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Functional Substrate Mapping: A New Frontier in the Treatment of Ventricular Tachycardia in Structural Heart Disease

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Abstract

Functional substrate mapping has emerged as an essential tool for electrophysiologists, overcoming many limitations of conventional mapping techniques and demonstrating favourable long-term outcomes in clinical studies. However, a consensus on the definition of 'functional substrate' mapping remains elusive, hindering a structured approach to research in the field. In this review, we highlight the differences between 'functional mapping' techniques (which assess tissue response to the 'electrophysiological stress' using short coupled extrastimuli) and those highlighting regions of slow conduction during sinus rhythm. We also address fundamental questions, including the optimal degree of electrophysiological stress that best underpins the critical isthmus and the role of wavefront activation in determining the most effective ablation site.

Keywords

Ventricular tachycardia, functional substrate, ablation, structural heart disease

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The rising burden of ventricular tachycardia (VT) in patients with structural heart disease (SHD) represents a significant challenge for cardiologists. Advances in medical therapies, improved MI survival and the increased use of primary prevention ICDs have resulted in more patients presenting with ventricular arrhythmias later in life. The effectiveness of antiarrhythmic drugs to treat these arrhythmias is often limited by ineffectiveness and poor tolerability secondary to adverse side effects and drug interactions, emphasising the critical role of invasive catheter ablation in this cohort.[1,2] However, despite significant improvements in mapping and ablation catheter technology, outcomes following VT ablation remain suboptimal, with high recurrence rates.[3–5] Reasons include the inability to create durable lesions and accurately identify all critical components of the VT circuit. The development of novel ablation methods, such as pulsed field ablation, ultra-low cryoablation and ultrasound catheter ablation, may improve lesion formation, but the identification of critical components of the VT circuit with effective electrophysiological mapping remains fundamental for the successful invasive treatment of VT with reliable long-term outcomes.[6–8]

Conventional Approaches to Ventricular Tachycardia Mapping

VT mapping techniques have evolved considerably over the past few decades, deepening our understanding of arrhythmic substrates. Initially, intraoperative endocardial and epicardial mapping were used to identify the VT site of origin with positive surgical resection outcomes and, in turn, provided momentum for further electrophysiological research in this field.[6] Since then, conventional mapping techniques, such as activation, entrainment and pace mapping, have become well established as standard techniques for identifying key ablation targets.[8–11] *Table 1* summarises these approaches. Activation mapping of VT with the use of local activation timing maps has long been considered the gold standard approach for identifying the VT circuit and critical isthmus by delineating the propagation of the tachycardia wavefront over specific time points, but is limited by non-inducibility and haemodynamic instability, with 60–70% of scar-related VT associated with cardiovascular collapse.[8,12] Entrainment of the tachycardia through overdrive pacing and assessment of the return cycle can also accurately identify critical ablation targets. Despite an effective method to confirm critical sites, entrainment mapping suffers from similar limitations as VT activation mapping. In addition, inability to pace capture within the low-voltage substrate can occur particularly with high-density mapping catheters due to the smaller electrode sizes.[10] The role of endocardial pace mapping was highlighted by Josephson et al., when they demonstrated similar surface ECG morphology when pacing at the VT site of origin.[13] However, this method may not always identify the optimal ablation target and is restricted by the need for a baseline 12-lead ECG, which is not available with device-detected arrhythmias.

Table 1: Summary of Conventional Mapping Techniques and Their Limitations

Mapping technique	Methodology	Advantages	Disadvantages
Activation mapping	Involves the use of local EGM and surface ECG data to determine the timing and direction of the electrical wavefront Aims to identify the critical isthmus of the macro re-entrant tachycardia as the site of continuous activity during diastole or isolated mid-diastolic potentials	Identifies the critical isthmus, which represents an ideal ablation target	Requires induction of clinical VT and its haemodynamic stability to allow mapping Requires a stable tachycardia morphology and CL for mapping Generating a full activation map can be time consuming
Pace mapping	Electrical stimulation from various endocardial sites will produce different surface ECG morphologies A comparison between the paced morphology and that of the clinical VT can identify the tachycardia exit site	Does not require the induction of clinical VT during the procedure Does not rely on the haemodynamic stability of the tachycardia to enable mapping	Requires ECG documentation of the clinical tachycardia morphology, which may not be possible with device-detected tachycardias The VT site of origin may not represent the optimal ablation target
Entrainment mapping	The re-entrant tachycardia is repeatedly reset by each consecutive beat from a drivetrain (delivered at a shorter CL to the tachycardia) Entrainment mapping enables the diagnosis and characterisation of re-entrant arrhythmias from analysis of the specific interaction between pacing manoeuvres and the tachycardia[11]	Can identify the underlying mechanism of the tachycardia rapidly (focal versus macro re-entrant) Can identify key ablation sites without the need to fully map the tachycardia chamber, which reduces procedure time	Requires induction of clinical VT and its haemodynamic stability to allow mapping Requires a stable tachycardia morphology and CL for mapping Tachycardia can be terminated by entrainment
Substrate mapping	Invasive electroanatomical mapping and local voltage data are used to identify regions of healthy and scarred myocardium, as well as border zones Conduction channels that may be used in a VT circuit are identified and targeted for ablation	Does not require induction of the tachycardia during the procedure Does not require prior documentation of the clinical tachycardia surface ECG morphology	Can identify a large ablation target area, which will prolong procedure time and increase risk Regions of the myocardium not involved in the tachycardia circuit may be targeted during ablation

CL = cycle length; EGM = electrogram; VT = ventricular tachycardia.

From Doubt to Promise With Mapping During Sinus Rhythm

Mapping during sinus rhythm provides a safer and more reproducible approach in patients with VT and has the potential to highlight substrates for future arrhythmia. However, this technique has not always been considered a viable alternative to conventional mapping of VT. In 1984, Cassidy et al. noted that bipolar electrograms (EGMs) obtained from VT site of origin were significantly lower in amplitude and longer in duration, suggesting areas of abnormal or scarred myocardium.[14] However, they noted that these characteristics lacked specificity, potentially leading to broader surgical targets involving healthy myocardium and occasional exclusion of the actual VT origin site, diminishing its perceived efficacy as an alternative to conventional approaches.[14] Despite these initial concerns, subsequent research (highlighted later in this review) has since demonstrated the transformative role of mapping during sinus rhythm, and its favourable outcomes following substrate elimination.

This review explores the role of sinus and functional substrate mapping in improving patient outcomes following VT ablation. We discuss mapping and ablation strategies beyond voltage-based scar homogenisation, which is no longer practical in patients with extensive myocardial scarring. Specifically, we aim to clearly define 'functional' substrate mapping approaches, highlighting their differences from other sinus rhythm mapping methods, and discuss the role of high-density mapping and its potential future developments aimed at improving patient outcomes in the near future.

Role of High-density Mapping in Improving Patient Outcomes

The integration of high-density mapping technology marked a paradigm shift in our ability to rapidly generate detailed intraprocedural substrate maps. Advanced mapping catheter designs, such as the Advisor HD Grid (Abbott Laboratories) and the Octaray (Biosense Webster), are able to use closely coupled electrodes to capture thousands of EGM signals and swiftly generate detailed high-density maps (*Figure 1*). The close coupling of the electrodes (3 mm in the Advisor HD Grid; 2–5 mm in the Octaray) uncovers low-voltage EGMs not previously identified with traditional point-by-point mapping catheters, providing further insight into arrhythmic substrates. Their multidirectional electrode orientation has also overcome the major limitation of bipolar blindness (seen with traditional catheters) by assessing the activation wavefront in multiple vectors regardless of catheter position, identifying potential conduction channels in what was previously seen as dense scar. The introduction of activation direction-based mapping with the Advisor HD Grid catheter (Abbott Laboratories), which does not rely on time annotation, but instead relies on waveshape relationship, has enabled wavefront direction for each heartbeat.[15] This can provide further valuable information regarding arrhythmia mechanism. Omnipolar EGMs have further improved our ability to identify conduction channels by providing voltage, timing and activation direction independent of catheter orientation.[15]

The positive clinical impact of high-density mapping was demonstrated in a recent study of 73 patients with SHD who underwent VT ablation.[16] The authors of that study demonstrated that using multipolar catheters facilitated the mapping of an increased number of haemodynamically stable/unstable VTs, which translated to a better procedural outcome. The use of the Advisor HD Grid catheter was associated with a remarkable 97% rate of freedom from any device-detected therapies over a mean (±SD) follow-up of 372 ± 234 days, compared with rates of 33% and 64% for point-by-point mapping and Pentaray, respectively.[16] Complementing this are advances in 3D mapping systems (e.g. EnSite X [Abbott Laboratories], Carto [Biosense Webster] and Rhythmia [Boston Scientific]), which have enhanced procedural efficiency and streamlined VT ablation workflows through automated signal annotation. These systems also

facilitate the generation of maps assessing local tissue voltage and activation timings to refine our understanding of arrhythmic substrates in diverse ways.

Yet, despite these technological leaps, we continue to see the recurrent VT and ICD shocks after ablation.[5] This highlights the need to deepen our insights into arrhythmic substrates and optimise the targeting of all the critical components of the VT circuit during ablation.

Slow-conduction Zones as a Target for Ablation

Re-entry serves as the major fundamental mechanism for VT in patients with SHD, relying on regions of slow conduction susceptible to unidirectional block, which constitutes a key component of the VT circuit (*Figure 2A*). Identifying and targeting these regions of slow conduction during sinus rhythm provides a procedural endpoint in patients with SHD and has been the focus of work by multiple research groups, as outlined below.

Early insights by Cassidy et al. using low-density mapping catheters noted abnormally prolonged and low-amplitude bipolar EGM signals during sinus rhythm at the VT site of origin.[14] However, performance analysis of these EGMs was constrained by poor specificity.[14] Since these seminal observations, the advent of high-density mapping catheters and electroanatomical mapping systems has enabled more precise high-density localised mapping.[16,17] The multiple close-coupled electrodes have enabled accurate mapping of low-amplitude signals, abnormal fractionation and delayed conduction within the scar substrate.[18]

Local Abnormal Ventricular Activity

A hallmark feature of slow-conduction zones is local abnormal ventricular activity (LAVA), defined as low-amplitude, high-frequency ventricular potentials occurring after or within the far-field ventricular EGM (*Figure 2B*). Jaïs et al. demonstrated that targeting LAVA was a valid and reproducible endpoint for VT ablation.[19] In their cohort of 70 patients with SHD (ischaemic and non-ischaemic dilated cardiomyopathy), LAVAs were identified in 67 patients and their elimination correlated with a reduction in recurrent VT or death (HR 0.49; 95% CI [0.26–0.95]; p=0.035) at a median follow up of 22 months.[19] Notably, despite successful LAVA elimination, 22 patients continued to exhibit VT inducibility.[19]

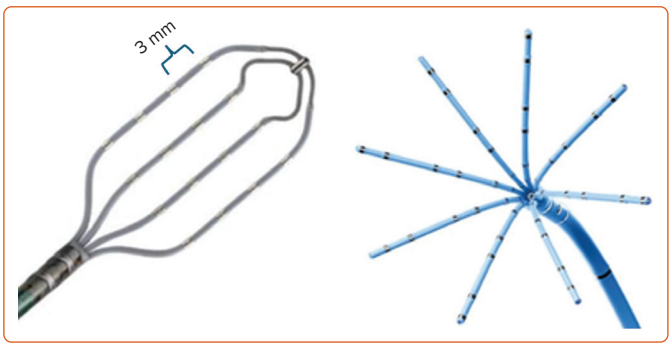
Late Potentials

Late potentials (LPs), identified as local signals occurring after the terminal portion of the surface QRS complex, have long been thought to represent regions of slow local conduction (*Figure 2B*).[20,21] These areas represent tissue susceptible to unidirectional block and re-entry, and hence potential targets for VT ablation. Vergara et al. assessed the role of LP abolition in improving outcomes for patients with scar-related VT in a cohort of 64 patients with ischaemic and non-ischaemic cardiomyopathy.[22] During a mean (± SD) follow-up period of 13.4 ± 4.0 months, 90.5% of patients with complete elimination of LPs were free from VT recurrence (p<0.0001).[22] Silberbauer et al. further expanded on this work by demonstrating a lower incidence of VT recurrence in patients who fulfilled the combined endpoint of LP abolition and VT non-inducibility.[23] In their cohort of 155 patients with ischaemic cardiomyopathy, VT recurrence was seen in 32%.[23] In the 73 non-inducible patients who achieved the combined endpoint, VT recurrence was significantly lower (16%) than VT non-inducibility alone (46%; log-rank p<0.001).[23]

Isochronal Late Activation Maps

Regions of slow conduction can also be highlighted through isochronal late activation maps (ILAM), indicated by a spread of closely packed isochrone lines (*Figure 2C*). In a retrospective analysis of 33 patients with SHD of ischaemic and non-ischaemic aetiology, Irie et al. demonstrated a correlation between critical re-entry sites and deceleration zones (defined as more than two isochrones within a 1 cm radius).[24] Importantly, defining LPs within gradients of activation highlighted that targeting of the latest LPs did not correlate with successful VT termination sites. The feasibility of this strategy was validated in a prospective cohort of 10 patients, where ILAM-guided VT termination was achieved in six cases.[24] Aziz et al. further evaluated ILAM-guided VT ablation in 120 SHD patients with scar-related VT and found that by targeting deceleration zones (more than three isochrones within a 1 cm radius; 80% in ischaemic cardiomyopathy, 63% in non-ischaemic cardiomyopathy), 70% freedom from VT recurrence was achieved at a mean (± SD) 12 ± 10 months follow-up.[25]

Figure 1: Image of the Advisor HD Grid and Octaray Mapping Catheters Demonstrating Multiple Close Coupled Electrodes, Enabling High-density Mapping



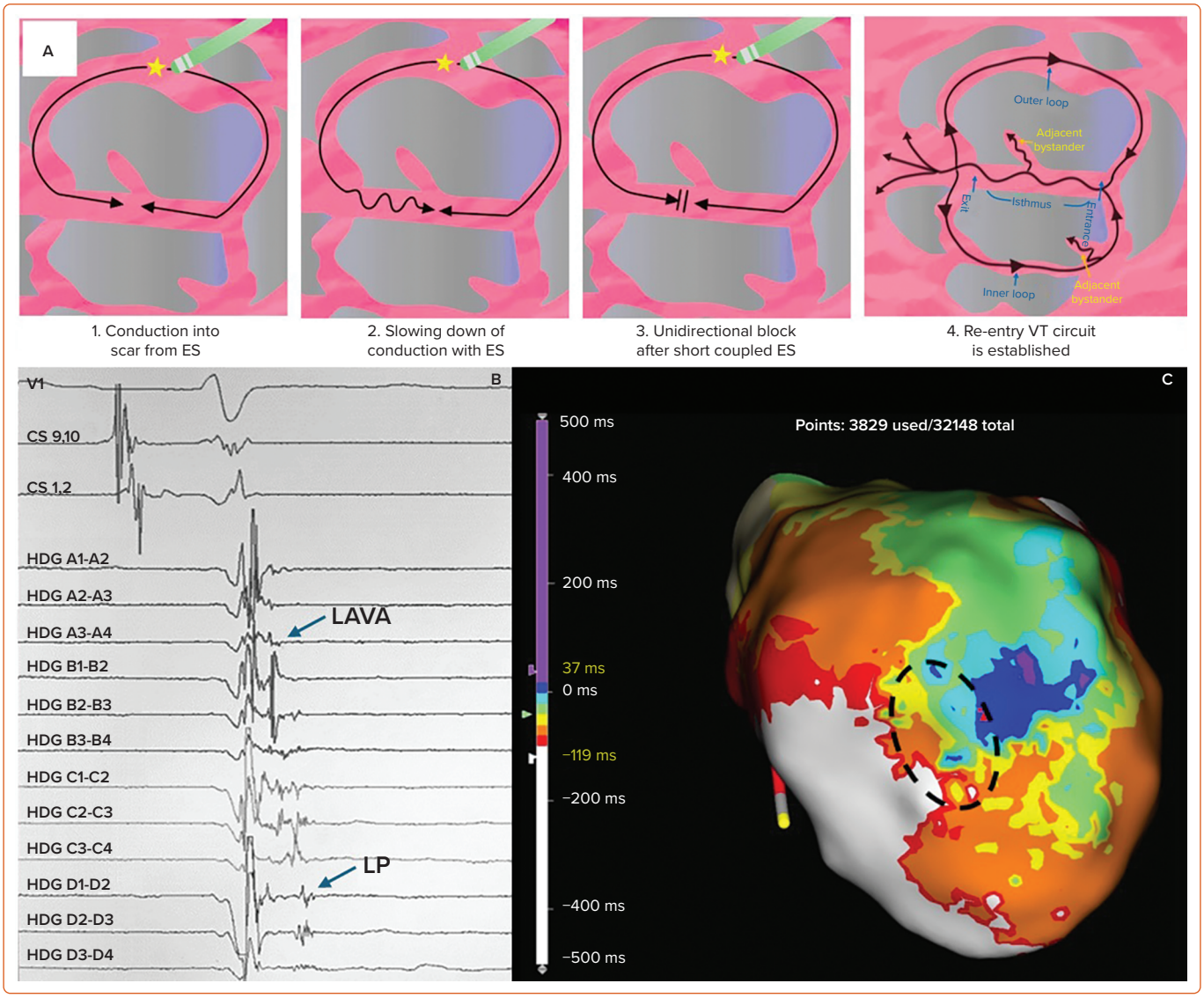
**3 mm spacing between electrodes on the HD grid catheter. Electrode spacing on the Octaray is 2–5 mm, depending on the catheter used.*

Ventricular Map of Electrogram Duration

In an attempt to identify conductive vulnerable zones of slow conduction within the VT circuit, Rossi et al. developed a novel ventricular map of EGM duration (VEDUM).[26] In their initial study of 21 patients with a total of 24 VTs, Rossi et al. verified that the zone of slowest conduction during VT represented an effective ablation target because 88% of episodes were terminated with radiofrequency ablation at the site of longest EGM duration.[26] In a subsequent prospective study of 32 patients with ischaemic and non-ischaemic cardiomyopathy undergoing VEDUM mapping during sinus (or paced) rhythm, Rossi et al. found that 93.5% of VT isthmuses were located within VEDUM zones with a mean (± SD) size of 12.1 ± 6.9 cm^2; 71.9% of the maps were collected during sinus rhythm (SR), with the remaining 28.1% collected during right ventricular pacing (RVp).[27] The authors found no statistically significant difference in the size of the VEDUM area collected during SR and RVp (10.9 ± 5.0 cm^2 [IQR 7.9–14.3 cm^2] versus 15.1 ± 10.2 cm^2 [IQR 7.8–18.0 cm^2]; p=0.13).[27]

The impact of the activation wavefront on substrate mapping and the optimal rhythm for mapping have been recent points of discussion. Lima da Silva et al. looked at 31 high-density maps (in 16 patients) and found no statistically significant difference in the total LAVA area between SR, RVp and left ventricular pacing, despite a trend towards a larger area in RVp maps.[28] However, there was a difference in the location of LAVAs identified during mapping at different rhythms. The spatial concordance for LAVAs between the SR, RVp and left ventricular pacing maps was only 33.3 ± 1.5%.[28] Lima da Silva et al. also noted that the location of deceleration zones was dependent on the activation wavefront, but 66% of conduction channels were identified in all three rhythms.[28] Of note, the conduction

Figure 2: Slow Conduction Facilitates Re-entry



A: Mechanism of re-entrant scar-related VT. 1. Wavefront conducts through the scar using channels of surviving myocardium. 2. Conduction slows down with ES. 3. Unidirectional block occurs with a shorter coupling interval. 4. This is followed by a re-entrant circuit, which sustains the tachycardia. B: Example of LAVA and LP seen during electroanatomical mapping. C: Example of isochronal late activation map. Highlighted is a region of isochrone bunching representing slow conduction. ES = extrastimulus; LAVA = local abnormal ventricular activity; LP = late potential; VT = ventricular tachycardia.

channel acting as the critical isthmus was identified in all the maps. Chrispin and Tandri assessed the impact of SR and RVp on the concordance of the site of latest activation to the VT isthmus and found a higher concordance during RVp (85%) than SR (75%).[29]

Repolarisation Gradient Mapping

Regions of slow conduction identified through EGM analysis are found throughout the myocardial scar, but there are only a limited number of conduction channels relevant to the VT circuit. Callans and Donahue noted that in a cohort of six patients with ischaemic cardiomyopathy, EGM abnormalities (fractionated, split and late components) were seen within and outside of the VT circuit.[30] However, assessing local action potential duration using the activation recovery interval as a surrogate for the monophasic action potential resulted in a more accurate localisation of the VT isthmus.[30,31] The activation recovery interval was noted to be significantly shorter at sites within than outside the VT circuit (420.2 ± 79.3 versus 462.5 ± 52.8 ms; p=0.01), with VT termination occurring after the first ablation lesions at the shortest activation recovery interval site in three patients.[30]

Overall, targeting zones of slow conduction identified during mapping in SR offers a reproducible and effective endpoint for VT ablation. However, there is a risk of inadvertently targeting regions of slow conduction that are not part of the VT circuit, which may be further influenced by the direction of activation during mapping. In our view, these mapping techniques do not represent true 'functional' substrate mapping because they fail to subject the tissue to electrophysiological stress: regions susceptible to decrement and block. In the next section we discuss mapping techniques that highlight this 'functional' substrate.

Unmasking the Functional Substrate

True functional substrate mapping aims to highlight tissue most susceptible to re-entry under electrophysiological stress by delivering close coupled extrastimuli (ES). This approach identifies regions of decrement and conduction block. It is well established that decremental conduction precedes unidirectional block, which precedes re-entry. Evidence suggests this may be a more specific marker for critical components of the VT circuit than slow conduction alone, highlighting a more refined ablation target area, obviating the need for VT activation

Table 2: Summary of Functional Substrate Mapping Publications Highlighting the Variability in S2 Coupling Interval and Functional Substrate Thresholds

Study	Functional Substrate Mapping Methodology	Cohort Size	Pacing Site	S2 Coupling Interval	Functional Substrate Threshold	Follow-up Duration	Outcome
Porta-Sánchez et al. 2018[33]	DeEP	20	RV	VERP + 20 ms	>10 ms increase in ED from S1 to S2	6 months	75% of patients were free from any VT after DeEP-guided ablation.
Shariat et al. 2019[37]	PEFA	10	RV	VERP + 50 ms	>240 ms from S2 pacing spike to the end of the EGM (ED ≥120 ms)	Mean (± SD) 345 ± 90 days	90% of patients were free from VT recurrence during follow-up
Srinivasan et al. 2020[36]	Barts sense protocol	30	RV	VERP + 20 ms	LP defined as isolated high-frequency local EGMs after the offset of the terminal portion of the QRS	Median 12 months	90% of patients were free from ATP/ICD shocks
Crinion et al. 2021[38]	PEFA	40	RV	VERP + 30 ms	>240 ms duration from the S2 to the last deflection and an ED of >120 ms were targets for ablation (areas where only latency was observed were not targeted)	Median 711 days (IQR 255.5–972.8 days)	89.7% of patients were free from VT recurrence
Al-Sheikhli et al. 2023[34]	DeEP	10	RV	VTCL 400 ms and VERP + 20 ms	>10 ms to 50 ms thresholds were individually assessed A >10 ms increase in ED from S1 to S2 was used to guide ablation	6 months	92% of patients were free from VT recurrence*
Mumtaz et al. 2023[35]	eLP	16	RV	VERP + 20 ms	eLPs defined as near-field EGMs timed later than the surface QRS	NA	NA

**All ablations were performed using decrement-evoked potential (DeEP) maps where the S2 was delivered at 400 ms, and DeEPs were defined as a decrement of >10 ms. ATP = antitachycardia pacing; ED = electrogram duration; EGM = electrogram; eLP = evoked late potentials; PEFA = paced electrogram feature analysis; RV = right ventricle; VERP = ventricular effective refractory period; VTCL = ventricular tachycardia cycle length.*

mapping and reducing the risk of procedural complications. Mapping approaches using close coupled ES include decrement-evoked potential (DeEP) mapping, paced EGM feature analysis (PEFA) and the "Bart's" sense protocol, described in more detail below with relevant pioneering studies summarised in *Table 2*.

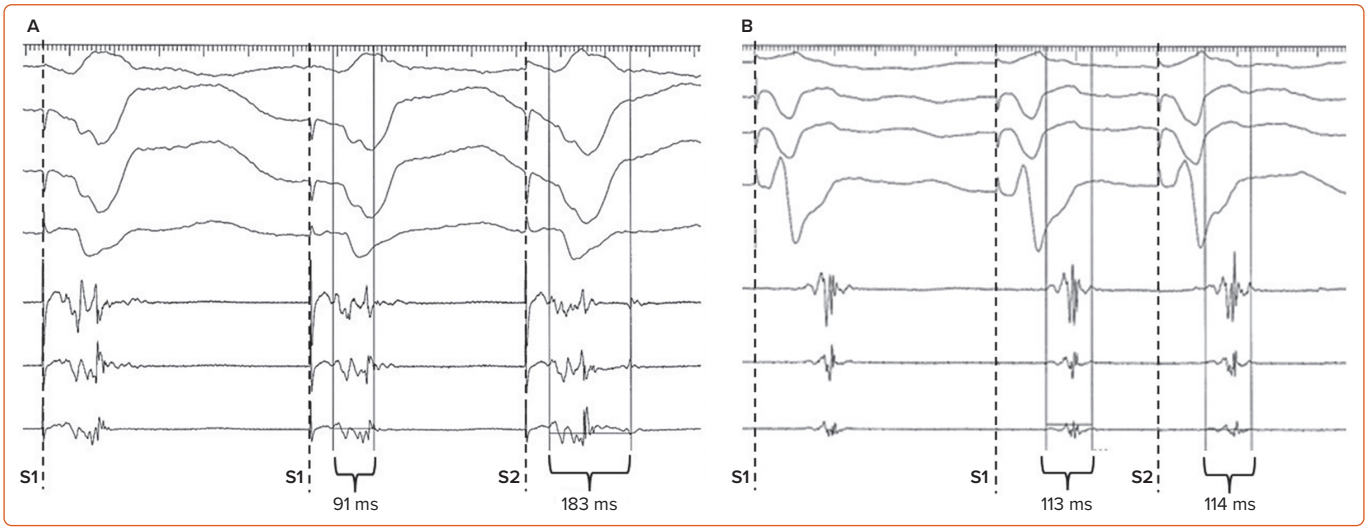
Several groups have demonstrated the benefits of analysing the EGM following delivery of an ES (S2) as part of a substrate VT ablation strategy. The pioneering LAVA approach of Jaïs et al. incorporated ES to distinguish LAVAs from ambiguous far-field ventricular EGMs, which can exhibit similar frequency components as LAVA.[19] It was observed that LAVAs progressively split further away from the far-field EGM after the delivery of a short coupled S2, which sometimes resulted in conduction block.[19] However, a systematic evaluation of the response to the ES was not undertaken, precluding an assessment of the impact of these signals on procedural outcomes.

Building upon the LAVA technique, Acosta et al. used double and triple ES to investigate whether LAVAs would decrement, referred to as potential 'hidden slow conduction' EGMs.[32] After determining the ventricular effective refractory period (VERP), a double ES was delivered from the right ventricular apex (RVA) at VERP + 60 ms and VERP + 40 to 20 ms. In more than two-thirds of patients, evidence of hidden slow-conduction EGMs was found. These EGMs were observed in scar core, border zone, and even normal voltage regions, relative to cardiac magnetic resonance-defined conduction corridors (i.e. bundles of viable myocardium inside scar). However, the study did not correlate the contribution of these hidden slow-conduction EGMs to the mapped VT isthmus of a re-entrant circuit.[32]

Decrement Evoked Potential Mapping

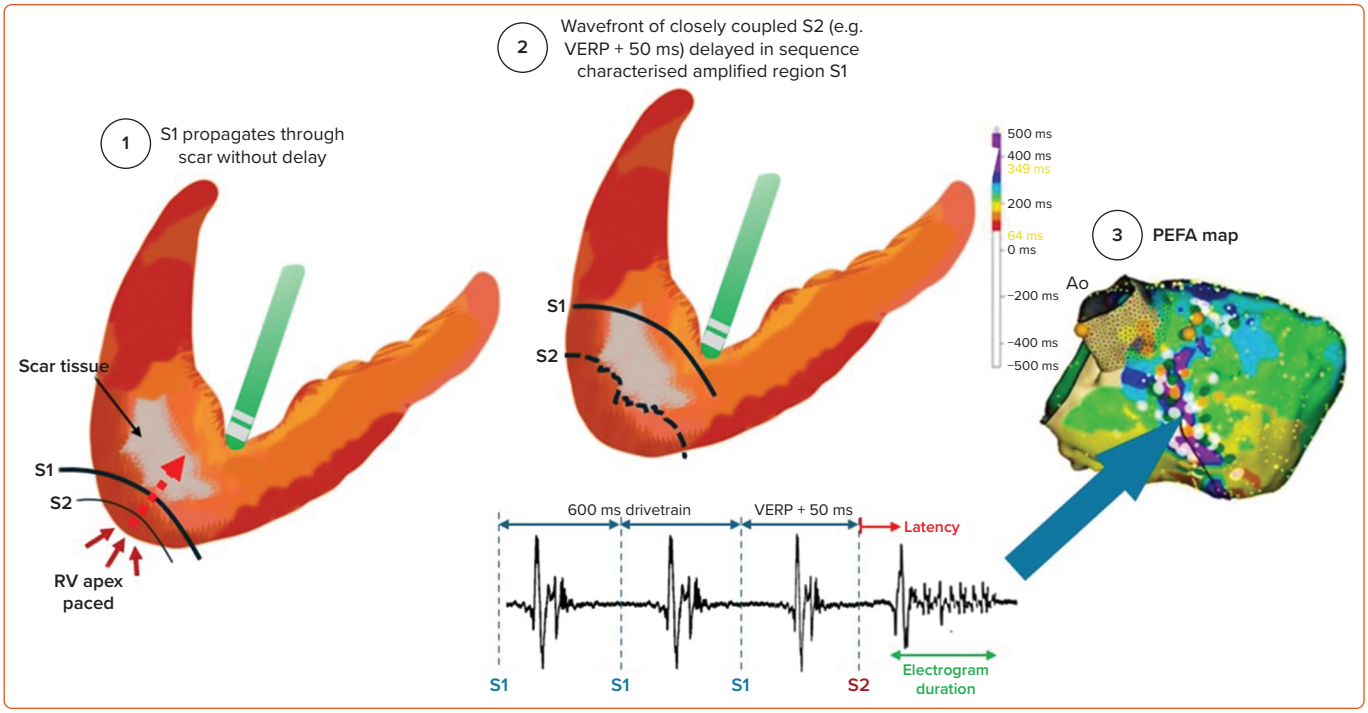
To determine the diagnostic accuracy of decrementing potentials in defining the VT re-entrant circuit, Porta-Sánchez et al. performed a study comparing LP maps and offline generated DeEP maps to the critical isthmus.[33] After an eight-beat drivetrain (S1) from the right ventricle at 600 ms, an ES (S2) was delivered at VERP + 20 ms to apply electrophysiological stress. A decrement of >10 ms immediately after S2 was deemed significant and defined as a DeEP (*Figure 3*). Porta-Sánchez et al. demonstrated that DeEPs (>10 ms decrement) were more specific to VT isthmus sites (97% specificity; 95% CI [0.95–0.98]) than non-isthmus sites (82% specificity; 95% CI [0.73–0.89]), with 75% of patients free of any VT after DeEP-guided ablation at the 6-month follow-up.[33] The approach to DeEP mapping was further optimised by Al-Sheikhli et al. in a mechanistic study by comparing the diagnostic accuracy of three different ES (S2) coupling intervals, and varying decrement thresholds (10–50 ms).[34] That study demonstrated that an S2 delivered at 400 ms or at the clinical VT

Figure 3: Decremental-evoked Potential Mapping



A: Example of a decrementing potential, where the electrogram duration increases from 91 (ms) during the drivetrain (S1) to 183 ms after a short-coupled extrastimulus. B: Example of a negative response, where there is no significant change in the electrogram duration after a short-coupled extrastimulus (S2).

Figure 4: Example of Paced Electrogram Feature Analysis



Electrogram during RV apical pacing with S2 at VERP+50 ms after a 600-ms drivetrain. Electrogram duration is examined, measured from the S2 pacing artefact to the last deflection of fractionated electrical activity, assessing the increase in latency and electrogram duration. Ao = aorta; PEFA = paced electrogram feature analysis; RV, right ventricle; VERP = ventricular effective refractory period. PEFA map source: Shariat et al. 2019.[39] Reproduced with permission from Elsevier.

cycle length with a decrement threshold of >20 ms more accurately localised critical components of the VT circuit.[34] In that study of 13 patients with SHD undergoing the optimised DeEP-guided ablation strategy, 92% were free from any device-dedicated VT at the 6-month follow-up.[34]

Mumtaz et al. sought to simplify the approach to DeEP mapping in their cohort of 16 patients with ischaemic cardiomyopathy by assessing the sensitivity and specificity of evoked late potentials (eLPs) to identify the VT diastolic pathway.[35] eLPs were defined as any near-field EGM occurring after the surface QRS, induced by an ES delivered at VERP + 20 ms with a drivetrain at 400/500 ms. This demonstrated improved sensitivity in identifying the diastolic pathway compared with SR or RVp, with no significant difference in specificity. A major limitation of that study is the lack of high-density mapping, or eLP-guided ablation outcomes.

Barts Sense Protocol

The Barts sense protocol study used automated last deflection mapping without incorporating a drivetrain, with an activation wavefront originating from the pacing electrode within the RVA. The protocol used a single sensed ES at VERP + 20 ms, which alters both the direction of wavefront propagation (now originating from the pacing electrode rather than conduction system) and coupling interval.[36] The Barts sense pacing protocol resulted in a larger area of ablation than SR LPs (19.3 versus 6.4 cm^2; p<0.001), with a sensitivity of 87% and a specificity of 96% (versus

78% and 65%, respectively). Long-term results were encouraging, with 90% of patients free from device therapies at a median follow-up of 12 months.

Paced Electrogram Feature Analysis

In a different approach, Shariat et al. examined EGMs during RVA pacing with an S2 at VERP + 50 ms/100 ms/150 ms after a 600-ms drivetrain.[37] Rather than interrogating the decremental conduction, the EGM duration from the S2 pacing artefact to the last deflection of fractionated electrical activity was measured. EGM characteristics examined were the degree of latency and EGM duration (ED; *Figure 4*). Using a cohort of 19 patients (five controls), the upper limits of normal for the degree of latency and ED were defined as 45 ms and 120 ms, respectively. In 10 patients, radiofrequency ablation was guided by PEFA maps generated with an S2 at VERP + 50 ms and ED >120 ms. All patients were free from VT at the end of the procedure, with nine patients free from recurrence over long-term follow-up (345 ± 90 days).[37] Crinion et al. assessed long-term outcomes after PEFA-guided ablation in a cohort of 40 patient with SHD.[38] S2 was delivered at VERP + 30 ms from the RVA after a 600-ms S1 drivetrain. Regions with a stimulus S2 to last deflection of >240 ms duration and an ED of >120 ms were targets for ablation. Areas where only latency was observed were not targeted. At a median follow-up of 711 days, 89.7% of patients were free from VT recurrence.[38]

Previous mechanistic studies have shown that a key factor that accounts for decrement and delay is conduction velocity restitution.[39] Most of the aforementioned groups incorporated a threshold of 10 ms of decrement of the near-field potential. The threshold of 10 ms for local decrement has been chosen based on intraoperative mapping data to reduce interobserver disagreement from small variations in measurements and results from *in silico* data simulations.[40] Delivering an S2 at VERP + 20 ms is expected to identify a much larger proportion of sites decrementing than at longer coupling intervals due to conduction velocity restitution.[41] This increases the number of false positives (healthy myocardium not involved in the VT circuit showing conduction velocity restitution) and decreases specificity. This was demonstrated by Orini et al. in a study of repolarisation and excitation restitution properties in cardiac surgery patients by using a multielectrode sock containing 240 unipolar electrodes.[41] Indeed, at VERP + 20 ms all viable myocardium was shown to manifest an increase in local activation time of >10 ms.

Re-entry Vulnerability Index and the Ventricular Tachycardia Circuit

Understanding the complex relationship between activation and repolarisation can provide further insight into functional substrate, better highlighting regions susceptible to re-entry. A prerequisite for re-entry is unidirectional block, whereby an activation wavefront blocks at a region of late repolarisation (where tissue is still refractory) but is able to circumvent the area of block through slow conducting pathways and re-enters at the proximal region.[42] The ability to re-enter the proximal region depends not only on the conduction delay around the blocked area but also on the timing of the returning wavefront relative to completion of repolarisation, and hence re-excitability in the proximal region. This is the basis of the re-entry vulnerability index (RVI). Child et al. demonstrated the feasibility of a novel algorithm for calculating the RVI using repolarisation and activation times.[43] After initial validation in an animal model, they successfully applied the methodology in a single case of scar-related VT ablation using a 600-ms, eight-beat S1 drivetrain and 500-ms S2 pacing protocol.[43] Orini et al. further evaluated the role of RVI at identifying the VT circuit in a cohort of 18 patients with ischaemic and non-ischaemic cardiomyopathy, using a five-beat S1 drivetrain followed by a short couple extrastimuli (median cycle length 360 ms [IQR 360–398 ms]).[42] Using RVI, Orini et al. were able to accurately localise (distance <10 mm) the VT site of origin in 72.2% of cases.[42] However, no RVI-guided ablation was performed to inform the long-term efficacy. A limitation of RVI-based mapping is the variability in repolarisation during sequential mapping and the challenge of performing measurements in diseased myocardium, which may require the use of ultrafast non-contact mapping technology to overcome.[42] Furthermore, commercial mapping systems do not allow for automated RVI substrate analysis.

Whole-chamber Double Extrastimuli: S3 Protocol

Guichard et al. recently demonstrated the feasibility of using a whole-chamber S3 protocol in identifying target substrate.[44] Using an RVA catheter, an S2 was delivered at VERP + 30 ms followed by an S3 at VERP + 50 ms. Functional substrate was identified through deceleration zones and LPs, whereas conduction channels were identified before the procedure using late gadolinium enhancement cardiac MRI. In their cohort of 40 patients, the S3 protocol was successfully completed in 34 due to recurrent VT induction in the remaining six patients.[44] The use of an S3 protocol identified more cardiac MRI conduction channels by assessment of deceleration zones (78%; 95% CI [55–102%]) and LPs (88%; 95% CI [67–110%]) than either an S2 protocol (65%, 95% CI [42–88%] (p=0.09) and 81%, 95% CI [60–102%] (p=0.46), respectively) or an S1 protocol (45%, 95% CI [21–68%] (p<0.001) and 68%, 95% CI [47–89%] (p=0.01), respectively).[44] This was associated with a 77.9±10.5% freedom from VT at a median follow-up of 13.9 months (95% CI [7.9–17 months]).[44] However, there was a progressive increase in the total area of LPs identified between S1, S2 and S3 mapping (area 29.4 cm^2, 95% CI [22.1–36.6 cm^2], 38.2 cm^2, 95% CI [30.9–45.5 cm^2] and 44.1 cm^2, 95% CI [36.6–51.5 cm^2] respectively; p<0.001), suggesting a larger ablation target area.[44]

It is apparent that the degree of stress induced by the ES that best identifies the VT circuit without highlighting areas of normal myocardium remains a point of contention. Another concern is the potential for haemodynamic instability induced by the ES, which can complicate procedural safety. Questions also persist about the ideal pacing site and need for a drivetrain to achieve a steady state, both of which must be answered to further develop our understanding of functional substrate mapping.[45] We advocate a structured research approach to resolve these fundamental questions.

Future Developments in Functional Substrate Mapping

Many of the functional mapping techniques remain heavily reliant on intraprocedural manual annotation of EGM signals, which is both time consuming and prone to errors. Thus, automating functional substrate mapping is pivotal for standardising these techniques and fostering a wider adoption among electrophysiologists. In a multicentre study, Niri et al. assessed the accuracy of automated DeEP mapping software against the gold standard of manual annotation by subject experts.[46] Retrospective analysis demonstrated that 91.6% of S2 algorithm markings coincided with the gold standard, 1.9% were false positives, and 0.1% were false negatives.[46] Although this demonstrates the feasibility of an automated mapping strategy, prospective studies are required to assess the long-term efficacy of automated DeEP map-guided ablation.

The ability to distinguish near-field EGMs from far-field signals will further optimise functional substrate mapping strategies. Historically,

differentiating between true localised abnormal signals and far-field elements has relied heavily on manual interpretation and annotation.[19] A novel algorithm within the Omnipolar Technology Near Field feature of the EnSite X electroanatomical mapping system (Abbott) offers automated unique insights into substrate characteristics through the quantification and annotation of EGM frequency components. Peak frequency mapping is an emerging technique that is designed to provide further definition of functionally relevant substrate and tissue contact by emphasising areas of high and low frequency specifically within areas of dense scar, scar border zone or healthy myocardium. The optimal use of peak frequency in functional substrate mapping strategies will require further research prior to clinical application.

Conclusion

True functional mapping has the potential to improve the outcomes and procedural workflow for VT ablation by highlighting the regions of myocardium most likely to participate in the re-entrant VT circuit. Moving beyond traditional approaches focused solely on slow-conduction zones, more novel functional techniques, such as DeEP mapping, during SR or paced rhythms offer improved specificity for identifying VT critical sites. Further mechanistic studies to answer some of the fundamental questions regarding the optimal degree of electrophysiological stress and large-scale randomised controlled trials to assess long-term outcomes are essential. Achieving this goal hinges on a structured research approach and continued technological advancements towards automated mapping capabilities. ❑

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