - when applied prospectively, this resulted in widespread absence of data.
- 2) The average length of a channel is known to be several centimeters in length - 3 points was insufficient to define a channel.
- 3) Only one fractionated or late potential was required to define a channel - studies following inter-connected EGM activation within scar have demonstrated all EGMs are fractionated or late, with increasing local activation delay
- 4) Far-field activation wavefront rather than local signal had been erroneously studied
- 5) Local activation within the QRS was ignored.

Therefore we had to revisit our approach to defining channels. Ripple bars of a typical bipolar EGM from an area of functional myocardium within ventricular scar is shown in figure 6-1. The EGM is composed of two components: a far-field component from the bulk of ventricular myocardium surrounding the scar (generally higher amplitude, lower frequency), followed by a delayed component from local tissue.

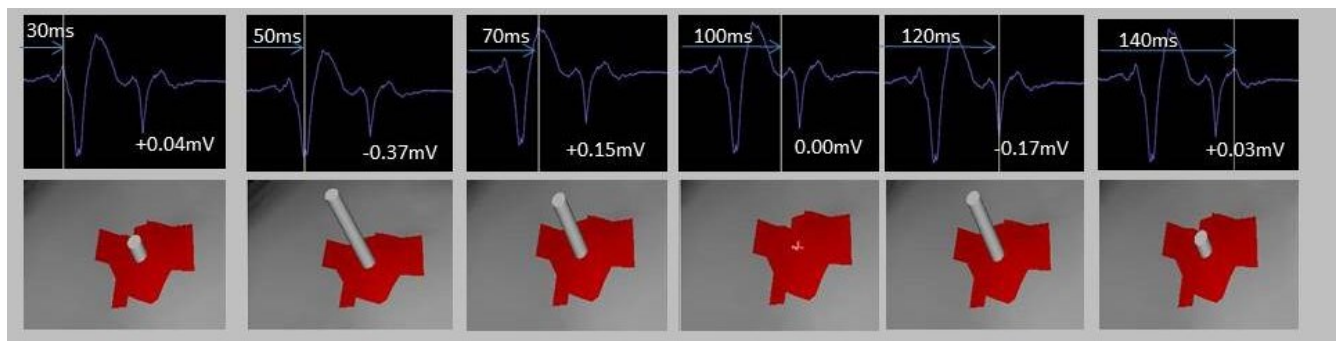


Figure 6-1: Ventricular EGM

A bipolar EGM (400m/sec sweep speed) collected within ventricular scar is displayed. The EGM contains 2 components. The initial component is a likely far-field signal (either epicardial or surrounding healthy tissue). The second component likely represents delayed local activation (late potential). Six time frames from the Ripple Map are displayed (1-3 occur during far-field signal; 5-6 occur during the local signal). The Ripple bar for each time point is seen, overlying a CARTO voltage colour. The height of the bar reflects the voltage amplitude at that time point. Negative deflections are displayed as an upward moving bar such that no component of the EGM is lost.

Substrate mapping relies upon differentiation of the local from far-field components. When multiple EGMs within ventricular scar are reviewed using RM, two wavefronts might be seen: an initial far-field wavefront that occurs in tandem with bars in the surrounding healthy tissue, followed by a delayed wavefront of local activation (figure 6-2, and video 6-2). We therefore redefined an RM Conducting Channels (RM-CC), as a channel of sequentially moving adjacent bars representing local activation within scar, distinct from the initial far-field wavefront. In this study, we describe how RM was used prospectively to study this local activation through the scar as a guide to substrate ablation.

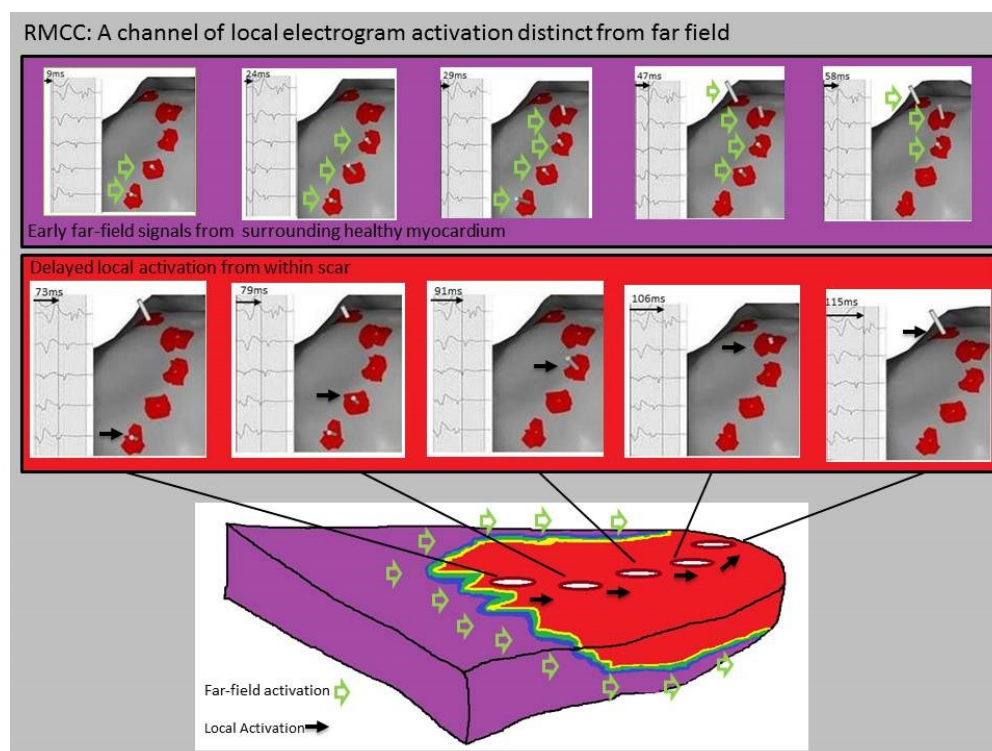


Figure 6-2: (see also video 6-2) RM-CC

Five adjacent points sampled within scar are displayed. Panel I: The Ripple map demonstrates bars (9ms, 24ms, 29ms, 47ms, and 58ms) associated with the initial wavefront (green arrows) ascending up the anatomy. This may represent far-field from either epicardial activation or activation from the surrounding healthy tissue.

Panel II: The Ripple map shows bars (73ms, 79ms, 91ms, 106ms, and 115ms) representing delayed activation (black arrows) ascending up the anatomy, forming a RM Conduction Channel. Importantly, the initial activation is still occurring in the dense scar when delayed activation commences at the border zone. Once the delayed activation has reached the scar core, the signal is clearly late and hence separated from the initial wavefront.

6.1.2 Methods

6.1.2.1 Study Sample

Consecutive patients referred for VT ablation secondary to documented episodes of sustained VT or appropriate ICD therapy post distant myocardial infarction were studied. This included patients late into the arrhythmic disease process who had already experienced multiple VT episodes, and even already undergone previous VT substrate ablation. All patients enrolled after providing informed consent to participate. This study was approved by a local human research ethics committee.

Details regarding procedural setup, ventricular access and the induction protocol have been described in section 2.1.2. Detailed maps of the endocardial LV surface were obtained in sinus rhythm (or during right ventricular pacing if the patient was pacing dependent) using a 3.5-mm tip SmartTouch Thermocool catheter (Biosense Webster).

Having demonstrated the feasibility and effectiveness of robotic navigation, mapping and ablation was supported using the Hansen Sensei Robotic system (Hansen Medical Inc., Mountain View, CA, USA).²⁰⁵ The multi-electrode PentaRay catheter (2-6-2mm spacing) was applied in the latter cases in this study without the robotic system. Interpolation was limited to a colour threshold ≤ 5 mm, with an emphasis on fully defining the scar and border zone of the infarcted tissue. No epicardial mapping was performed.

Normal bipolar endocardial voltage was defined as a peak-to-peak amplitude ≥ 1.5 mV, “core scar” as < 0.5 mV, and “border zone” was between 0.5-1.5mV.⁹⁵ Electro-anatomical data were collected either point by point, or using the automated point collection facility (ConfiDENSE) as per operator preference. The automated system relied on filters for each beat based on a series of pre-assigned parameters, described in section 2.3.1. We applied the same ConfiDENSE filters as we used within atrial scar, as described in section 5.1.

6.1.2.2 Analysis of a Ripple Map within ventricular scar

Whilst the patient underwent VT induction, CARTO Ripple Maps were analysed for RM-CCs. EGM deflections less than 0.05mV were hidden from the Ripple Map to reduce background noise, and the bars were clipped at 0.30mV to allow low voltage signals to be displayed more clearly. These parameters could be adjusted during analysis. Ripple Maps were studied from the onset of QRS until the end of ventricular depolarisation (onset of the T wave). The map was first played to appreciate the global

pattern of activation through the scar. Design lines were drawn on the anatomical shell to encircle the entire RM-CC or clusters of late local activating Ripple bars that activated simultaneously, and adjacent clusters were joined to form the path of the RM-CC. If the initial and delayed wavefronts were difficult to differentiate, maps were analysed frame-by-frame in reverse towards the onset of the QRS. EGMs along each RM-CC were then analysed using the CARTO Ripple Viewer, which enabled multiple Ripple bars to be selected, and the corresponding EGMs to be displayed together. This was used to validate the RM-CC design-lines that had been drawn. No pacing manoeuvres were performed to confirm the distinction between local and far-field components within the RM-CC. A summary of this approach is illustrated in figure 6-3.

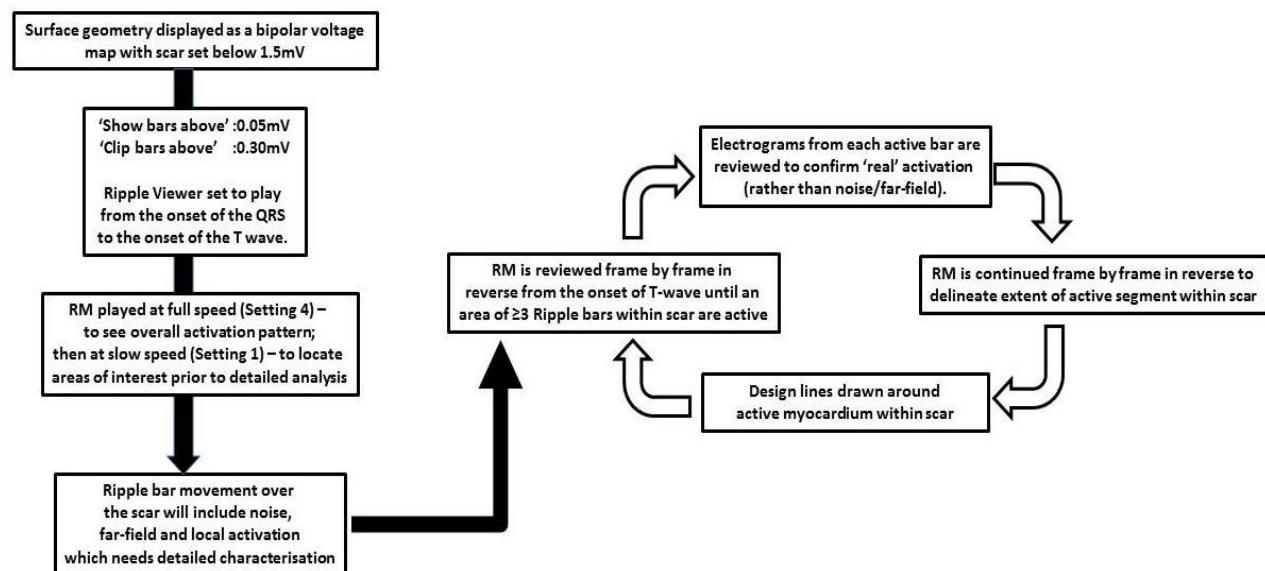


Figure 6-3: Algorithm for identifying RM-CCs within a scar

Where VT was mapped, Ripple Maps were studied over the complete TCL to identify the location of ripple bar activation during the diastolic interval. Design lines were drawn to encircle the boundaries of this diastolic activation to highlight the diastolic pathway (RM-DP).

6.1.2.3 Radiofrequency Ablation

Ablation was delivered within each RM-DP where VT was mapped, followed by all RM-CCs identified. Discrete clusters of late activating ripple bars were also ablated as they were considered an endocardial component of an epicardial RM-CC. Ablation was performed with a 3.5-mm irrigated-tip contact force sensing catheter (Thermocool-Smarttouch catheter (Biosense Webster). Using the Hansen system to increase catheter stability during ablation, each RF delivery was limited to 30W at 60secs with a flow

rate of 17mls/min and a temperature limit of 40°C (as we have previously described), with a target contact force of 10-20g aiming for the local signal to diminish. No other ablation was performed within this protocol.

6.1.2.4 Endpoints

Post ablation ventricular stimulation was used to assess VT inducibility as a marker of immediate ablation efficacy. Patients were defined as either “non-inducible” or “inducible” for VT.

ICD interrogations were conducted at 1, 3, 6, and 12 months and arrhythmia logs were retrieved. Endpoints were defined by the time to the first VT episode recurrence (first ATP or shock therapy, or sustained VT captured within a monitor zone or 12 lead ECG). All patients were offered remote monitoring, and additional ICDs were interrogated whenever symptoms suggested delivery of device therapy.

6.1.2.5 Statistical Analysis

Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for normally distributed data and/or median (lower quartile – upper quartile) for non-normal data. Paired non-normal data were analysed using the Wilcoxon Signed Ranks test. A two sided p value ≤ 0.05 was considered significant.

6.1.3 Results

6.1.3.1 Study Population

Baseline clinical characteristics of 15 consecutive patients (median age 68yrs (58-77), LVEF 30% (30-40) studied in this protocol are listed in Table 6-1. Previous VT ablation had been performed in 6/15 (40%) patients, and 11/15 (73%) patients were already prescribed Amiodarone. Pre-procedural ICD therapy burden over the previous 6 months or last VT ablation included 19 ATP events (4–93) and 1 shock (0–3).

Patient No	Age, y	Revascularization Approach	LVEF, %	Amiodarone	Device	Previous Ablations	Preprocedural ATP	Preprocedural Shocks
1	71	Medical	42	N	ICD	0	167	26
2	79	CABG	38	Y	CRT-D	1	1325	13
3	78	CABG	22	Y	ICD	3	7	2
4	57	PCI	30	Y	ICD	1	0	0
5	67	CABG	35	Y	ICD	1	0	8
6	89	Medical	20	Y	CRT-D	0	57	0
7	75	Medical	30	Y	ICD	0	12	4
8	78	CABG	20	Y	ICD	0	1	1
9	49	PCI	35	Y	ICD	0	52	1
10	46	CABG	42	N	ICD	0	99	0
11	64	CABG	30	N	ICD	1	87	0
12	38	PCI	45	Y	ICD	0	19	2
13	75	PCI	30	Y	ICD	1	201	1
14	68	CABG	45	Y	ICD	0	7	0
15	58	CABG	30	N	ICD	0	0	1
Median	68		30				19	1
LQ	58		30				4	0
UQ	77		40				93	3

CABG indicates coronary artery bypass graft; CRT-D, cardiac resynchronization therapy with defibrillator; LQ, lower quartile; LVEF, left ventricular ejection fraction; ICD, implantable cardioverter defibrillator; PCI, percutaneous coronary intervention; and UQ, upper quartile.

Table 6-1: Study population

6.1.3.2 Map collection

Ventricular scar maps in the first 12/15 cases (80%) were collected with a SmartTouch catheter supported by the Hansen Sensei Robotic System. The latter 3/15 (20%) maps were collected using the PentaRay. Voltage maps were collected in an RV paced rhythm in 9/15 (60%) patients (pacing dependent/operator preference). Chamber geometry and electro-anatomical data were collected simultaneously (median chamber area of 258cm² (235-298), median 714 points per map (55–1107), median mapping time of 79mins (63–90)). Detailed mapping was performed within scar ((median 540 points per map (365-742); (median 6.6 point per cm² (5.3-8.7); (median scar area 77cm² (62-120)). Scar represented median 29% (26–37%) of the total endocardial surface area.

Details of LV map collection are summarized in Table 6-2.

Patient No	Rhythm	Mapping Catheter	Total LV Area/cm ²	EA Points	Scar Location	Total Scar Area, cm ²	Scar Proportion, %	Scar Points	Scar Points/cm ²	Mapping Time, min
1	Sinus	SmartTouch	206	556	Basal: septum	58	28	340	5.9	89
2	RV paced	SmartTouch	211	1180	Basal: septum/posterior	55.5	26	760	13.7	76
3	RV paced	SmartTouch	258	1573	Basal: inferior/posterior	184	71	1101	6.0	37
4	Sinus	SmartTouch	320	552	Apex: anterior	240	75	385	1.6	79
5	Sinus	SmartTouch	166	390	Apex: anterior	66	40	301	4.6	92
6	RV paced	SmartTouch	501	714	Apex: anterior	125	25	535	4.3	60
7	RV paced	SmartTouch	299	1321	Basal: inferior/posterior	70	23	925	13.2	99
8	Sinus	SmartTouch	282	1034	Basal: inferior/posterior	123	47	724	5.9	105
9	RV paced	SmartTouch	255	691	Mid: anterior	83	33	550	6.6	75
10	RV paced	SmartTouch	229	520	Basal: inferior	32	14	300	9.4	82
11	Sinus	SmartTouch	240	891	Apical	79	33	630	8.0	90
12	Sinus	SmartTouch	246	720	Basal-mid infero-septal	75	30	540	7.2	65
13	RV paced	PentaRay	265	2599	Basal-mid posterior	77	29	1689	21.9	80
14	RV paced	PentaRay	296	531	Basal infero-posterior	44	15	345	7.8	45
15	RV paced	PentaRay	432	630	Basal-mid infero-posterior	117	27	510	4.4	52
Median			258	714		77	29	540	6.6	79
LQ			235	554		62	26	365	5.3	63
UQ			298	1107		120	37	742	8.7	90

EA indicates electro-anatomical; LQ, lower quartile; LV, left ventricle; RV, right ventricle; and UQ, upper quartile.

Table 6-2: Mapping details

6.1.3.3 VT induction

VT was non-inducible in 2/15 (13%) patients from the start. In 10/15 patients, VT was either non-sustained or poorly tolerated requiring termination with overdrive pacing or defibrillation. VT was mapped in only 3/15 (20%), enabling detailed review as a Ripple Map to characterize the RM-DP. No entrainment was performed in VT, but ablation was delivered within the mapped RM-DP. In all patients, after the first VT was induced, no further attempts to induce VT were performed till after RM-CC ablation.

6.1.3.4 Ripple mapping within ventricular scar

RM-CCs were identified in all patients and 3 patients also had induced VT mapped. Figure 6-4 illustrates the RM-CCs identified in patient 9 using the raw data shown in video 6-4. The two RM-CCs (enhanced with design lines) are seen as late activating channels separate from the initial wavefront. The direction of activation is readily apparent, and the channel is seen without any manual annotation or point tagging. In this example, the RM-CCs are broad and cover a relatively large area of the scar.

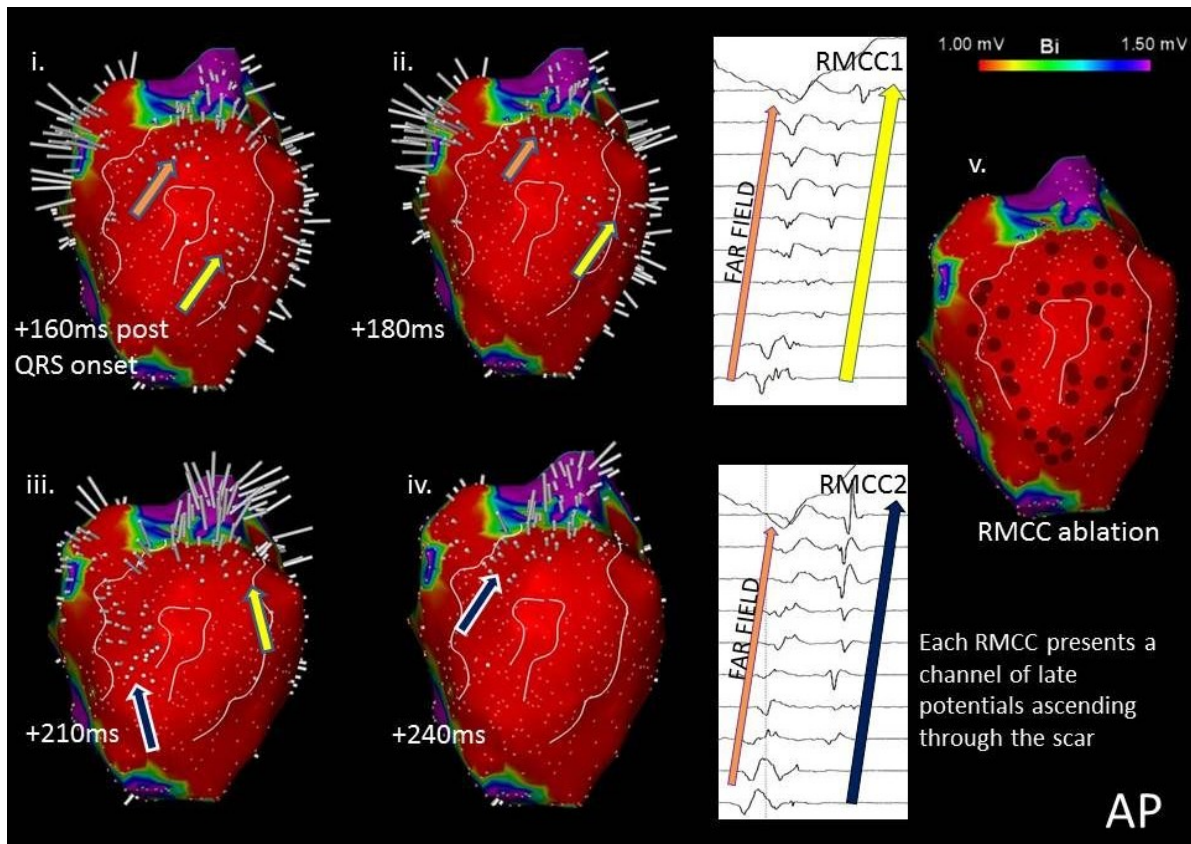


Figure 6-4: (see also video 6-4) Clear direction of RM-CC activation (pt. 9)

The map was collected in a paced rhythm. Scar ($<1.5\text{mV}$) was identified on the anterior wall (83cm^2 , 550 points). Panel I: Design lines have outlined the path of RM-CC activation. The terminal end of the first wavefront of Ripple bars (orange arrow) is seen at +160ms and +180ms post QRS onset. These bars are concurrent with activation from the surrounding healthy tissue and likely correspond with far-field activation. At +160ms, a second cluster of Ripple bars is noted in the mid-lateral wall (yellow arrow). At +180ms, these bars have ascended up towards the base of the LV corresponding with late potentials ascending up the scar with increasing activation delay; this represents RM-CC1. At +210ms, a further cluster of very late activating ripple bars is now seen on the mid-septal side (blue arrow). By +240ms, these bars have ascended up the scar towards the base of the LV. Sampled EGMs along the blue arrow path again demonstrate late potentials ascending up the scar with increasing activation delay; representing RM-CC2. The distribution of ablation within the RM-CC by the location of maroon coloured disks.

In figure 6-5, the corresponding VT circuit is shown as a Ripple Map and local diastolic activation is clearly differentiated from systolic activation. The entire RM-DP is seen from entrance to exit, with varying diameter along its length, and a possible inner loop near the entrance. Ablation within the RM-DP interrupted the VT circuit.

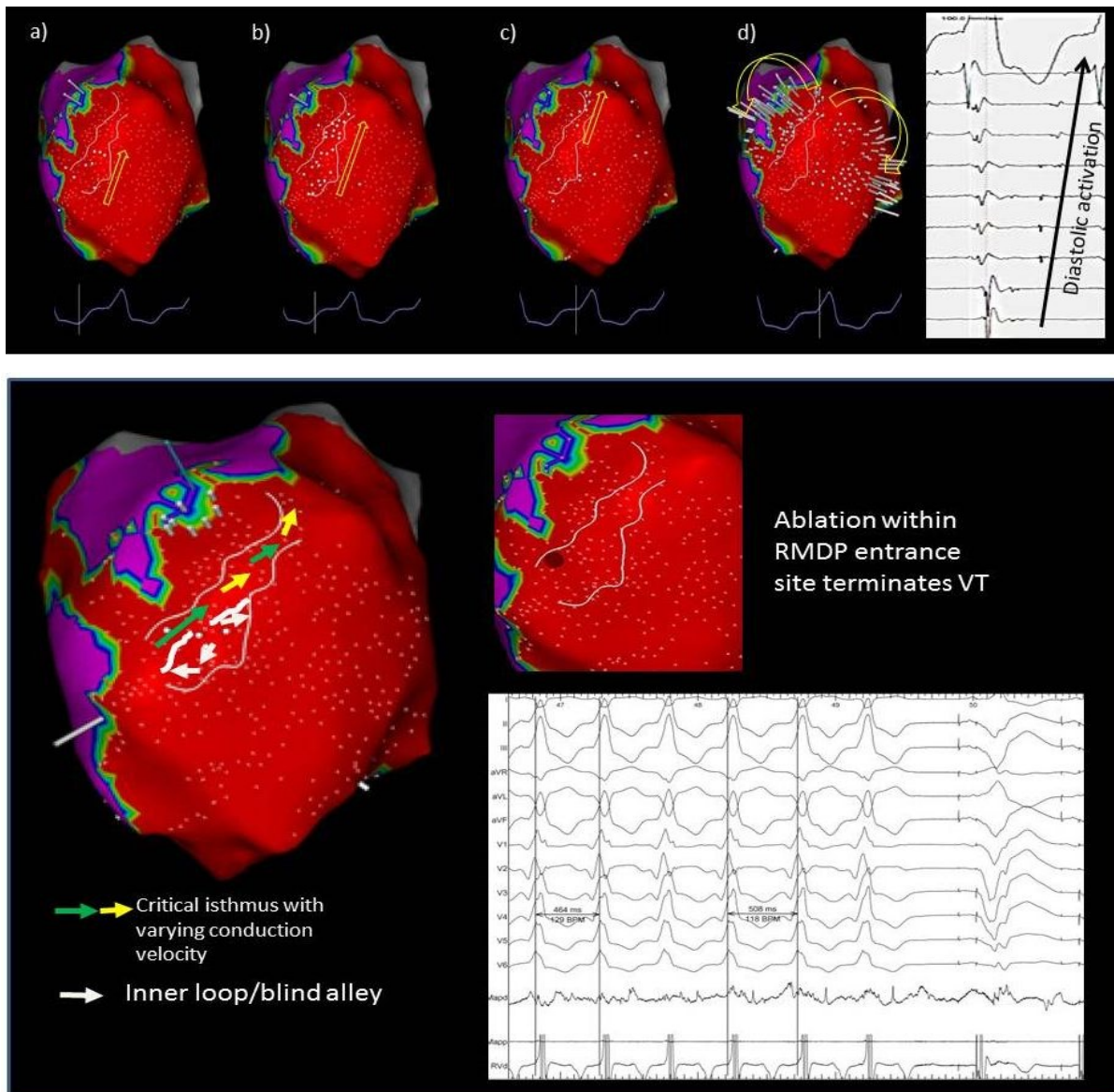


Figure 6-5: (see also video 6-5) RMDP activation (pt 9)

4 time points during the diastolic period are presented. A channel of Ripple bars reflecting mid diastolic potentials ascends from apex to base through scar. EGMs sampled along this path cover the diastolic interval. An outline of this path is drawn on the map and represents the RM-DP. As ripple bars travel up the RM-DP, activation is also seen to curve back towards the entrance, suggestive of an inner loop.

The corresponding unadjusted LAT maps in figure 6-6 both demonstrated the incorrect pattern of local activation as all annotation of activation time was directed to the far-field component.

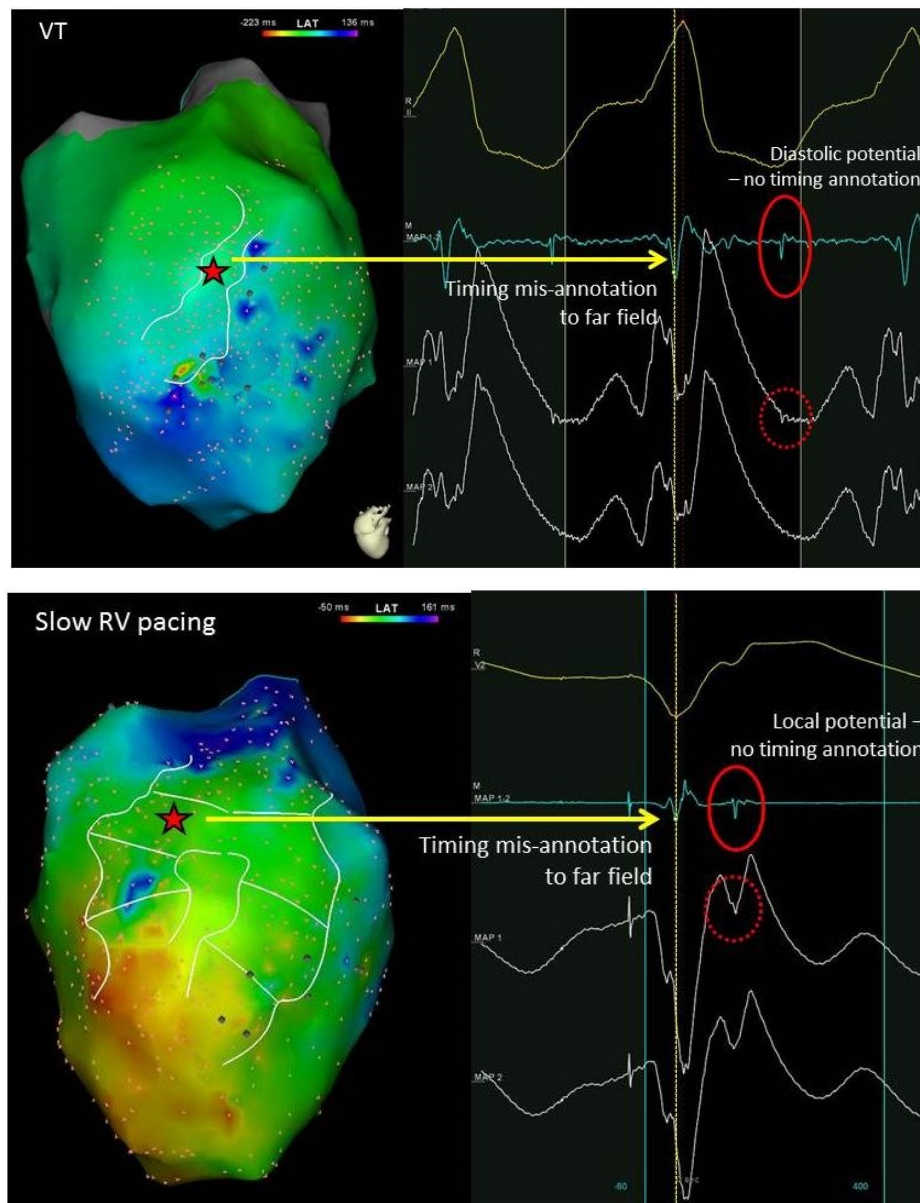


Figure 6-6: Automated LAT ventricular scar map.

The unadjusted LAT maps in VT and slow RV pacing from the same case is presented. The colour code in both cases suggests an activation pattern which is not in keeping with local late activation. Upon close inspection, having sample an EGM from both cases, it is apparent that the system has annotated activation time according to the maximum $-ve$ dV/dT of the larger far-field component seen in the distal unipolar channel, and ignored the local bipolar signal owing to the lack of a significant contemporaneous unipolar signal (dotted red circle).

In some cases the RM-CCs were difficult to see during forward play and needed step-by step reverse play. Figure 6-7 Panel I summarize the three RM-CCs identified from patient 5. The RM-CCs were seen closer to the conventional scar border on the bipolar voltage map. Isolated clusters of very late activating ripple bars that do not appear connected to the RM-CCs identified are also apparent, and it is assumed that these arose from channels that are deep to the endocardium.

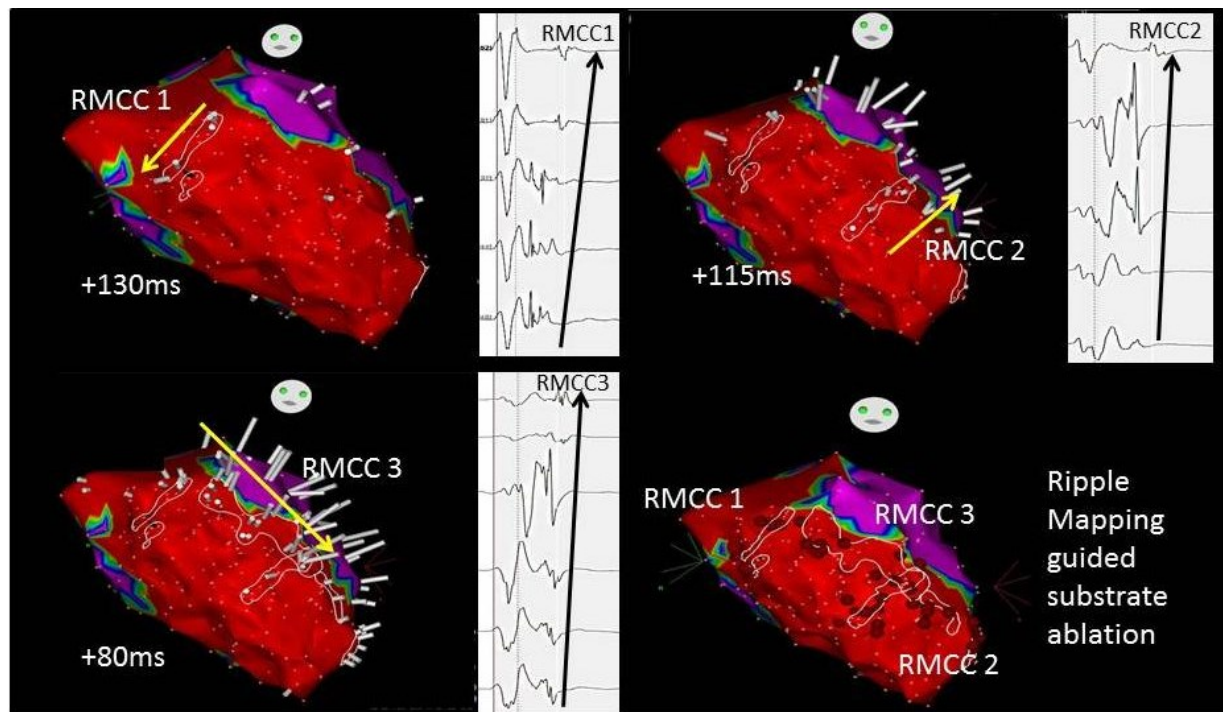


Figure 6-7: (see also video 6-7) RM within ventricular scar to guide substrate ablation (pt. 5)

The map was collected in sinus rhythm. Scar ($<1.5\text{mV}$) was identified on the anterior wall (66cm^2 , 300 points). Panel I: Ripple bars were seen to propagate from the septum to the lateral wall. The map is presented in reverse. A cluster of late activating bars approximately +130ms post QRS onset is seen within basal scar, and corresponds to late potentials travelling from the lateral wall to the septum, representing RM-CC1. RM-CC2 is encountered +115ms post QRS onset, this time travelling mid scar from septal-lateral LV. RM-CC3 is seen +80ms post QRS onset travelling down the lateral wall from base-apex. In the presented time frame, bars are seen along each RM-CC as the corresponding late signals are at different time points away from the iso-electric line. Our approach to substrate ablation is presented, with ablation delivered along all RM-CCs and at late activating clusters.

In figure 6-8, the diastolic component of the induced VT is shown. The complete RM-DP was not seen, due to either insufficient point collection or non-endocardial components to the circuit. Despite this, using the RM-DP, there appears to be a central refractory core in this circuit within the scar. A single ablation lesion within the RM-DP interrupted VT.

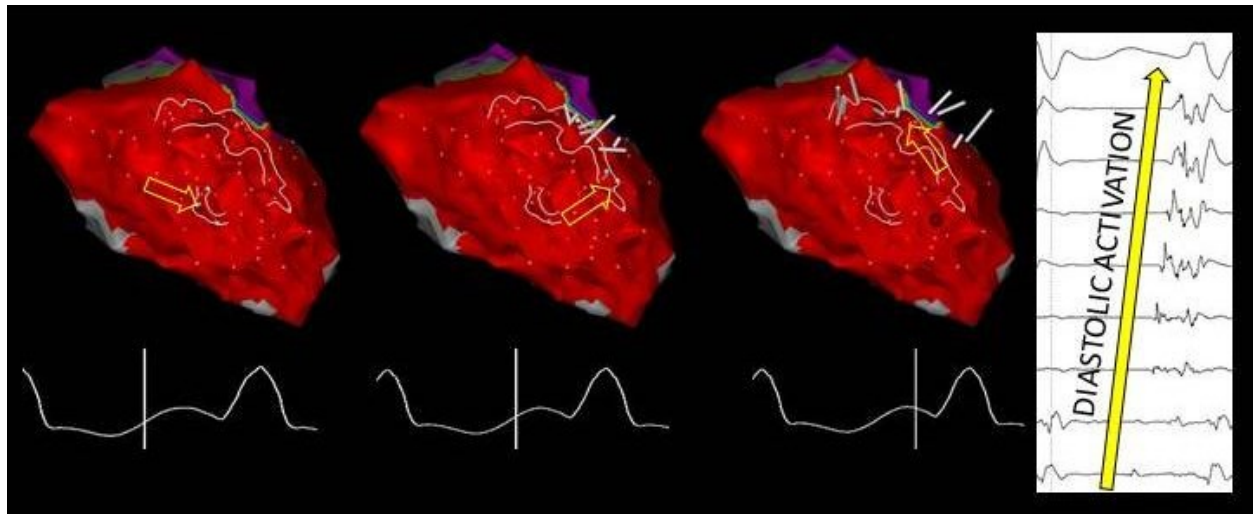


Figure 6-8: (see also video 6-8) RMDP pt. 5

VT was induced (CL 440ms) and mapped. 3 time points within the diastolic period are presented. RM tracked diastolic signals travelling around a counter-clockwise loop within the scar.

Centripetal pattern of activation into the scar core has also been described previously.²⁰⁶ Figure 6-9 illustrates how this pattern might occur with regions of functional tissue activated by any number of RM-CCs.

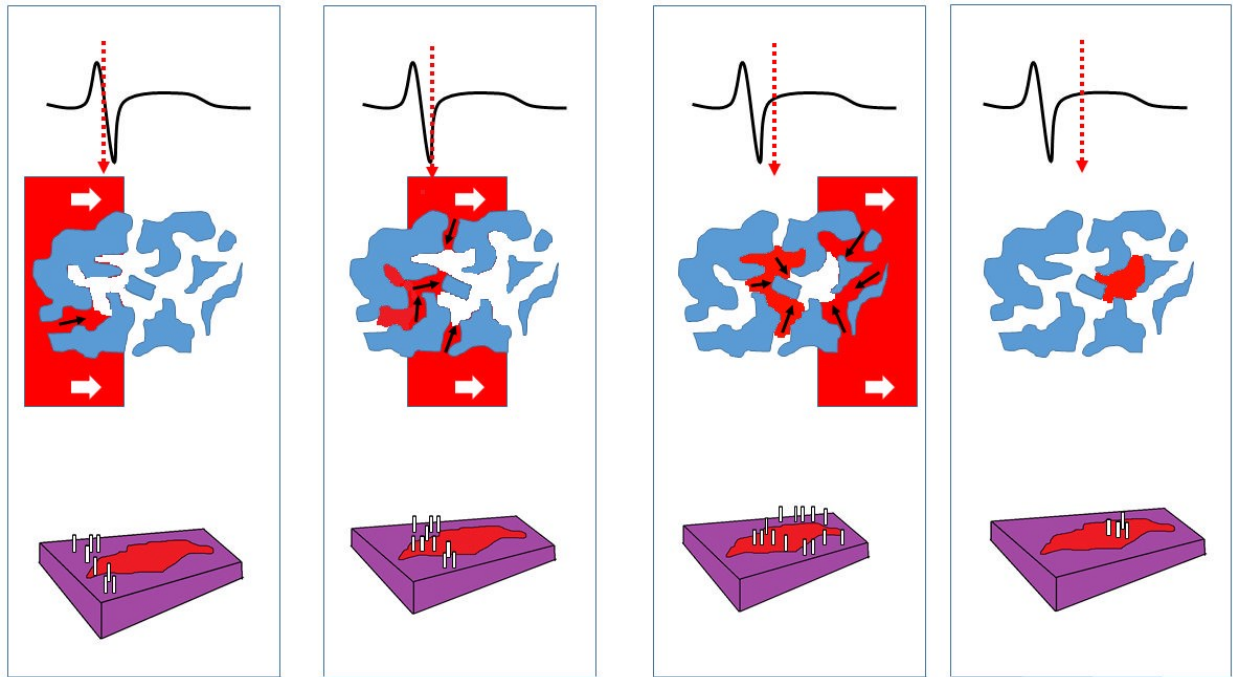


Figure 6-9: An illustration of centripetal channel activation towards the centre of the scar.

A diagrammatic representation of post infarct endocardial ventricular scar is presented (blue islands) which includes areas of residual surviving myocardium within the scar (uncoloured white areas). An activation wavefront (red) is seen progressing from left to right through 4 time frames within the scar (mid QRS - very late post QRS). Whilst the wavefront in healthy tissue progresses in a linear direction, the wavefront enters the scar from multiple sites, and zig-zags slowly towards channels of active tissue towards the centre of the scar. Regions of active tissue could have been activated by any number of pathways.

Beneath each time frame is an illustration of how this might be depicted on a Ripple Map overlying a display of bipolar voltage (purple represents healthy tissue, and red represents scar). A wavefront of Ripple bars rapidly travels within the healthy tissue around the scar border-zone in a linear direction. Within the scar, ripple bars enter from all directions towards the scar core

An example of such activation is seen in figure 6-10 (and video 6-10). This map was collected with the PentaRay (2599 points). By playing the RM backwards and encircling each patch of simultaneously activating tissue, interconnecting RM-CCs were gradually built up.

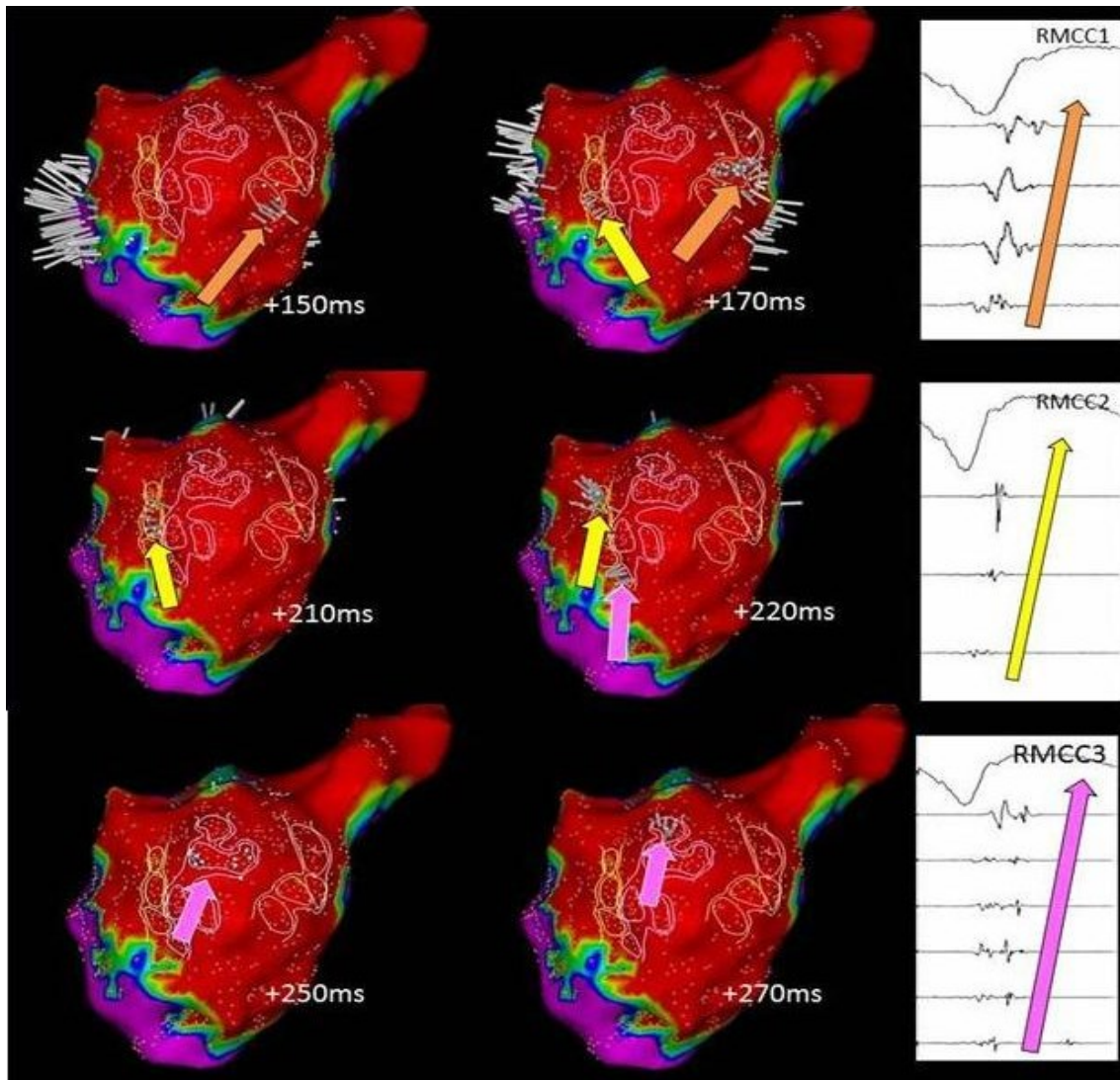


Figure 6-10: (and video 6-10) RM-CCs in close proximity with probable path of activation towards the centre of the scar (pt. 13)

The map was collected in a paced rhythm using a PentaRay catheter. Scar ($<1.5\text{mV}$) was identified on the infero-posterior wall (77cm^2 , 1689 points). Each cluster of ripple bar activation has been encircled. Adjacent circles have been connected in order of time to form the outline of each RM-CC. Ripple bars enter the scar at a mid septal site (brown arrow) +150ms post QRS onset. At +170ms, this activation has ascended towards the LV base. Adjacent EGMs analysed along the brown arrow path are shown and demonstrate increasing local activation delay and are labelled RM-CC1. Also at +170ms, Ripple bars enter the scar at a mid-lateral site (yellow arrow). By +210ms, this activation ascends up the scar. At +220ms, Ripple bars again enter the scar from a mid-lateral site (pink arrow). At the same time, activation designated by the yellow arrow has now ascended towards the scar core. EGMs analysed along the yellow arrow path demonstrate increasing local activation delay and are labelled RM-CC2. Activation designated by the pink arrow slowly ascends up the scar (+250ms), reaching the site of latest activation at +270ms within the scar core. EGMs analysed along the pink arrow path demonstrate increasing local activation delay and labelled RM-CC3.

As mapping times were shorter with the Pentaray (median 52mins (IQR=49-66mins) vs. Smart-touch (median 80mins (IQR=76-91mins) $p=0.17$), this allowed time for remapping of the scar post ablation to look for elimination of activation along RM-CCs, an example of which is seen in figure 6-11.

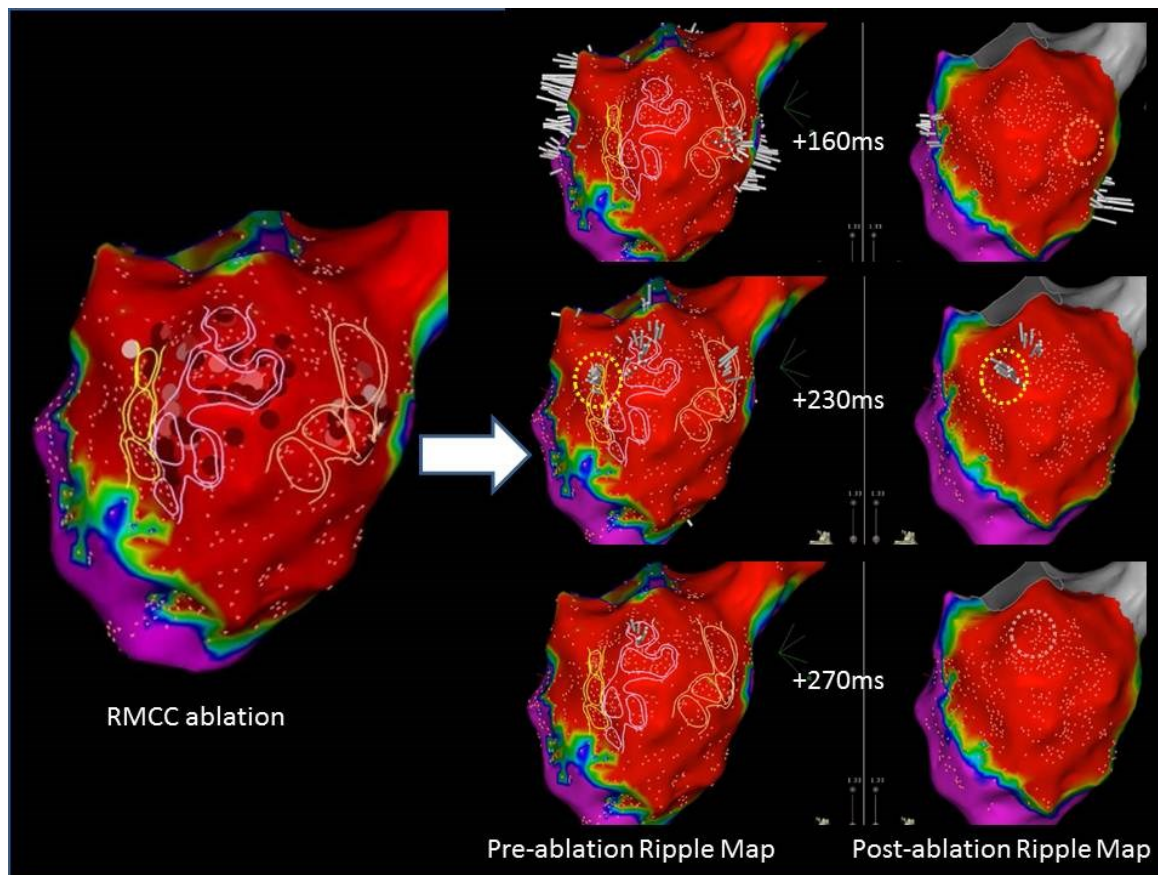


Figure 6-11: RMCC remapping post ablation

The distribution of RM-CC ablation is highlighted as pink/maroon coloured tags. Using a multipolar catheter, we were able to rapidly remap the scar to determine whether the RM-CC had been eliminated. Ripple activation along RM-CC1 (+160ms) and RM-CC3 (+270ms) is no longer apparent. Residual activation remains along RM-CC2 (+230ms) which was targeted for ablation.

Figure 6-12 also shows the corresponding VT map. In this example there was a narrow RM-DP which opened into a broad region of diastolic activation before the systolic activation occurred. Ablation within the RM-DP interrupted VT.

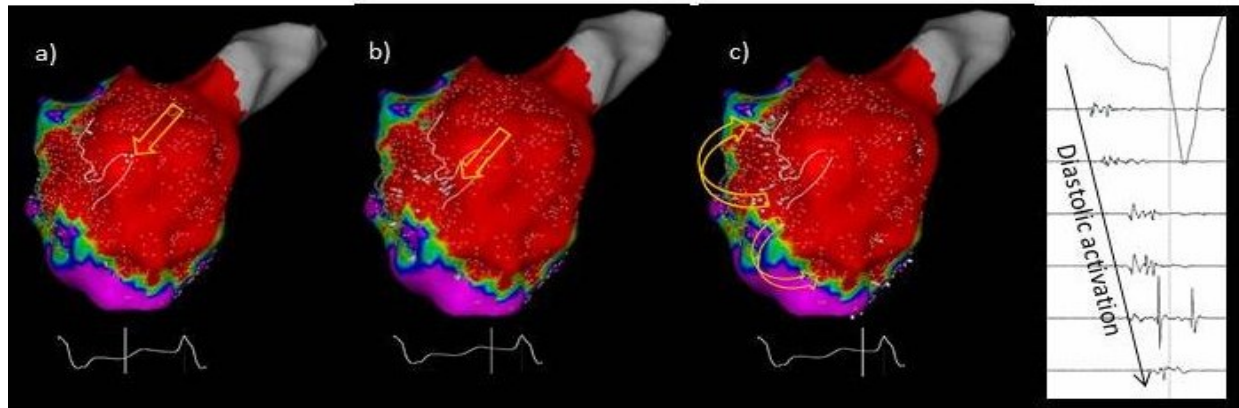


Figure 6-12: (see also video 6-12) RMDP pt. 13

VT induced (CL 500ms) and mapped. 3 time points within the diastolic interval are presented. Mid diastolic potentials were identified in the scar core. RM clearly tracked diastolic signals towards the lateral wall within the scar. Design lines have outlined the RM-DP on the map.

A median of 2 RM-CCs were identified within each scar. The median RM-CC length was 60mm (40-80). EGMs were sampled for analysis every 10mm along each RM-CC. The median amplitude of the initial component (presumed far-field) was significantly greater than the delayed component (presumed local), (initial component 0.44mV (0.25-0.68); delayed component 0.20mV (0.13-0.30); $p < 0.001$). RF ablation was delivered along each RM-CC (median 18 lesions per RM-CC (9-22)). Further ablation (median 6 lesions (2-12)) was performed within isolated clusters of late activating ripple bars, considered an endocardial component of an epicardial RM-CC.

6.1.3.5 Clinical outcome

This has been summarized in Table 6-3. At the end of the procedure, no VTs were inducible in 11/13 (85%) patients where VT was induced from the start (VT occurred in the remaining 2 cases only with a more aggressive programmed stimulation for induction). There were no complications during the procedures, but 1 patient died a week later from worsening heart failure and no ventricular arrhythmic episodes were identified on post mortem device interrogation. In those patients already on long-term Amiodarone, it was continued. Patients were followed up for a median of 6 months. 10/14 (71%) patients remained free of VT recurrence. VT recurred in 4 patients - within 1 month (Pt. 11, Pt. 12), at 2 months (Pt. 13) and 6 months (Pt. 3) post-ablation. Of note, despite VT non-inducibility immediately post procedure, Pt. 12 presented again with ICD storm, and importantly, during redo ablation, the RM-CCs identified during the index case had not been completely eliminated. This has been illustrated in figure 6-13.

Patient No	Post procedural VT Stim	Follow-Up (months)
1	Non inducible	14
2	Non inducible	14
3	Inducible for VT	6*
4	Non inducible	12
5	Non inducible	12
6	Non inducible	12
7	Non inducible	<1**
8	Not performed	8
9	Non inducible	6
10	Not performed	6
11	Non inducible	1*
12	Non inducible	1*
13	Non inducible	2*
14	Non inducible	2
15	Inducible for VT	1
Median		6

Table 6-3 Acute and long term outcomes

“*” – VT recurrence noted at follow up

“**” – Patient died at day 7 from heart failure; no ventricular arrhythmia detected on post mortem device interrogation.

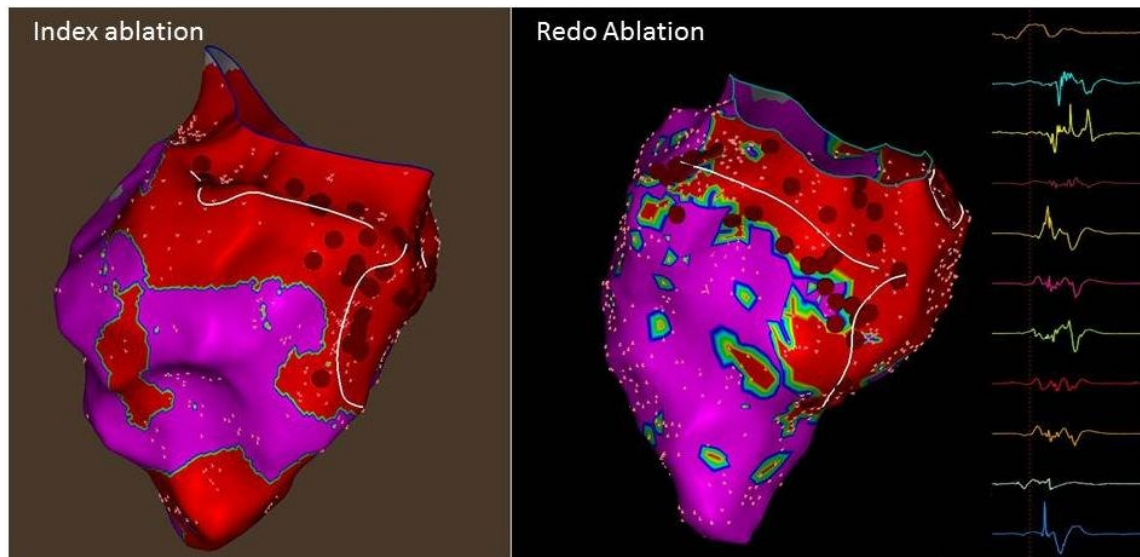


Figure 6-13: RM-CC recurrence post ablation

A patient with previous inferior MI, mildly impaired LV function and secondary prevention ICD underwent ablation for recurrent VT. An endocardial CARTO map was created in sinus rhythm (LV area 246cm², 720points) and collected with a Navistar. Scar was identified on the infero-septal wall (75cm², 540 points). The bipolar voltage map is displayed in modified PA. The voltage threshold is set below 1.5mV. Design lines have outlined the location and global direction of delayed activation and the ablation lesions delivered are demonstrated. The patient represented in storm within the first month. The patient underwent redo-procedure with the LV mapped with a Pentaray. Solitary design lines have again outlined the location and global direction of delayed activation which are similar to the index case. EGMs along one channel of late activation is displayed, and is composed of residual fractionated and late signal from a persistent RM-CC.

6.1.3.6 Additional insights

Tiered Voltage Channels:

Figure 6-14 illustrates how the location of most RM-CCs did not correlate with 'voltage channels' as voltage was usually annotated to the largest EGM component rather than the local signal within the RM-CC.

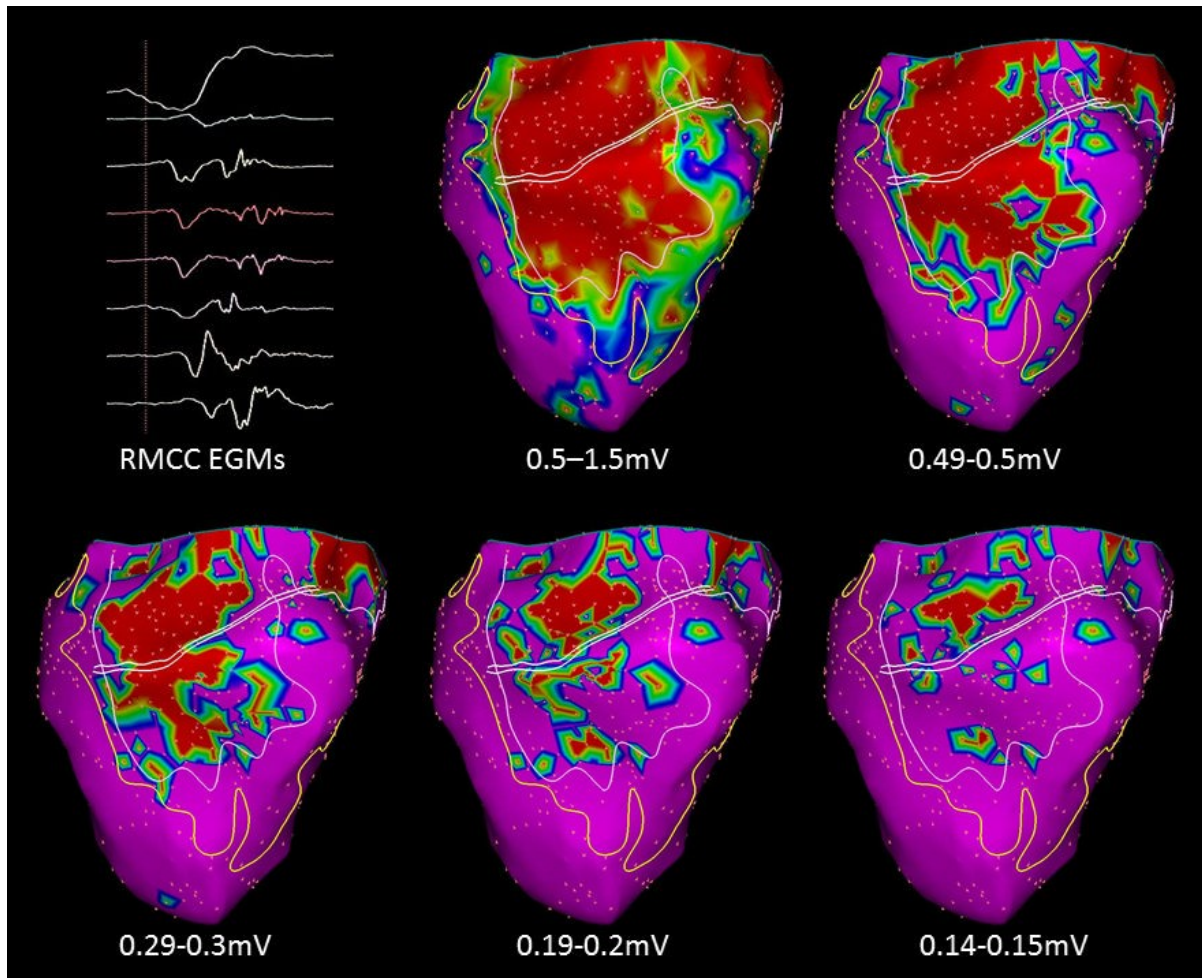


Figure 6-14: RM-CCs cannot be identified by voltage thresholding (pt. 7)

The location of the RM-CC identified within scar has been drawn as a double white design line and the accompanying EGMs along the RM-CC displayed in the Ripple Viewer. Yellow and pink design lines highlight the scar border and scar core zones. Voltage maps annotate the peak amplitude within an EGM which is usually a far-field component. Reducing the voltage threshold shows no correlation between the voltage channels seen and the RM-CC.

Early potentials:

Where scar was in close proximity to the onset of ventricular activation, the local RM-CCs signal would precede the far-field, as seen in septal scars mapped in sinus rhythm. An example of such an “early potential” is presented in figure 6-15.

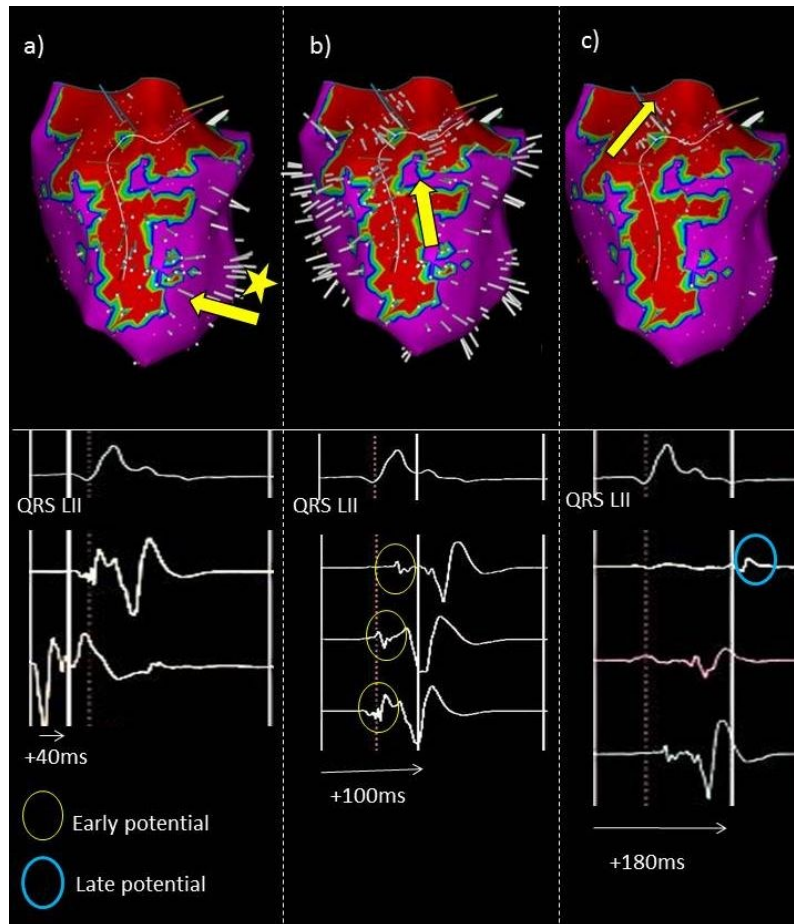


Figure 6-15: Early potentials are seen within scars close to the onset of ventricular activation. Map 10 was collected in sinus rhythm, with scar identified in the inferoseptum. The voltage map is displayed to present “scar” below 1.5mV. Three time points of activation through the scar are displayed. a). The onset of left ventricular activation from the native LV conduction system is highlighted as a yellow star. The location of the scar is close to the origin of ventricular activation. When activation enters the scar borderzone (+40ms), local signal can not be differentiated from far-field. b) Activation enters the scar before healthy tissue, and the local signal preceeds far-field. This local signal is also well within the QRS. This local signal is thus an early potential. By (+100ms), far-field activation is subsequently seen within scar on time with activation in the surrounding healthy tissue. c). (+180ms) Very delayed local signal is seen within the scar, ahead of the far-field and also post QRS. This is consistent with a late potential. Identification of this early potential as part of the RM-CC was achieved by understanding the global pattern of activation within scar, and by detailed EGM analysis using the Ripple Viewer.

Ventricular Scar Thresholding:

Three maps were collected using the Pentaray catheter, which incorporates a 1mm small tip and narrow (2mm by 6mm by 2mm) inter-electrode spacing. The local voltage amplitude was numerically greater (median Pentaray 0.39mV (IQR=0.31-0.51mV; median Smart-touch 0.20mV (IQR=0.12-0.35mV); $p=0.06$). Figure 6-16 illustrates a case of stable and tolerated VT arising, in the presence of aneurysmal scar, where the contribution of far-field signal was less owing to the discontinuity between the aneurysm and normal tissue. Mapping with the Pentaray, we were able to effectively eliminate the far-field contribution when mapping and apply the scar thresholding technique, of which we were normally restricted by the presence of the far-field component. This demonstrated channel exit within tissue measuring 0.15mV, a value normally considered dense scar.

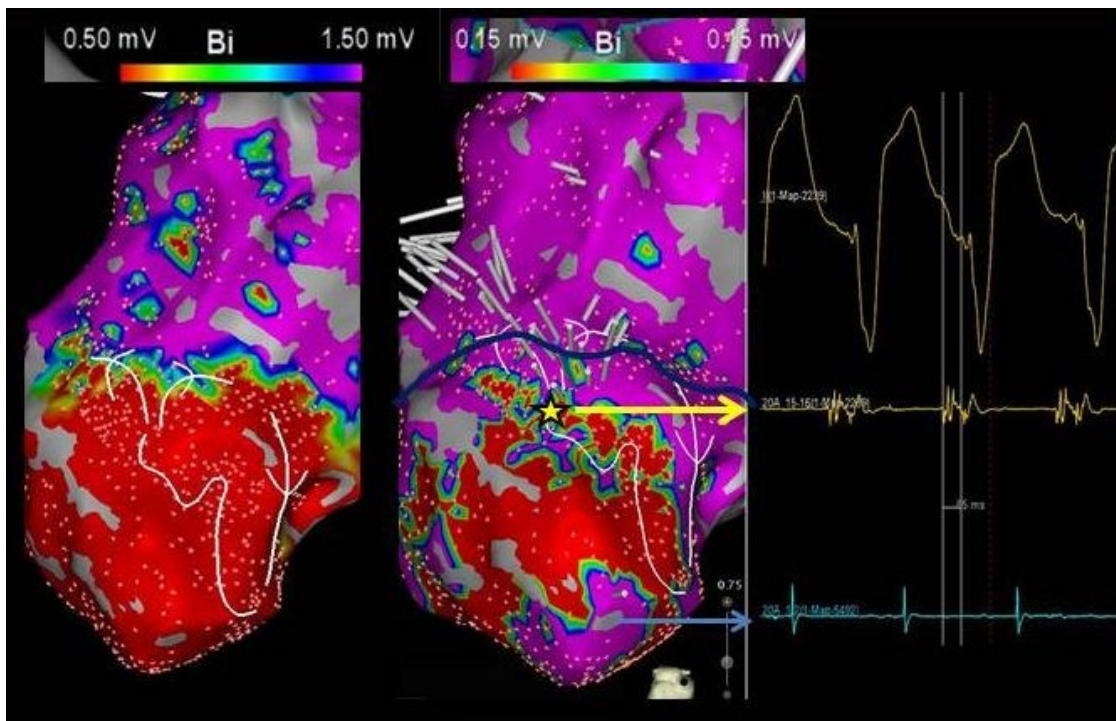


Figure 6-16: Scar Thresholding in post infarct Ventricular Tachycardia.

An activation map was collected in VT using a Pentaray catheter from a patient with apical aneurysmal scar. (Left) A bipolar voltage map set to display scar at conventional thresholds (0.5-1.5mV) outlines the extent of the apical aneurysm. (Right) An outline of the VT circuit as illustrated by RM is seen. Having travelled through scar, breakout occurred (yellow star) within apparent core scar <0.5mV (contained within blue outline) 60ms ahead of the QRS onset. Scar thresholding to a value of 0.15mV differentiated active tissue in purple and scar in red. Thus the channel exit did not reside in the “scar borderzone” as currently defined (0.5-1.5mV). Furthermore, the ripple map highlighted a bystander region of mid diastolic activation at the true apex which was disconnected from the VT circuit.

6.1.4 Discussion

In this study, we describe our early experience of Ripple mapping within the post-infarct ventricular scar to identify channels of local activation that might support reentry. Ablation of these channels rendered 85% of patients non-inducible for VT and 70% free from ICD therapy at 6 months. We showed that it was feasible to remap the scar post ablation to demonstrate RM-CC elimination post ablation and this may offer an alternative endpoint for substrate ablation.

Ripple Mapping is uniquely suited to mapping EGMs within ventricular scar. These EGMs are often multi-component, either due to fractionation within regions of slow conduction, or far field signal. Whilst LAT mapping annotates only a single activation time within these complex EGMs, RM presents each EGM in its entirety. In this study, we observed how LAT maps assign activation time to the higher amplitude far-field signal creating an incorrect propagation appearance, but with RM, delayed low-amplitude local activation within scar could be followed as a separate wavefront from an initial far-field wavefront that occurred in tandem with activation in the surrounding healthy tissue. RM enabled a detailed anatomical and functional characterization of conduction channels within scar. In other scars, it was not possible to identify a discrete channel. Rather, there appeared to be broad areas of late activation culminating in the centre of scar (centripetal activation) that we assumed implied multiple channels. Finally, some patients had discrete islands of activation with no apparent link to the bordering endocardial tissue and we assumed these were connected to healthy tissue epicardially.

We previously used RM in a retrospective observational study to visualise conduction channels within the ventricular scar.¹²⁸ This prior study was limited by low point density, analysis of predominantly far-field signal and a timing restriction to that only after the QRS. In this prospective series we aimed to refine this approach. The maps were of improved resolution, as evident by a mean point density collected in the scar of 6.6 per cm² compared to 3.4 per cm² in our prior retrospective study, and it was possible to add further points during map review. The sequence of activation from encircled clusters of late potentials (and not far-field signal) was used to 'connect' each cluster and define the RM-CC. Although this could be seen with a trained eye whilst RMs were played, this was less susceptible to operator variation when played backward frame-by-frame, checking the EGMs to exclude noise and far-field repolarization. Finally, as RM is not dependent on timing in relation to the surface QRS, we

displayed the Ripple Maps from the onset of the QRS, identifying those local signals originating before the end of the QRS, during 'local diastole' while a remote portion of the ventricle was being activated.

Despite these advantages, far-field contributed a significant amount of visual data to most of the maps collected. Mapping with the PentaRay, employing narrow spacing and smaller electrodes, increased the amplitude of the local signal, even allowing us to apply scar thresholding within the ventricle (so often limited by the presence of the far-field component) to define a considerably lower value for dense scar (0.15mV) than is convention (<0.5mV). Mapping in a ventricular paced mode that preserved AV synchrony was effective in delaying the local signal by avoiding the intrinsic conduction system (without compromising blood pressure), thus making it more apparent on a Ripple Map. Pacing as far from the scar as possible further delayed the timing between far-field and local signal (e.g. RV apical pacing in the presence of basal, inferolateral scar; or LV only pacing if anteroseptal scar).

RM-CC ablation reduced the likelihood of future VT recurrence, with medium term results consistent with other studies.⁸⁹ Ablation did not eliminate VT. We opted for a cluster of lesions to try and transect the RM-CC at several sites along its length, using VT inducibility as an acute endpoint. Pt. 12 was non inducible at the end but had recurrence, and importantly, the RM-CCs identified during the index case were still apparent at restudy. This may have been the result of ineffective ablation, related to our restriction to power and RF time during robotic ablation as described in chapter 3.¹⁶³ The patients in this cohort had advanced arrhythmic disease, having experienced multiple prior VT episodes, with many already having undergone VT ablation procedures. We may have had improved outcomes ablating this population earlier into their disease course. Furthermore, the median EF % in this cohort was 30%, and our meta-analysis in chapter 3 suggested that recurrence was to be expected in those with severe LV impairment. A study combining the RM substrate approach in patients earlier into their disease course and with EF >30% would be of value.

The failure to prevent VT recurrence may also be related to an incorrect assumption that pre-supposes that these channels within ventricular scar are anatomically fixed in location, bordered by non-conductive fibrous scar tissue. We have seen using the non-contact mapping system that these boundaries can be functional with relatively normal EGMs in sinus rhythm, arising in regions non uniform anisotropy that can slow conduction in the absence of fibrosis.¹¹⁷ The distinction between fixed and functional barriers is explored in the next chapter.

6.1.5 Limitations

This was a small, single-centre and non-randomised feasibility study where we describe our early experience using RM to guide substrate ablation. This study was not designed to compare the RM technique to other methods of VT substrate ablation. Ripple maps were collected in sinus rhythm in some patients and RV pacing in others, and was not standardized from the start. Due to the complexity of the EGMs within scar, interpretation of RM-CCs is liable to operator subjectivity – no reproducibility analysis has been conducted on the detection of these RM-CCs. Because CCs are three-dimensional, a planar construct on the endocardial surface may be an oversimplification, and more accurate channel determination may require a combined endo-epicardial approach.

6.1.6 Conclusions

We describe a technique using RM to study the functional substrate of post-infarct scar. We were able to identify conduction channels of local late activation, distinct from far-field signal, through the scar, ablation of which was effective in reducing VT recurrence, but not eliminating it. The application of catheters with short tip and narrow inter-electrode spacing appeared better suited to presenting only the local signal, especially within homogenous scars, and collecting the maps in a paced rhythm as far from the scar as possible. The failure to eliminate VT recurrence may have been related to incomplete ablation, as evident by the recurrence of the same conduction channel during redo-procedures, and functional boundaries, which would not have been identified using this anatomical EGM approach.

Chapter 7

7 - The electro-architecture within Arrhythmic Scar

Whilst only half way through our randomised AT study (described in chapter 5.4), we have observed approximately 25% of patients as non-inducible for tachycardia on the day of the procedure, prohibiting complete mapping of the tachycardia circuit. In chapter 6, we were only able to map a stable and tolerated VT in 20% of cases. Substrate mapping was developed for such cases, as a means to predict the regions of slow conduction supporting reentry outside of tachycardia.

All methods of substrate mapping assume that these regions of slow conduction and their surrounding regions of conduction block are fixed in location. However, previous studies have demonstrated that these regions of block mapped in tachycardia can be functional, with relatively normal EGMs in sinus rhythm.

Ripple Mapping offers a unique method to study activation over regions of low voltage and a means to differentiate scar from conducting tissue. This chapter studies Ripple Maps within atrial and ventricular scar where more than one rhythm was mapped to determine whether the electro-architecture within scar is fixed in location, to improve our understanding of the likely effectiveness of a substrate based ablative approach.

7.1 The electro-architecture of atrial scar under changing electrophysiological conditions

7.1.1 Introduction

Linear ablation lesions delivered within the left atrium during AF ablation can set up reentrant activation by creating fixed nonconductive constraining barriers and unidirectional block. Alternatively, recovery of conduction along a previously blocked line can occur, creating zones of slow conduction, and the potential for gap reentry.^{112, 201, 204} In chapter 5, we observed how scar thresholding in the atrium during tachycardia was able to determine the location of the critical isthmus, bordered by non-conductive tissue, as a guide to ablation.

Assuming these isthmuses are bordered by ablation related scar, they should be fixed in location and mappable in any rhythm, and thus potentially a target for ablation using a substrate based approach. The contribution, if any, of functional block to the boundaries of these isthmuses must be studied before considering this substrate based approach.

Changes in polarity and amplitude of a bipolar EGM can occur according to the wavefront direction and atrial rate. In this study, we studied left atrial maps where more than one rhythm was mapped, with either different wavefront direction or atrial rate, to determine whether the boundaries of the isthmuses mapped in tachycardia were anatomically fixed in location.

7.1.2 Methods

We reviewed our CARTO database to identify all RM guided iatrogenic AT ablations in our centre where more than 1 rhythm was fully mapped. These additional maps had been collected to check for block across an ablation line in sinus or paced rhythm, or for remapping of a second AT.

Only those maps collected using CARTO ConfiDENSE were studied, as this feature was designed to help exclude ectopic beats (using the cycle length filter), movement artefact (using the position stability filter) and non-contact points (using the tissue proximity indicator). Maps were studied only in regions with colour threshold <5mm. All internalized points >10mm from the endocardial surface and any acquired non-respiratory gated points, and any “non-proximity” points that may have been collected were deleted from the map. In order to avoid discrepancies in bipolar EGM amplitude related to electrode tip size and inter-electrode spacing, maps were only studied where the catheter used for remapping was the same.

Having identified the scar threshold of the presenting AT, the Ripple map was used to characterize every potential wavefront and isthmus on the bipolar voltage map. Isthmuses were defined over an 8 segment model of the LA (1=anterior, 2=lateral, 3=LAA, 4, roof, 5=posterior, 6=mitral isthmus, 7=floor, 8=septum). Isthmuses were characterized by the borders as either “non-conducting (NC) – non-conducting”, or “non-conducting – anatomical structure.”

Statistical analysis: Categorical variables were expressed as percentages. Continuous variables were expressed as mean $\pm$ 1 standard deviation for parametric data and/or median (lower quartile – upper quartile) for non-parametric data. Paired data were analysed using the Wilcoxon Signed Ranks and unpaired data were analysed using a Mann-Whitney U-Test for non-parametric data. A two sided p value was determined where applicable and a value of $p \leq 0.05$ was considered significant. SPSS Version 22 (IBM) was used for statistical analysis.

7.1.3 Results

A total of 10 patients (68+/-7 yrs, 8 male) where more than 1 left atrial activation pattern was mapped were studied. All patients had undergone previous AF ablation (percutaneous pulmonary venous isolation (CPVI) in n=9, surgical AF ablation as part of concomitant mitral valve surgery in n=1). Additional lesions sets included a combination of roof (n=5) and mitral isthmus ablation (n=4) and EGM defragmentation (n=6). There was n=7 patients who had undergone 2 or more ablation procedures including 3 patients who had been treated for an AT. Patient demographics and ablation history are summarized in Table 7-1.

Pt no	Age	Gender	Previous Ablation history
1	56	M	1. WACA and CFAE. MIG, Roof
2	77	M	1. PVI; 2. Redo PVI + Roof + CFAE
3	60	M	1. PVI + CFAE
4	70	M	1. PVI; 2. Redo PVI + CTI
5	72	M	1. WACA + CTI. 2. Redo PVI, Roof + MI, 3. Focal AT from anterior LA
6	69	M	1. PVI, 2. Roof + MIG
7	67	M	1. Surg AF abl. (with MVR)
8	77	M	1. PVI + MIG + CFAE
9	73	F	1. PVI x2 and CFAE
10	58	F	1. PVI. 2. PVI, Roof, floor, CFAE, CTI

Table 7-1: Baseline demographics

A dense map of AT1 was collected in each patient (median 2265points (1554-4308). Coronary sinus atrial activation was distal-proximal in n=5, proximal-distal in n=5. The median AT CL was 250ms (238-300). Low voltage area (<0.3mV) encompassed 25% (14 – 53) of the total left atrial surface. The bipolar voltage map was adjusted to the scar threshold in order to display non-conducting tissue, where wavefronts of Ripple bars could not be identified, in red. The median scar threshold was 0.16±0.08mV.

A total of 31 isthmuses were identified in AT1 (median 3 per map; width 27±15mm; 7 anterior; 6 roof; 8 mitral; 9 septal; 1 posterior). The isthmuses were bordered by non-conductive tissue on either side in n=14 (45%), and an anatomical structure on one side in n=17 (55%). As part of the clinical procedure,

11/31 (35%) of these isthmuses were clinically ablated, resulting in a change or termination of AT1 in every case (2 anterior; 4 roof; 5 mitral).

A second tachycardia was mapped in n=7 (as defined by a change in activation sequence (n=3) or >10% change in cycle length n=4), either spontaneously post ablation or re-induced following atrial burst pacing. The median CL was 260ms (245-280). This tachycardia was found to be CTI dependent flutter in n=2 with passive activation over the left atrium. The remaining 3 patients were mapped in sinus rhythm (n=1), LAA pacing (n=1), and CS pacing (n=1) following termination of AT1. A comparison between map 1 and 2 is presented in table 7-2.

Map 1 – AT1					Map 2			
No	CL/ms	CS activation	Points	Scar Threshold/mV	Rhythm	CL/ms	CS activation	Points
1	240	D-P	2103	0.15	Sinus	1080	P-D	1039
2	240	P-D	1618	0.15	A.flutter	270	P-D	1521
3	255	D-P	1696	0.40	A.flutter	290	P-D	954
4	300	P-D	4328	0.15	AT2	260	D-P	5672
5	240	P-D	1362	0.2	AT2	300	P-D	2427
6	300	P-D	4406	0.07	Paced CS	600	D-P	2549
7	260	P-D	2426	0.06	AT2	240	D-P	1760
8	360	D-P	832	0.2	AT2	240	D-P	1683
9	230	D-P	2823	0.2	Paced LAA	780	D-P	1507
10	220	D-P	4301	0.1	AT2	250	D-P	3034

Table 7-2: Map data

There was no difference in point density between the maps for each patient (1722 points in Map 2 (1390-2670), p=0.58) though 4 isthmuses (adjacent to the trans-septal puncture site) were incompletely mapped and could not be used in the comparison. Low voltage area <0.3mV encompassed 33% (19 - 53) of the LA surface area (p=0.63). Of the remaining 16 isthmuses, 14 (88%) matched Map 1 for location and width (4 anterior; 2 roof; 3 mitral; 5 septal). These matching isthmuses were bordered by non-conductive tissue on either side in n=5 and non-conductive tissue and an anatomical obstacle n=9. Examples of matching isthmuses are seen in figure 7-1.

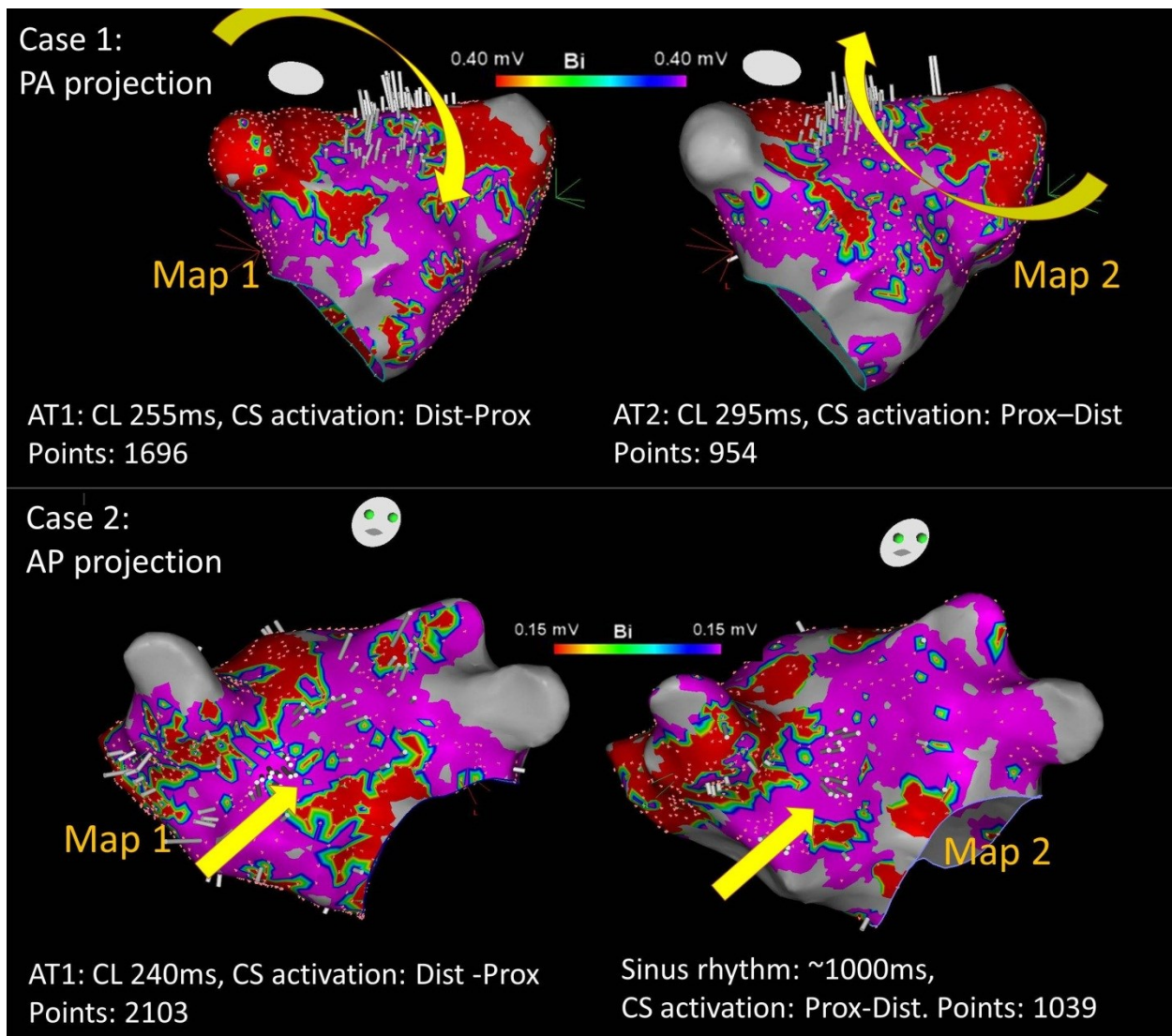


Figure 7-1: (see also video 7-1) Matching isthmuses at the same scar threshold

Case 1: High density LA bipolar voltage maps were collected in AT1 and AT2 (CTI dependent flutter). RM demonstrated activation wavefronts above 0.4mV. Both maps are displayed in the same PA orientation, at this voltage setting. In AT1, a wavefront of Ripple bars are seen to travel down the posterior wall from the roof bordered on either side by low voltage tissue secondary to previous wide area circumferential ablation. In AT2, Ripple bars travelled up the posterior wall towards the roof again bordered on either side by fixed low voltage sites.

Case 2: Video 7-1 presents this case. RM demonstrated activation wavefronts above 0.15mV. Both maps are displayed in modified AP. In AT1, a wavefront of Ripple bars were seen to travel across the anterior surface, from the septum to lateral wall. Activation was contained between an isthmus on the anterior wall formed of non-conductive tissue from previous right CPVI and on the anterior wall adjacent to the mitral annulus. The remap was collected in sinus rhythm AT1 termination, and activation is again seen to travel in the same direction constrained by the same non-conductive borders.

Changes in activation wavefront interactions between different rhythms resulted in the identification of regions of functional block in n=2 (13%) (1 anterior; 1 posterior). An example of functional block is presented in figure 7-2.

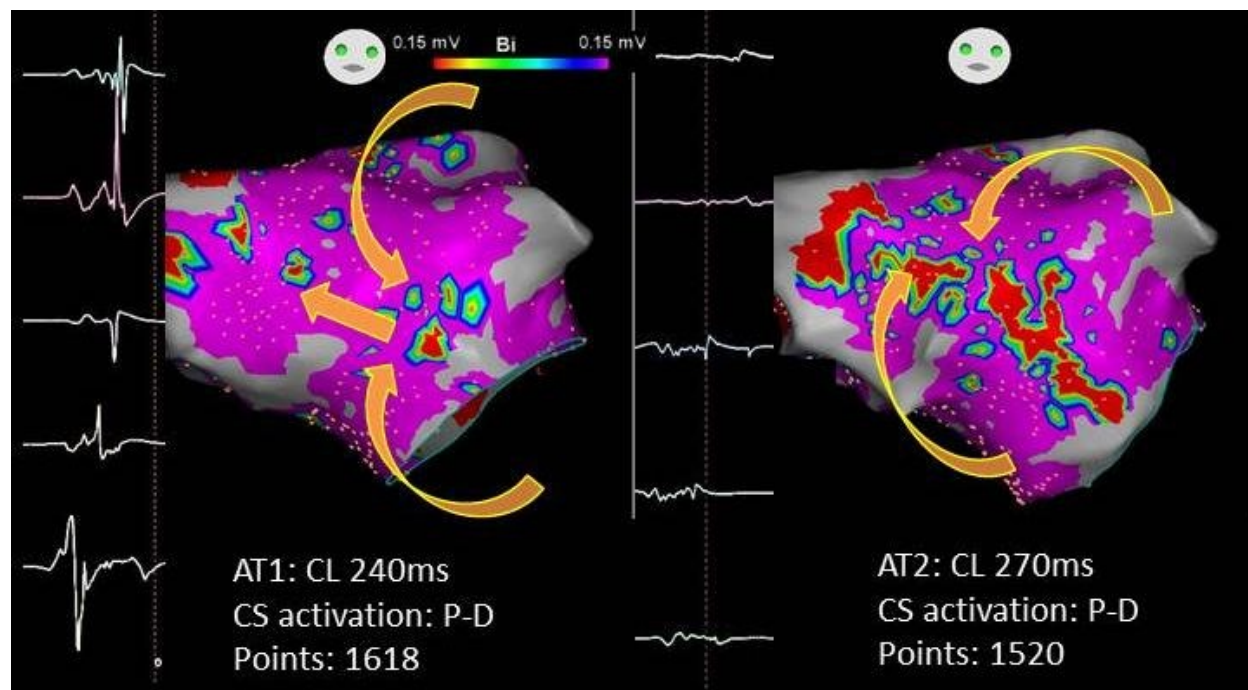


Figure 7-2: (see also video 7-2) Functional isthmus

RM demonstrated activation wavefronts above 0.15mV. Both maps are displayed in AP. In AT1, a wavefront of activation travelled from the roof down the anterior wall towards the septum, and is bordered on either side by non-conducting tissue formed from the previous R sided CPVA and an area of low voltage close to the mitral annulus. A second wavefront travelled from the septum towards the anterior wall. The two wavefronts collide on the anterior wall and coalesce to form a single body of activation towards the RPVs. In AT2, both wavefronts are again present; however, the timing of the ascending wavefront is earlier resulting in wavefront collision in the mid anterior wall. Bipolar EGMs sampled along this isthmus measured >0.5mV. EGMs from the same site collected from AT2 at the site of wavefront collision revealed very low voltage signal.

A comparison between the isthmuses in Map 1 and 2 is summarized in table 7-3 and illustrated in figure 7-3.

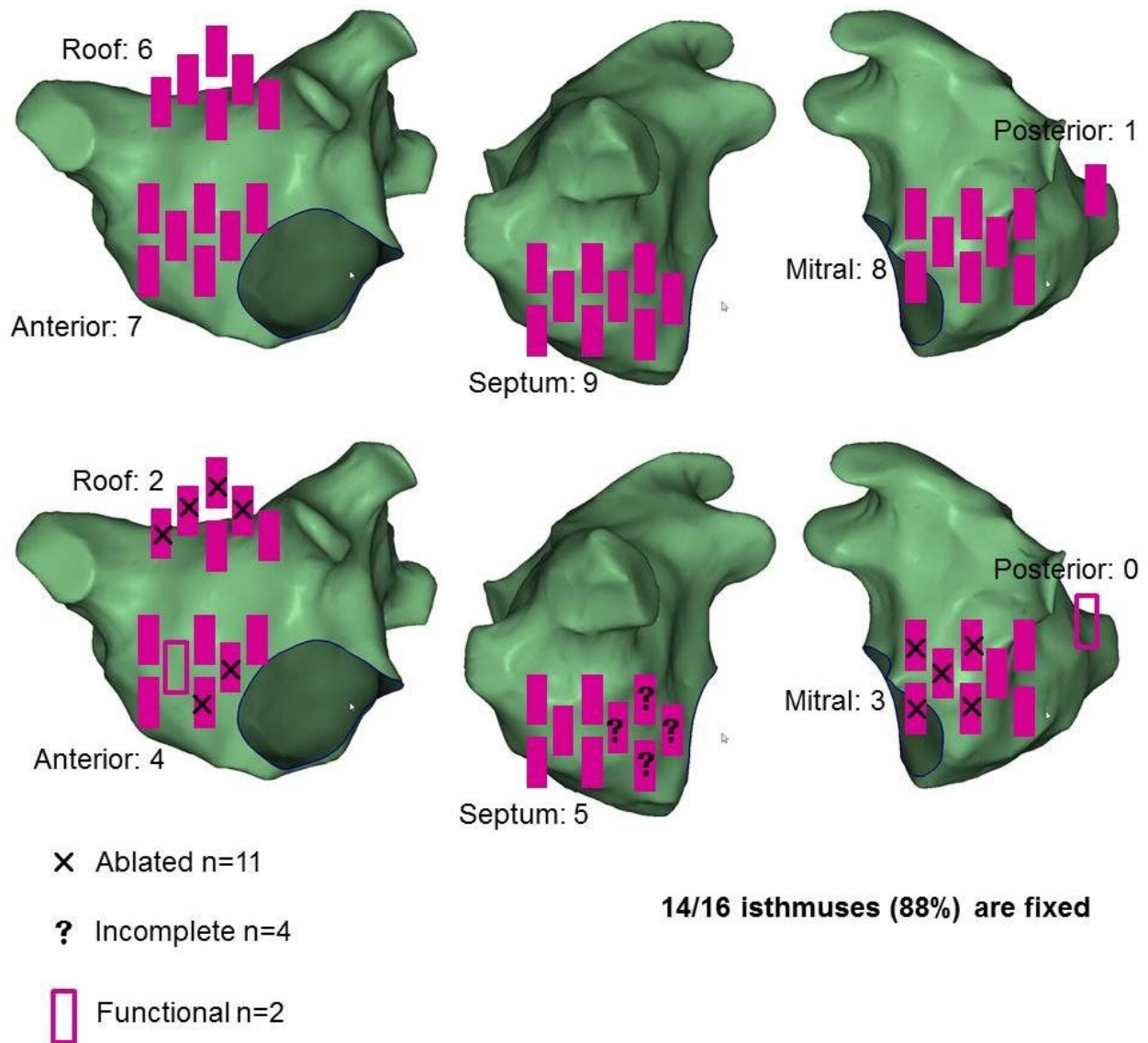


Figure 7-3: Isthmus comparisons

An illustration of the location of the isthmuses (purple tab) identified in map 1 (top panel), and a comparison of the isthmuses identified in Map 2 (bottom panel)

7.1.4 Discussion

This study demonstrates that in the ablated left atrium, the location of an isthmus identified using RM, bordered by either non-conducting tissue or an anatomical obstacle, is generally fixed in location. Therefore, in cases of AT non-inducibility or frequently changing activation sequences, ablation of these isthmuses mapped outside of tachycardia may be considered a novel substrate ablation strategy for the long term freedom of future ATs.

AT mapping relies on the patient being in AT. Patients with troublesome paroxysms of AT planned for ablation may be non-inducible or poorly sustained on the day of the procedure thus precluding effective mapping. In iatrogenic ATs, an understanding of the scar distribution has been used to predict potential circuits, however, as there exists no universally accepted threshold to define atrial scar, atrial based substrate approaches have yet to be routinely adopted in clinical practice.^{108, 121, 190, 204}

In chapter 5, we described RM scar thresholding as a novel approach to differentiate scar from conducting tissue. Using this technique, the underlying bipolar voltage map was adjusted to highlight areas devoid of Ripple wavefronts during tachycardia in red (considered scar), and conducting tissue as purple. However, whilst it is normally assumed that bipolar voltage is a measure of tissue health, it is only a measure of the potential difference between 2 electrodes.²³ It can be influenced by multiple variables, leading to significant change in the recorded bipolar voltage amplitude at any single recording point.¹⁰⁵ Changes in polarity and amplitude of a bipolar signal can occur according to the electrode orientation, wavefront direction, wavefront collision and atrial rate.¹⁰⁵ As each tachycardia is somewhat unique in its direction of activation and rate, repeat mapping may not necessarily create the same voltage display. Therefore, what is perceived to be scar according to the scar thresholding technique may not necessarily represent fixed conduction block, but rather non-conductive tissue relevant only to the mapped tachycardia.

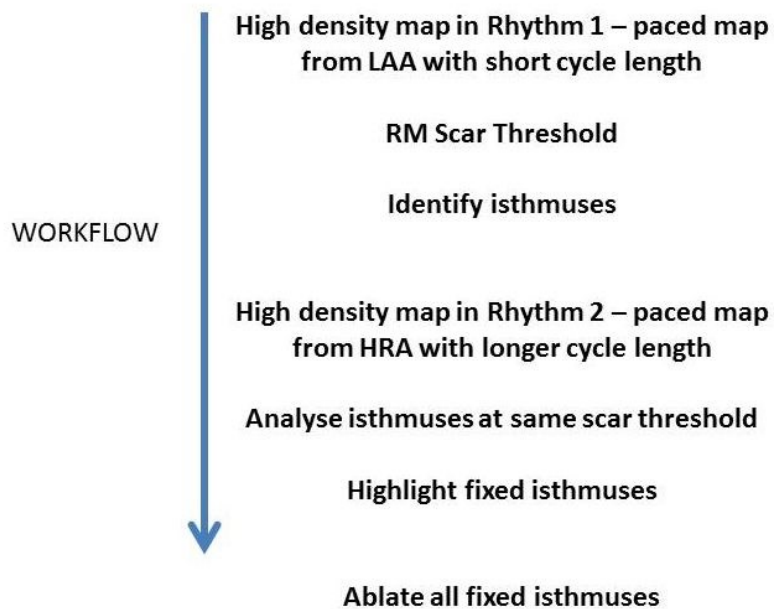
Early validation studies of voltage displays compared histo-pathological specimens to scar patterns obtained in sinus rhythm.⁹⁹ Despite this, electro-physiologists often interpret scar patterns by the voltage displays mapped in tachycardia. Nakagawa et al used the bipolar voltage and LAT display of a single tachycardia to define and eliminate all putative isthmuses that might be related to otherwise unmappable ATs in patients with prior surgical repair for congenital heart disease.⁶⁷ Areas with no atrial

potential <0.03 mV were considered dense scars and displayed in grey. Ablation was performed across as many narrow (3.0 cm in width) channels as possible. This study was performed approximately 15 years ago, using large tip, non-contact sensing linear catheters, collecting data point by point and manually annotating activation times. This approach led to high rates of acute non-inducibility and low recurrence rates at >1 yr median follow up, supporting the feasibility of adopting this clinical approach. However, more recent studies have demonstrated variation in voltage displays between different rhythms.^{108, 109}

Our study is the first attempting to understand whether a voltage map in the previously ablated left atrium obtained in different rhythms appear the same, i.e. whether the location of low voltage tissue is fixed; a necessary pre-requisite before considering a substrate based ablative approach. The patients included had all undergone previous ablation for persistent AF and ATs. An understanding of the substrate was determined in sustained AT. High density mapping was used to characterize the substrate in detail (>2500 points). Contact with the endocardial surface was reliably determined using a tissue proximity filter based on impedance. Multi-polar mapping catheters with smaller tips and narrower inter-electrode spacing compared to conventional linear catheters were used to record more accurate EGMs from smaller tissue diameter.¹⁰⁴

We found the voltage displays were generally concordant between rhythms. In the ablated left atrium, this is somewhat expected, as an isthmus bordered by an area of ablated tissue is inevitably bound by fixed conduction block on either side, which will always be seen whatever the rhythm. This is particularly the case in isthmuses formed from CPVI where the roof and mitral isthmus is a natural path of subsequent conduction activation, and as such is often addressed empirically in AF ablation procedures. We infrequently observed non-conductive tissue in one rhythm which was conductive in another. As regions of functional block within the ablated left atrium can still occur, an empirical substrate ablative approach based on the isthmuses identified in one rhythm alone would not be recommended.

Therefore, on the basis of this study, a putative workflow for future substrate ablation approach for patients presenting with non-inducible or poorly sustained AT could be considered using the workflow summarised below.



Note: LAA - left atrial appendage, HRA – high right atrium

7.1.5 Limitations

This was a retrospective study with a small sample size, though the concept is hypothesis generating for future prospective studies.

The absolute value of the scar threshold determined by this method of identifying conducting tissue is dependent on the recording technique and noise threshold of the recording system which will influence the resolution and quality of the EGMs that are used for the Ripple maps. Thus, these areas of non-conducting tissue identified using RM may have been considered as conductive tissue with higher resolution mapping.

7.1.6 Conclusions

The majority of isthmuses defined by RM scar thresholding appear anatomically stable when remapped between different rhythms, with different cycle length and activation directions. As approximately 25% of patients recruited to the randomised Ripple AT study have been non-inducible on the day procedure, identifying these stable isthmuses outside of tachycardia could offer a potential substrate based ablative approach.

7.2 The VT diastolic pathway and its electro-architectural relationship to the Ripple mapping conduction channel.

7.2.1 Introduction

Much of what is known of the electro-architecture within human scar is based on EGM studies of infarcted ventricular tissue in arrhythmia and sinus rhythm.³¹ The identification of fractionation and local potentials outside of the QRS window (preceding the QRS in VT, and after the QRS in sinus rhythm) was recognized as surrogates of slow conduction within scar, critical for reentry, and lead to an understanding that this electro-architecture was formed of islands of unexcitable myocardium with interconnected channels of relatively viable and electrically active tissue.^{48, 52} This model is supported by electrophysiological responses to entrainment as seen during VT ablation procedures, histological studies within scar, and the fact that local ablation targeting the “earliest” late potential eliminates neighbouring and remote areas of slow conduction.^{53, 54, 126} In Chapter 6, we showed that RM was able to define this electro-architecture by presenting local EGMs with increasing activation delay organized within channels.

This underlying electro-architectural model pre-supposes that these channels are anatomically fixed in location, bordered by non-conductive scar. However, we have seen using the non-contact mapping system that these boundaries can be functional with relatively normal EGMs in sinus rhythm.¹¹⁷ In this study, we used RM to carefully investigate the relationship between the diastolic pathway (RM-DP) in VT with conducting channels (RM-CC) in sinus/paced rhythm.

7.2.2 Methods

From the patient cohort studied within chapter 6 (n=15), we identified all patients where the scar was mapped in both tolerated VT and sinus rhythm/controlled pacing (n=3). These maps had been collected using a SmartTouch Thermocool catheter (n=2), and PentaRay (n=1) with colour threshold <5mm to ensure adequate point density for comparison. The details of RM-CC and RM-DP identification have been already described within chapter 6. For this analysis, bars were clipped at 0.30mV to allow low

voltage signals to be displayed more clearly, and bars less than 0.05mV were hidden from the Ripple Map to reduce background noise.

The CARTO system allows multiple maps to be displayed simultaneously, as an overlay, one on top of the other. Furthermore, the EGM data for the “live” map remains accessible for review within the overlay. The CARTO Ripple viewer, described in chapter 2.5, allows EGMS of multiple sampled points collected within the map to be displayed together, with each sampled point highlighted using a stationary coloured bar (ripple marking).

Design lines were drawn to encircle the boundaries of activation to highlight the RM-DP and RM-CCs. These RM-DP and RM-CC outlines were subsequently overlaid (figure 7-4). A series of equally spaced EGMS along the RM-DP were marked for display in the Ripple Viewer. Subsequently, corresponding EGMS immediately outside the RM-DP were also marked for review. By changing the underlying “live” map, we studied the EGM signals both inside and immediately outside our design line construct of the RM-DP, during both controlled pacing and during VT.

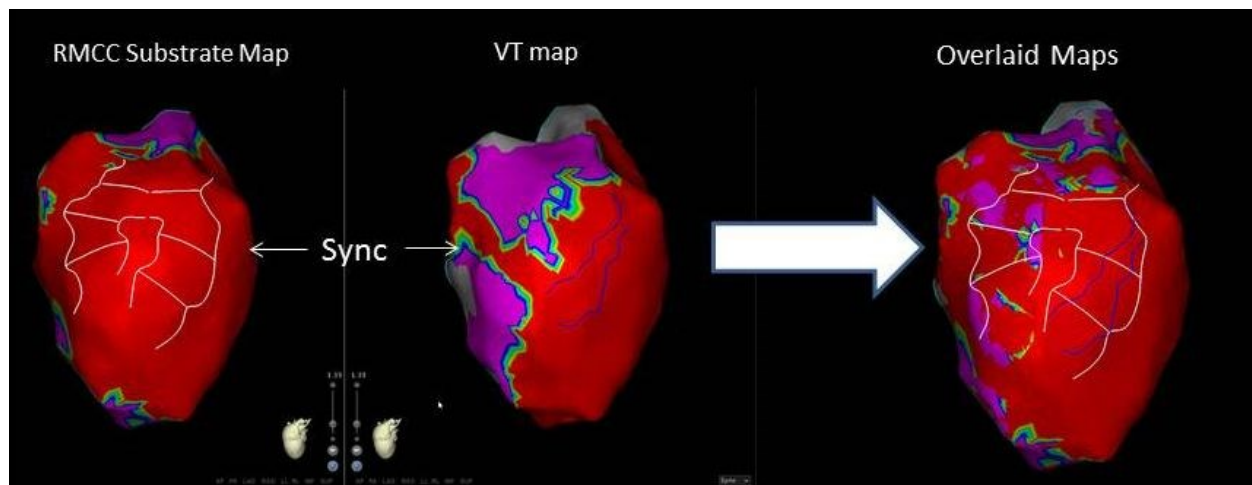


Figure 7-4: RM-CC and RM-DP overlay

The RM-CC substrate map (left) and VT map (right) from figure 4 in chapter 6 (Pt. 9) are displayed in identical orientations (“sync views”). In order to demonstrate the location of the RM-DP in relation to the RM-CCs, the VT map has been opened directly on the RM-CC map. The CARTO system merges the colours represented by the voltage map.

7.2.3 Results

Ripple maps in tolerated VT and controlled pacing were accomplished in only 3 patients. These maps included high point density within the scars for comparative analysis (1205 ± 1026 EGMs in VT, and 846 ± 740 EGMs in controlled pacing). A single RM-DP was mapped in VT in each case (length 61 ± 17 mm, area $5 \pm 0.3 \text{ cm}^2$, amplitude of the diastolic component $0.27 \pm 0.18 \text{ mV}$), and occupied 46% of the tachycardia cycle length. A total of 8 RM-CCs (length 60 ± 23 mm, area $5.4 \pm 3 \text{ cm}^2$, delayed component $0.21 \pm 0.17 \text{ mV}$) were identified in the corresponding substrate maps mapped during controlled RV pacing. By overlaying the 3 RM-DP and RM-CC maps, it was possible to understand the relationship between these. Importantly, figure 7-5 demonstrates that each RM-DP collocated within the area of an RM-CC. This supports the functional significance of the RM-CCs identified in chapter 6.

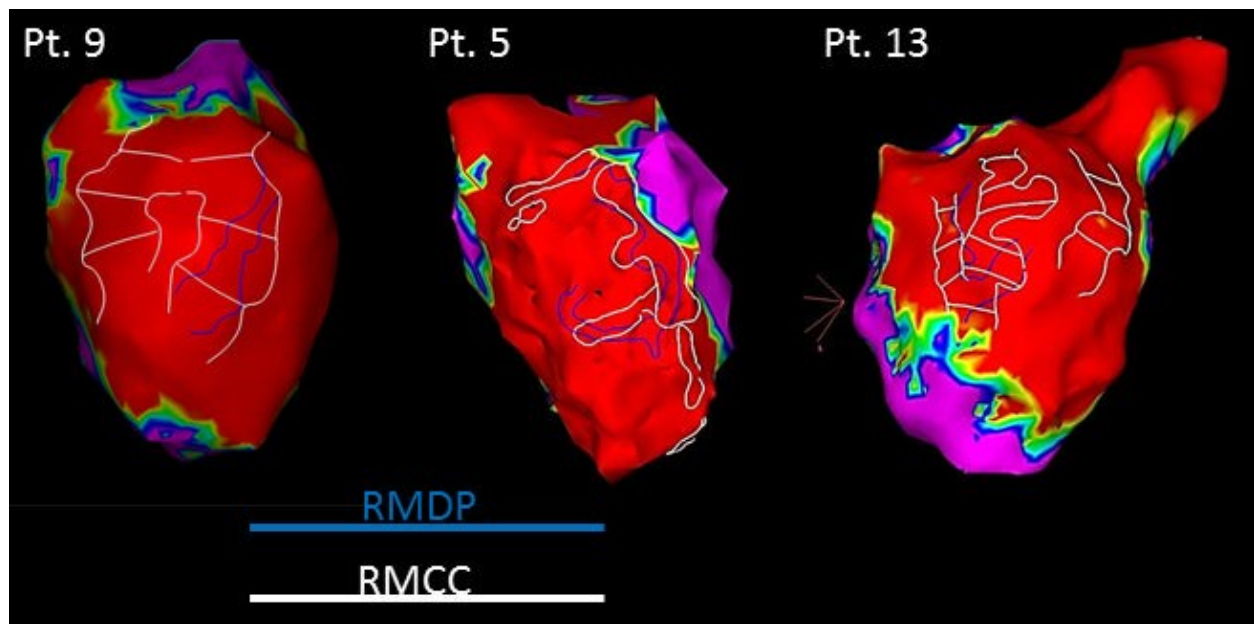


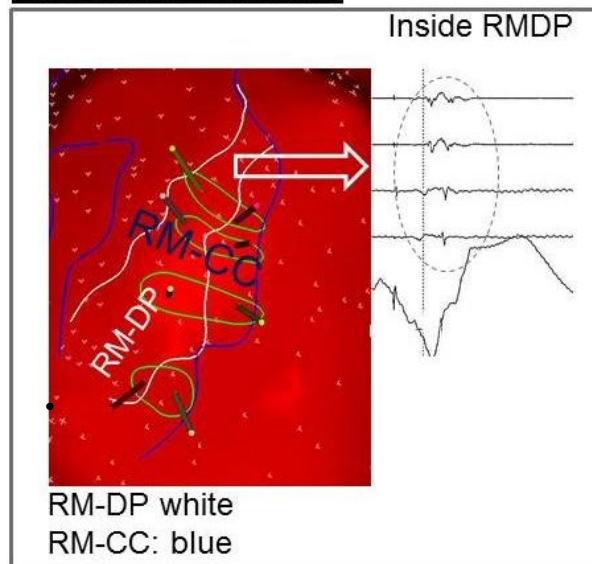
Figure 7-5: RM-CC and RM-DP collocation

VT was mapped in the 3 cases presented (Pts. 9, 5, 13). The VT map was opened on its corresponding RM-CC map and the RM-DP is outlined in blue and the RM-CC in white. The RM-DP collocates within the corresponding RM-CCs, reinforcing the functional significance of the RM-CCs identified.

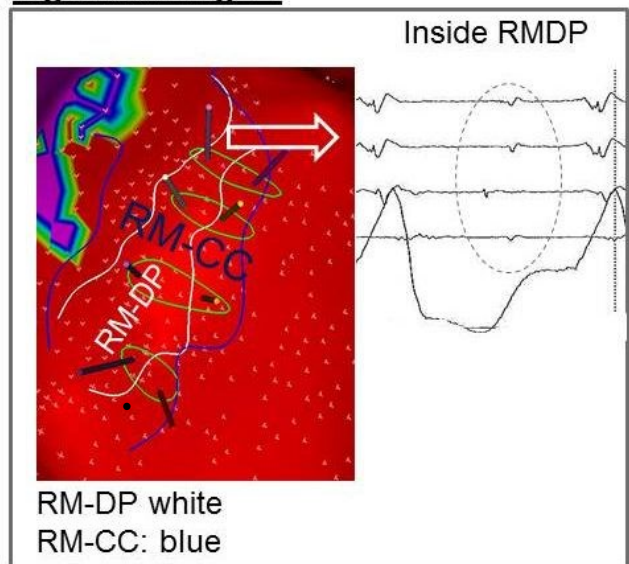
Interestingly, figure 7-6 demonstrates how the lines of block bordering the RM-DPs were formed of myocardium with no signal during VT but of conducting myocardium during sinus rhythm (peak amplitude $0.22 \pm 0.1 \text{ mV}$). This suggests that the RM-DP borders were formed of functional block, and that

that these areas of functional block were within the RM-CC borders ($20 \pm 13\%$ of total RM-CC area), and not at the scar border-zone. A further example is presented in figure 7-7.

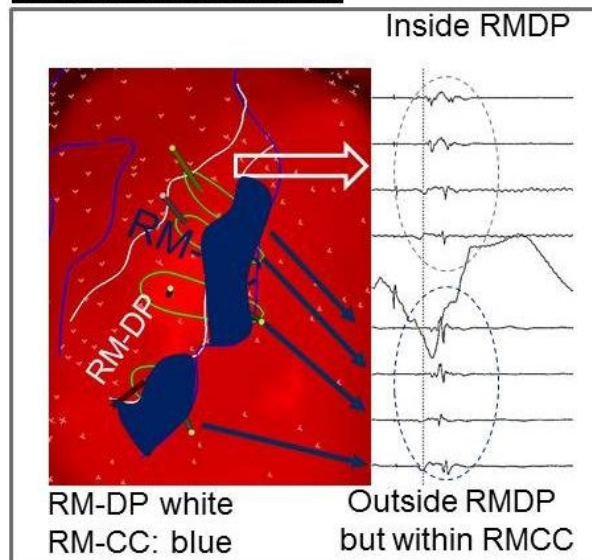
Signals during pacing



Signals during VT



Signals during pacing



Signals during VT

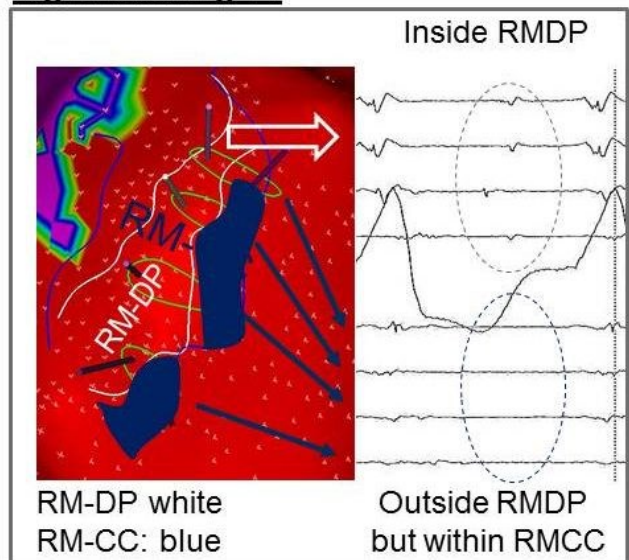


*Figure 7-6: An example of functional lines of block border the RM-DP
The lines of block bordering the RM-DP (white outline) mapped in VT from Pt. 9 were analysed in greater detail. The area of the RM-DP is contained within the edge of the RM-CC (blue outline) mapped in paced rhythm. The area immediately outside the RM-DP border, but contained within the RM-CC (blue patch) was formed of myocardium that has signal during pacing but without any diastolic potentials during VT confirming this is an area of functional block.*

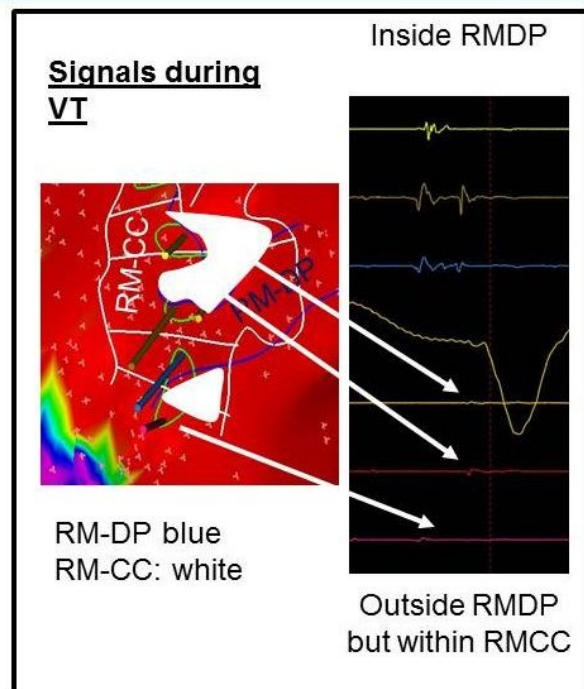
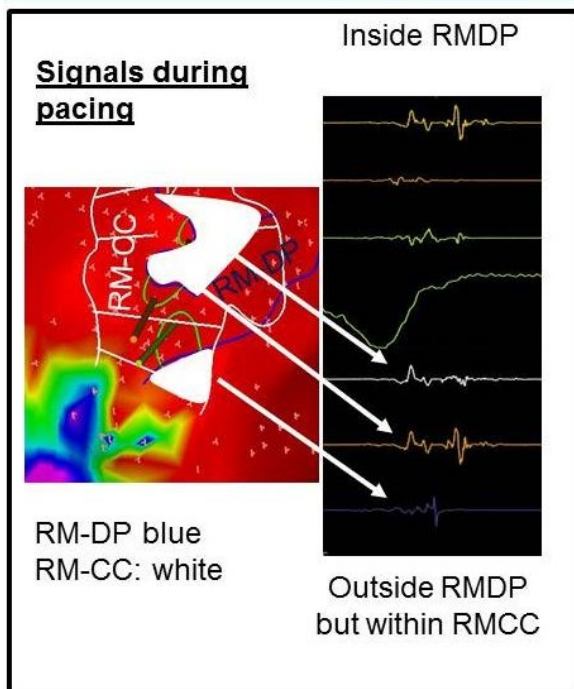
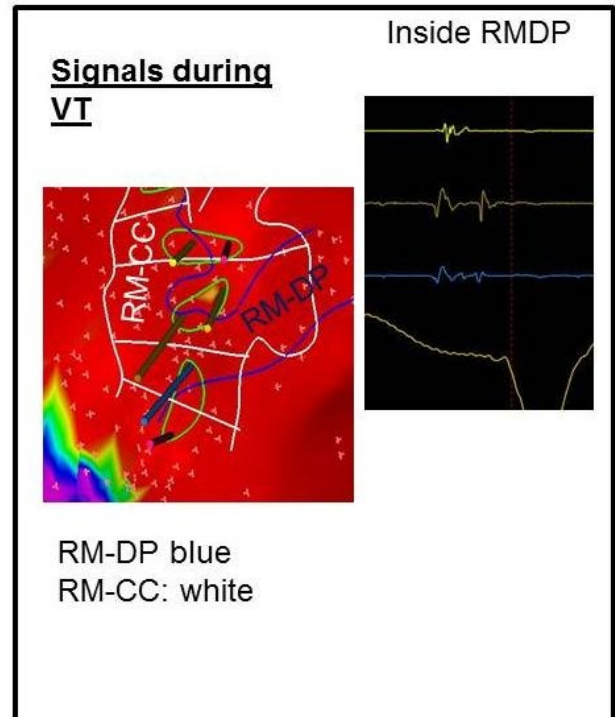
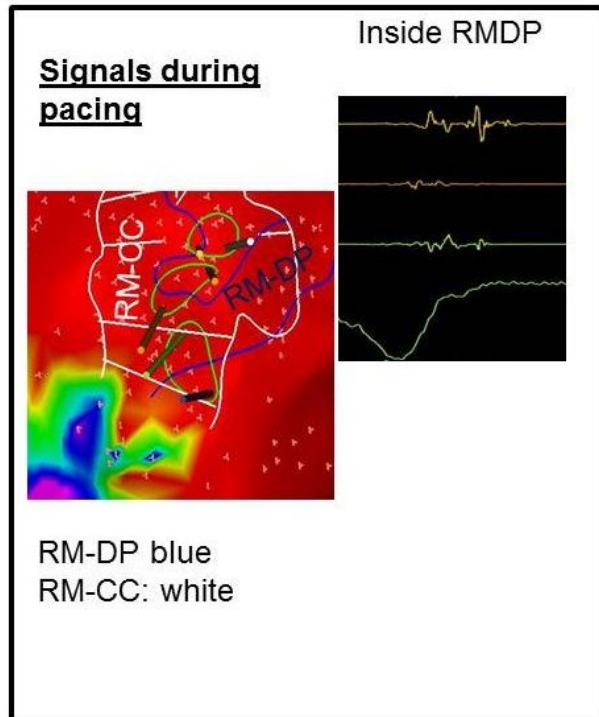


Figure 7-7: Another example of functional lines of block border the RM-DP
The lines of block bordering the RM-DP (blue outline) mapped in VT from Pt. 13 were analysed in greater detail. As seen previously, the area of the RM-DP is contained within the edge of the RM-CC (white outline). The area inside the RM-DP has signal during pacing and VT. However, the area immediately outside the RM-DP but within the RM-CC (white patch) had signal during pacing but nil during VT suggesting this was an area of functional block.

7.2.4 Discussion

This study describes an analysis of ventricular scar mapped in tolerated VT and controlled pacing using RM, and has identified that the VT diastolic isthmus co-located with RM conduction channels (though this analysis was limited to 3 cases), supporting the functional significance of conduction channels mapped outside of tachycardia using RM.

At present the only mapping system to directly correlate the electro-architectural model of the diastolic pathway in and out of VT was the non-contact mapping system, as it was able to acquire global data from the entire left ventricular endocardium in just a single beat. This was achieved using a multi-electrode array balloon with 64 electrodes on its surface (Ensite, Endocardial Solutions) situated mid cavity, that was able to sense and record far-field endocardial activity throughout the chamber and transform this into “nearfield” points. Early work with this system suggested that channels of slow conduction were fixed in location, as these regions of slow conduction in sinus rhythm overlapped the region of slow conduction during tachycardia.¹¹⁹ Subsequent work into VT mechanisms disproved this model, suggesting that isthmus borders can be partially functional with relatively normal EGMs in sinus rhythm, arising in regions of non-uniform anisotropy that can slow conduction in the absence of fibrosis.¹¹⁷

In this study, we were able to show that where the RM-DP could be mapped, it was contained entirely within the RM-CCs. In certain areas, it was formed by functional block within the RM-CC borders. The RM-DPs did not always co-locate to the latest late potentials within scar, nor did they locate to the infarct-border zone as defined by conventional bipolar voltage mapping. Therefore ‘lateness’ per se is not always the key determinant of arrhythmic potential, nor is the scar-border zone. It is possible that at shorter pacing intervals the local EGMs of the RM-CCs may become more delayed and eventually exhibit functional block, resulting in smaller RM-CCs, that are more specific for diastolic pathways, though this hypothesis requires further study, and is explored in the final chapter. At present, from this analysis, it seems apparent that only a portion of the RM-CC is needed to produce a diastolic pathway and complete RM-CC homogenization may not be a necessity.

7.2.5 Conclusions

RM can identify channels of local activation within the post-infarct endocardial VT substrate that co-locate with the VT diastolic isthmuses, and offer a novel target for substrate ablation. RM-CC borders appear to be the location of stable, functional lines of block within the diastolic pathway. Further study in a higher number of patients is required to support these findings.

7.2.6 Summary

In this chapter, we have studied Ripple Maps within atrial and ventricular scars, where maps have been collected in stable tachycardia and a second rhythm (either a different tachycardia or during controlled pacing, with different cycle length and activation direction), to determine whether the electro-architecture is fixed, and the significance of functional block that contributes to non-conducting areas mapped during tachycardia.

We have seen that in the previously ablated atrium, non-conducting areas tend to be fixed in location. Therefore, in cases of AT non-inducibility or frequently changing activation sequences, ablation of these isthmuses adjacent to these non-conducting regions mapped outside of tachycardia may be considered a novel strategy for the long term freedom from future ATs.

Within ventricular scar, functional block supporting reentry appears more significant. We found that non-conductive tissue bordering part of the diastolic pathway was conductive when mapped during controlled pacing. Only a portion of the RM-CC, mapped during pacing, was needed to produce the diastolic pathway. This suggests that at shorter pacing intervals, the local EGMs within the RM-CCs may eventually exhibit functional block, resulting in smaller RM-CCs that are more specific for the diastolic pathway, and a more refined target for ablation.

Chapter 8

8 Conclusions

The ablation of scar based arrhythmia is challenging for several reasons, including the difficulty defining the electro-architecture within scar, the inability to deliver durable ablation lesions within this unhealthy tissue, and an arrhythmic substrate often left to evolve for too long. This thesis has explored new clinical approaches into the mapping and ablation of scar based arrhythmia, focusing on patients with post-AF ablation AT and post-infarct VT.

The Hansen robotic system offers increased catheter stability to target myocardial tissue with deeper lesions.^{147, 152} We demonstrated the feasibility of using this system in performing LV endocardial ablation within post-infarct scar in a small series of patients with mostly severe ventricular dysfunction, and this included patients presenting in ICD storm, and those who had failed manual ablation. Robotically guided ablation resulted in a significant reduction in ICD therapies over a 6 month averaged interval. When compared to a matched cohort of non-robotic ablations, despite a potentially more arrhythmic substrate in the robotic arm, the acute and long-term (2 year follow up) outcomes between the two groups were similar.¹⁶⁷

On the basis that robotic VT ablation was safe and feasible, we considered the optimal timing for VT ablation in a randomised control trial recruiting patients earlier into the arrhythmic disease process after their first ICD therapy to a treatment strategy of either robotically guided VT ablation or a non-ablative approach (ERASE-VT). We were able to show the earlier robotic ablation delayed the time to VT recurrence, though this finding was non-significant. Post hoc analysis of those patients with EF $\geq 30\%$ demonstrated a statistically significant delay in time to VT recurrence and reduction of overall therapy burden post ablation, though this finding was under-powered to make any firm conclusion. A systematic review of our data with three other completed randomised controlled trials all exploring the efficacy of early ablation on recurrent episodes of VT found that early VT ablation is associated with increased survival from further ICD therapy compared to a non-ablative approach, and that ejection fraction (EF $>30\%$) was a key determinant in this effectiveness.

The recurrence of VT in some patients despite ablation suggested a failure of mapping to accurately define the arrhythmic substrate. The Rhythmia mapping system employs a 64 mini-electrode basket catheter, each with small tips and narrow inter-electrode spacing, to achieve ultra-high point density

and increased EGM resolution.¹²⁰ The system uses an automated means of assigning LAT to study activation, and we were able to visualise regions of conductive tissue with voltage amplitude 5-10 times smaller than conventional mapping systems. Before contemplating its use in VT, we tested the system mapping ATs within post ablation atrial scar. We were able to delineate the activation of localised reentry as small rotatory activations around scar approximately 1cm in diameter, ablation of which interrupted the tachycardia circuit. However, we observed small rotational activations on most maps collected, though this represented LR in only a small proportion. The majority were pseudo-reentrant, either a result of wavefront collision, mis-annotation of artefact and interpolation in areas of incomplete mapping.²⁰⁷ Therefore, we felt this would be inadequate for VT mapping.

RM was developed in our institution as an alternate method of activation visualisation without annotation of LAT and interpolation between unmapped sites.¹²³ EGMs are displayed as a moving bar at its corresponding 3D coordinate perpendicular to the cardiac chamber in relation to a fiducial reference, without a WOI. We demonstrated the feasibility of using RM in a prospective series of post ablation ATs, with very high ablation success rates, a combined effect of reducing errors related to WOI assignment and activation time annotation, as well as a new method to help define activation through low voltage functional tissue.¹⁹¹ By playing the RM over a bipolar voltage map, we determined a voltage threshold to define non-conductive tissue in each patient by identifying the lowest signal supporting activating wavefronts of ripple bars. We called this technique “scar thresholding.” This technique enabled a more precise visualisation of activation through non-conductive, defining reentry by the location and dimensions of the critical isthmus, the path-length, as well as the number of bystander circuits formed as activation split around regions of block. Despite appearing somewhat different to traditional colour coded LAT maps, new users to RM found it easy to adopt with high diagnostic success. An interim analysis half way through an RCT comparing RM with LAT maps, RM has demonstrated non-significant superiority suggesting this method of mapping is optimal within atrial scar. Approximately 25% of patients recruited to the randomised Ripple AT study have been non-inducible on the day procedure. Errors in LAT mapping have been related to the interpolated “backward wavefront” where the apparent site of “early meets late” fail to actually meet, and WOI errors when mapping in areas surrounded by scar, leading to regions that activated so ‘late’ in relation to the assigned window that they appeared ‘early’ in the LAT map in relation to the next timing cycle.

The technique of RM scar thresholding allowed us to learn that the majority of isthmuses of conducting tissue within atrial scar appear anatomically stable when remapped between different rhythms, with different cycle length and activation directions. These stable isthmuses mapped outside of tachycardia could offer a future atrial substrate based ablative approach.

The approach to RM within ventricular scar was quite different to that in the atrium because of the extent of far-field EGMs from the surrounding healthy myocardium when substrate mapping in sinus rhythm/controlled pacing. We observed how automated LAT systems incorrectly annotate voltage and timing to the far-field component, though with RM we could differentiate an initial far-field wavefront that occurred in tandem with bars in the surrounding healthy tissue, from a delayed wavefront of local activation. By studying the path of the ripple bars in the delayed wavefront, we were able to define conduction channels through scar, which co-located with the VT diastolic isthmus.¹⁸⁰ However, our approach to ablation still resulted in a 30% recurrence rate at 6 month follow up, comparable with several other approaches to VT substrate ablation.^{89, 97, 116} The patients in this study had advanced arrhythmic disease with median ejection fraction of 30% both of which we had shown are associated with high recurrence rates.

One of the reasons for VT recurrence may be related to a false assumption that VT channels are bordered by fixed block of fibrous scar. We were able to show that where the diastolic pathway could be mapped, in certain areas, it was formed of functional block during tachycardia with preserved EGMs in sinus rhythm. If the barriers of conduction are functional, then our current approaches to all methods of substrate ablation are limited. In one of the last public speeches made by the late Mark Josephson, when he spoke at the New York international VT symposium in November 2016, he echoed these sentiments.

"After spending 40 years looking at substrates and activation...I've come to the conclusion that the understanding of VT is relatively naïve...Everyone is focused on scar, and we assume that the isthmus is bounded by fixed scar...the barriers of conduction are really functional, because they are not there in sinus rhythm. A more accurate analysis of the functional characteristics responsible for creating and maintaining the VT circuit is needed before we can move on."

The final section proposes a future prospective study using RM to understand how EGMs within ventricular scar behave under different electrophysiological stressors as a means to further understand the contribution of functional block within reentrant circuits.

8.1 Future directions – Using Ripple Mapping to study EGM behavior within ventricular scar

EGMs within ventricular scar that are found to be low amplitude, multicomponent, high frequency, and late occurring are often targeted during substrate ablation.^{54, 208-210} Recent studies have demonstrated how EGM characteristics, notably their bipolar amplitude and timing can change according to the direction of activation and pacing rate. Tung et al elegantly demonstrated how mapping the scar from the RV apex and basal LV can create different voltage patterns.¹⁰⁹ DEEP mapping (delayed evoked extra-stimulus potentials) has also demonstrated that with shorter coupling intervals, these EGMs can either decrement or block, changing the pattern of local activation through scar.²¹¹ Understanding the behavior of an EGM within scar under different electrophysiological environments is important before assuming it is an appropriate target for substrate ablation. For example, EGMs with decremental conduction are more likely to participate in reentrant circuits, as regions where conduction completely blocks, without delayed conduction, may not have a sufficient excitable gap to initiate or sustain reentry. The proposal for the next study is to use RM prospectively to study this EGM behavior within ventricular scar.

The combination of RM with CARTO is uniquely suited to study this EGM behavior. Each acquired point on the CARTO system records a total of 2.5 seconds of EGM data at a time (-2 seconds before the assigned reference to +0.5 seconds after). RM is able to display all the EGM information collected from each channel over this 2.5 second period, with the ability to clip the Ripple viewer to truncate the information desired. Thus a map of a pacing drive train can be seen, and by adjusting the timing window, a map of a closely coupled extra-stimulus can also be seen. For example, if the effective refractory period (ERP) is 250ms, acquiring a point whilst pacing at 600ms (100bpm) for 3 beats (1800ms) and at ERP + 50ms for 2 beats (600ms) will create 2 simultaneous maps at 600ms and 300ms respectively for comparison. This avoids remapping at 300ms continuously, which is time consuming and likely to be poorly tolerated.

Potential changes in ventricular EGM behavior within a slowly conducting isthmus with extra-stimulus testing are illustrated in Figures 8-1 and 8-2. Tissue has been mapped with small electrodes, where the amplitude of the local signal can exceed the far-field.

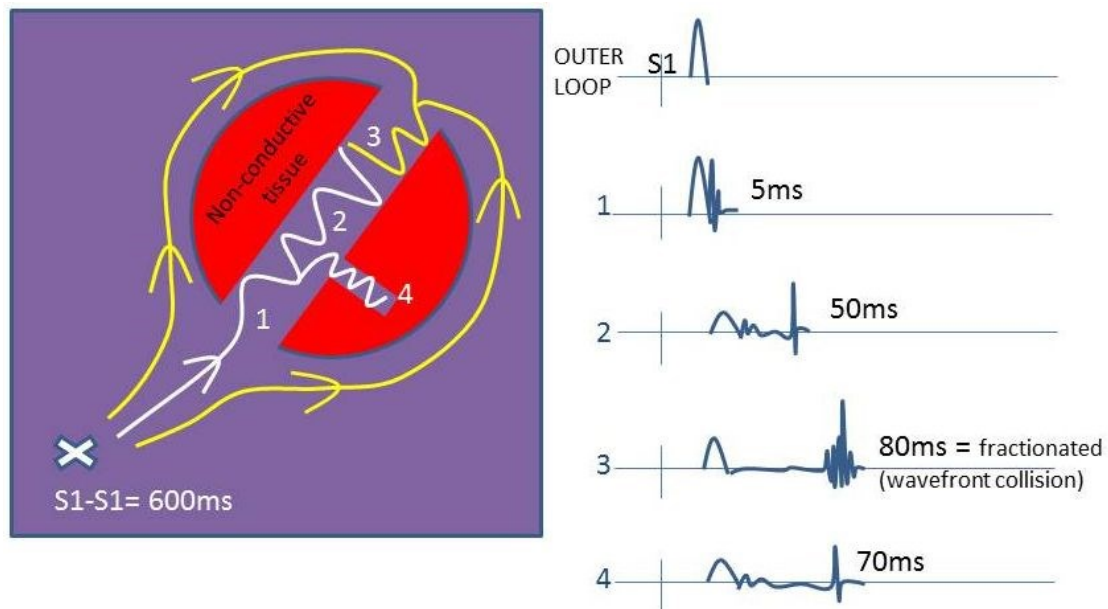


Figure 8-1: Pacing from the right side of the heart at a 600ms drive. Myocardial wavefront travel across the endocardial surface, invades an area of slow conduction from both ends bordered on either end by non-conductive tissue (note, whether this is fixed or functional block at this stage is unknown). At site 1, the local EGM is fused with far-field. At site 2 within the centre of the slow conduction isthmus, a late activating and sharp local EGM is evident. At site 3, this antegrade slowly conducting wavefront collides with a retrograde wavefront from the opposite side, creating a low amplitude and fractionated signal. Site 4 represents a dead end bystander, which in isolation presents an interesting late and local signal, but elimination of which will not prevent reentry.

By introducing a closely coupled extra-stimulus, considerable changes in EGM timing can arise from local decrement, as well as EGM morphology from alterations in wavefront-wavefront interaction and changes in tissue refractoriness. RM allows immediate visualisation of these changes.

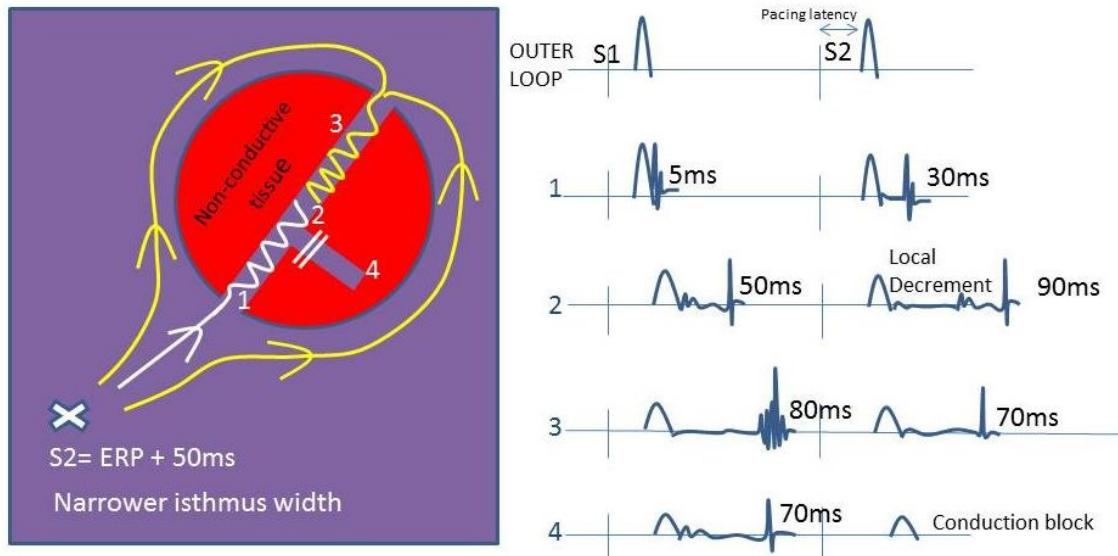


Figure 8-2: Extra-stimulus mapping

Pacing at a shorter coupling interval (ERP+50ms), isolated near-field potentials exhibit decremental conduction and delay in timing (sites 1 & 2). At site 1, this allows improved differentiation of the local from far-field signal. At site 2, the antegrade slow conduction wavefront has delayed such that the retrograde wavefront arrives to this site earlier, advancing the local activation time by 10ms, and the fractionation within the signal is lost as wavefront collision does not occur. At site 3, ERP of the bystander is reached. Under greater electrical stress, the width of the isthmus has also shortened.

As illustrated in figure 8-3, changes in activation direction can alter the local EGM timing from changes in fibre orientation in relation to the wavefront direction (non-uniform anisotropy), as well as EGM morphology from changes in electrode orientation (perpendicular or parallel) in relation to the wavefront direction. Again RM allows visualisation of these changes.

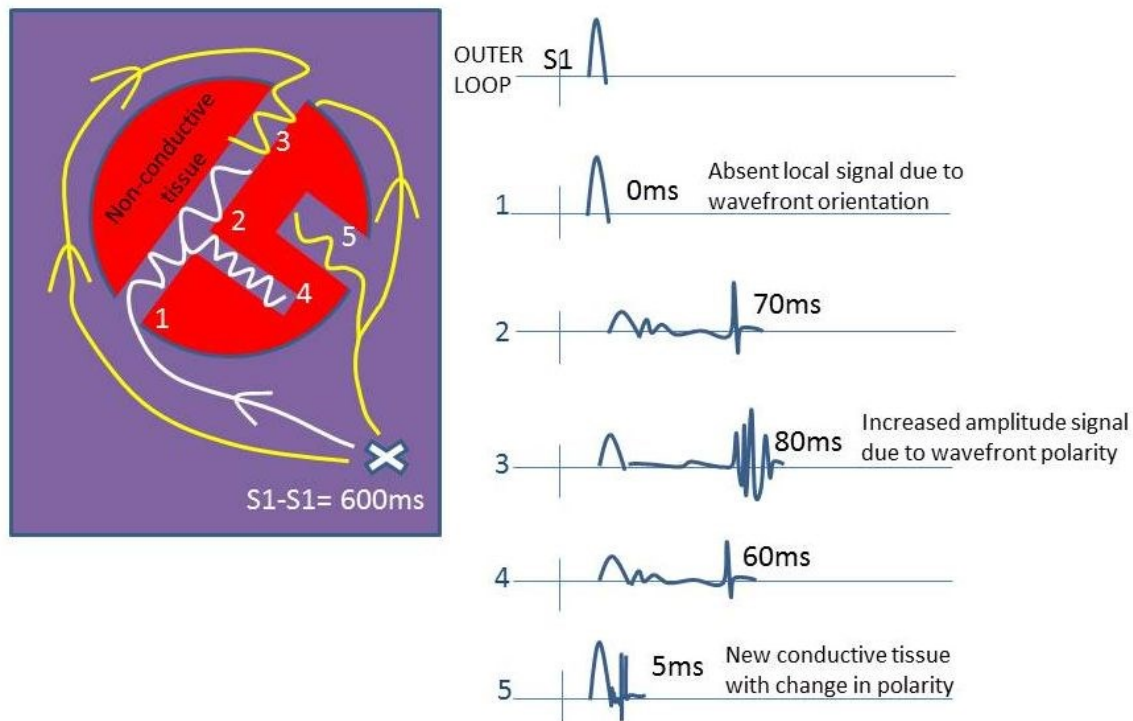
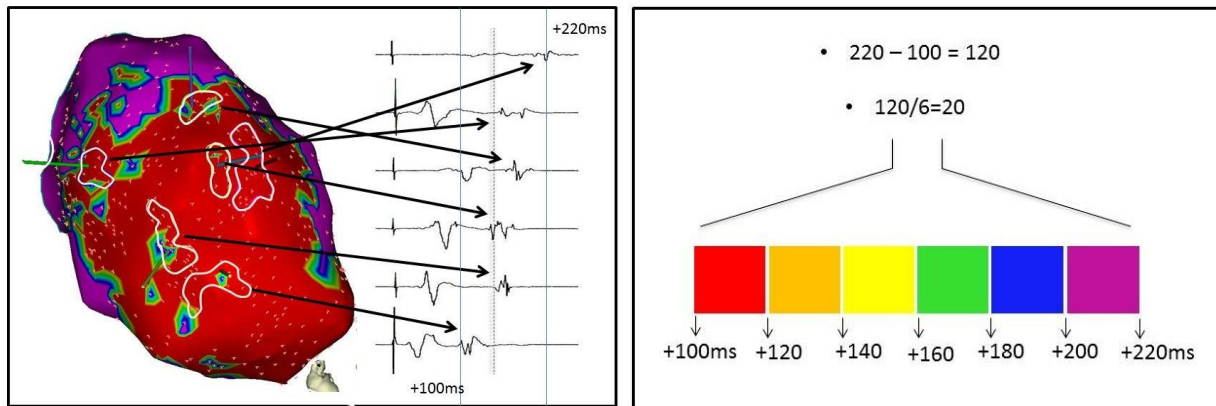


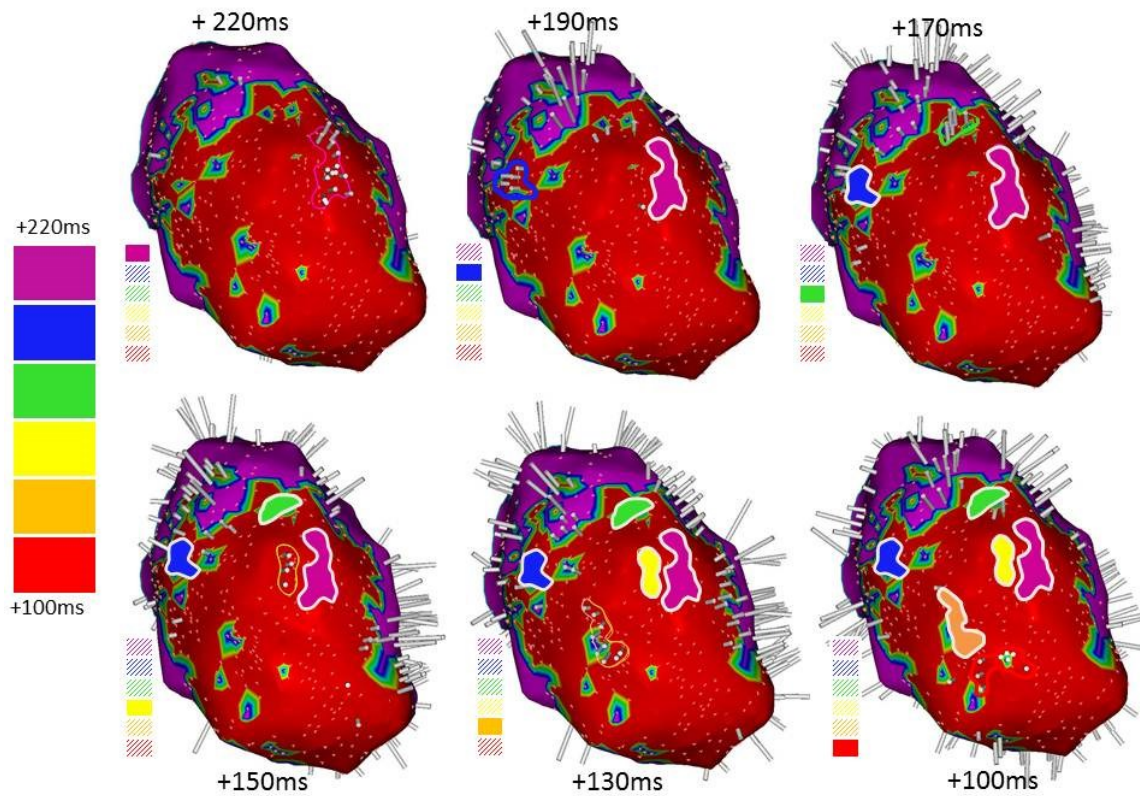
Figure 8-3: Pacing from the left heart at 600ms drive

At site 1, the local signal is no longer evident as the wavefront arrives perpendicular to the slowly conducting isthmus, cancelling out the bipolar EGM signal. In contrast, the local signal happens to be higher at site 3, likely related to the catheter orientation parallel to this zone. At site 5, a zone of conductive tissue is seen, which was non-conductive with right sided pacing, from functional block associated with the wavefront direction.

In order to help our visualisation of the changes in local EGM activation through scar, we developed a simplified approach to displaying this information within ventricular scar - Ripple activation patch mapping" (RAP MAP) approach. As described in chapter 6, ripple maps are played frame by frame in reverse and design lines are used to highlight patches of late local activation. The example below presents an LV apical scar, where white design lines have been drawn around individual patches of late activation (as depicted by their associated EGMs). The RAP MAP approach use the same colour coded spectrum employed with conventional LAT maps, i.e. according to the colours of the rainbow. The "earliest" local signal and the "latest" local signal within scar are identified to determine the temporal period of interest for the Ripple analysis. The relative timing between these two intervals is divided by 6 (according to the six colours used within the rainbow spectrum – Red, Orange, Yellow, Green, Blue, and Violet), to determine the time subsets for the colour-coded scheme in Ripple analysis. Thus in the example below, the latest patch occurred 220ms post reference (stim artefact) and the earliest patch occurred 100ms post this reference – thus 20ms divides each colour subset.

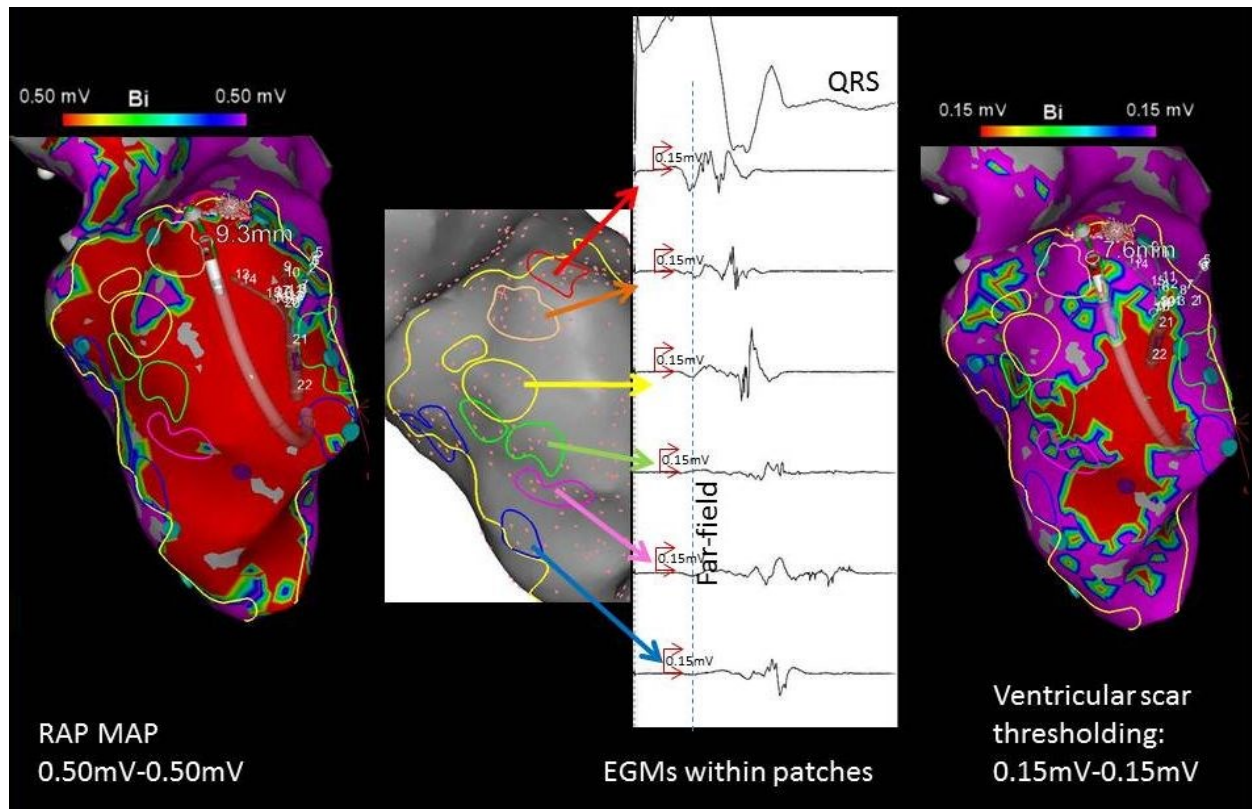


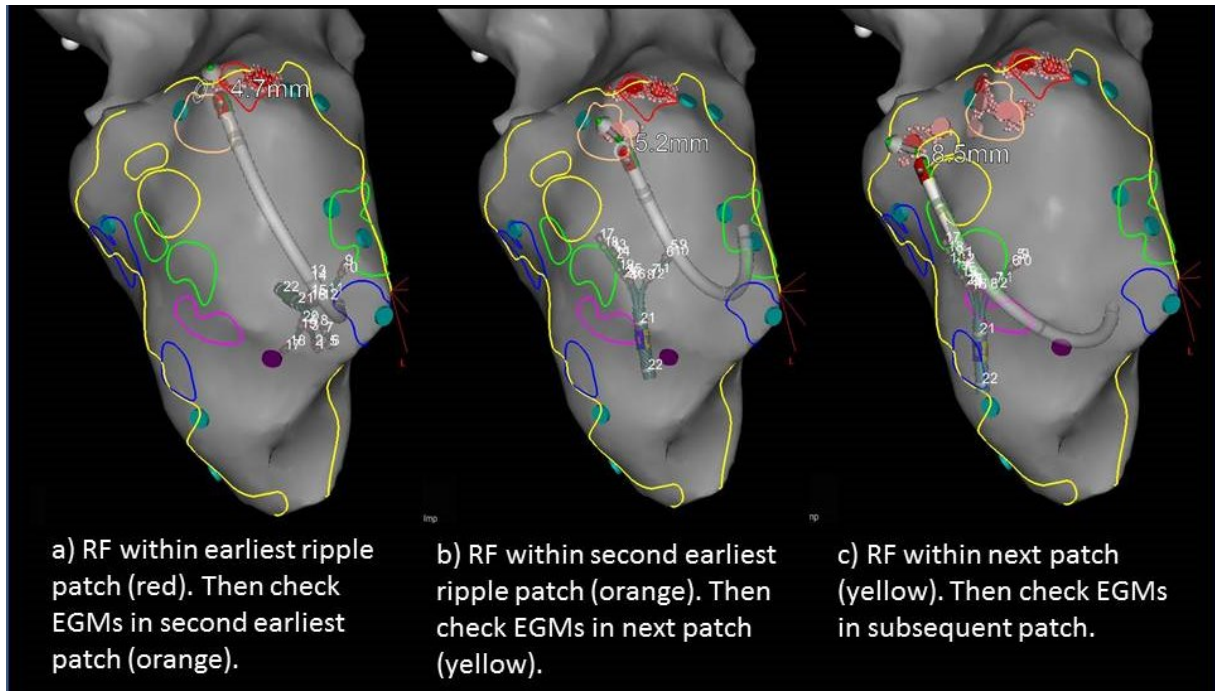
Each patch is subsequently coloured according to this colour scheme.



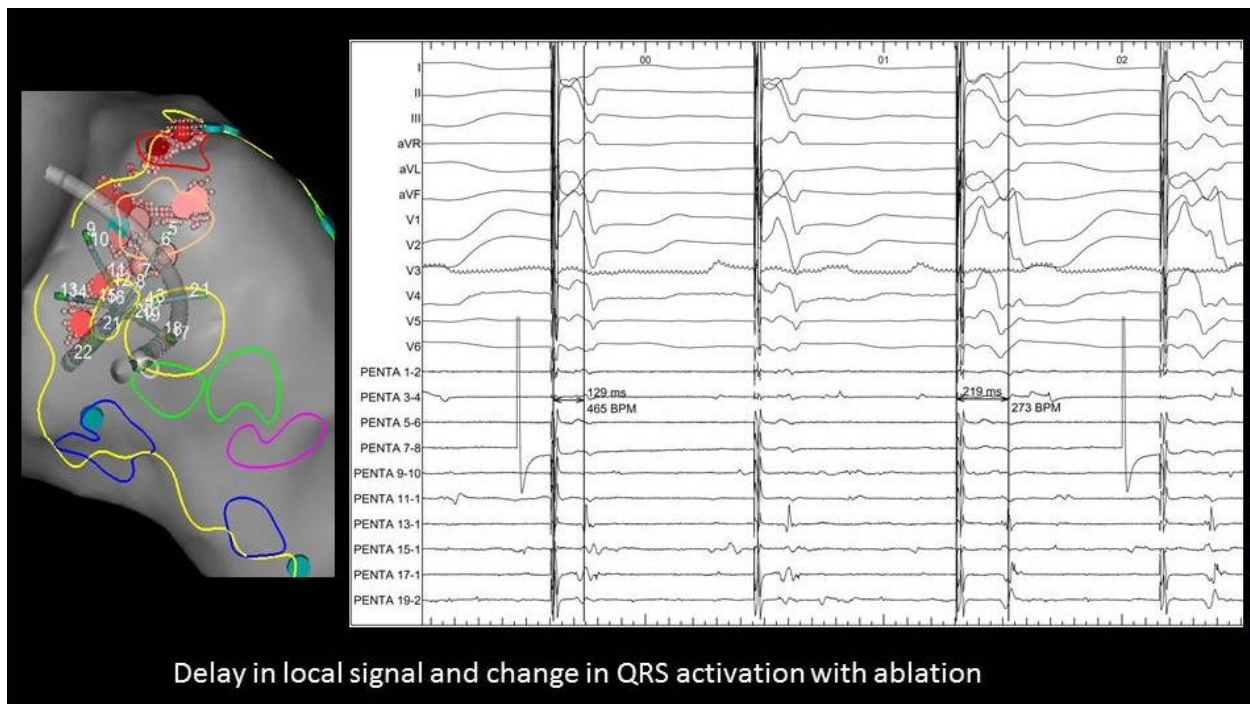
By comparing the RAP MAPs under different electrophysiological environments, we will be able to understand how local activation changes under these different circumstances.

The RAP MAP can also be used to guide ablation. We conclude this thesis with a case example of such an ablation approach.

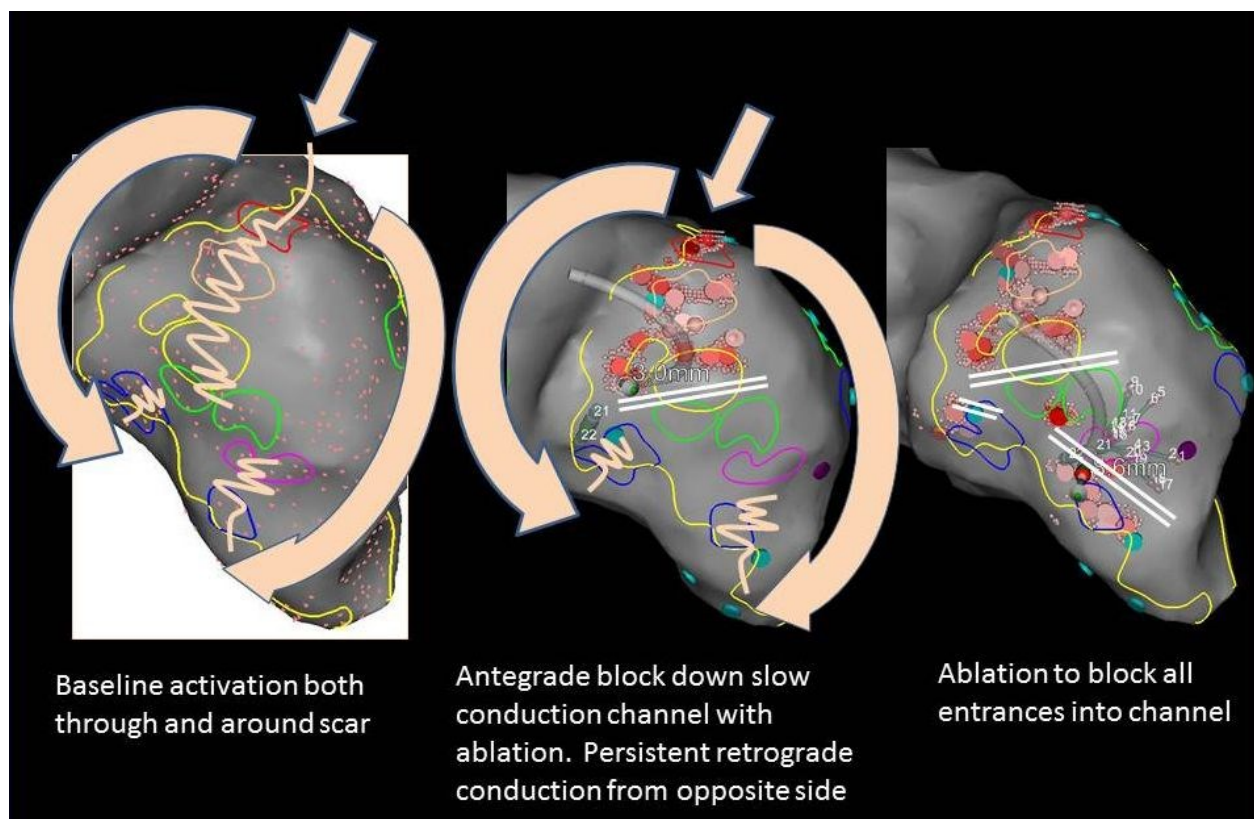




During ablation within the yellow patch, we observed a change in both local signal inside this patch, as well as a change in global activation, as manifest by a change in QRS morphology. With the Pentaray positioned inside the yellow patch, stim-local signal increased from 129ms to 219ms during ablation.



At the start of the case, it appeared that activation travelled around both sides of the low voltage zone (<0.5mV) as well as slowly through this channel of slow conduction mapped using the RAPMAP approach. This model of activation is highlighted below in the left sided image. Ablation within the earliest series of patches blocked antegrade conduction through the channel, as evident by the change in local activation and QRS morphology (middle). Activation was still able to enter the channel from the opposite side, and further ablation was performed at the scar border (right) at both these entrance points (blue patch) to eliminate retrograde channel activation. There-after the patient was non-inducible for further VT.



8.2 Final Summary

This thesis has described how outcomes can be improved in scar based arrhythmia such as post ablation AT and post infarct VT using the new RM technique. We have also identified that VT ablation by robotic manipulation is feasible and optimally performed early in the arrhythmic disease course in patients with left ventricular ejection fraction $>30\%$ after their first ICD therapy. This thesis would recommend that an RM based substrate ablation in patients with EF $>30\%$, after their first ICD therapy, mapped with ultra-high density and small tip and narrowly spaced electrodes, would next be studied.

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