



Review Article

Substrate-based approaches in ventricular tachycardia ablation

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ABSTRACT

Catheter ablation for ventricular tachycardia (VT) in patients with structural heart disease is now part of standard care. Mapping and ablation of the clinical VT is often limited when the VT is noninducible, nonsustained or not haemodynamically tolerated. Substrate-based ablation strategies have been developed in an aim to treat VT in this setting and, subsequently, have been shown to improve outcomes in VT ablation when compared to focused ablation of mapped VTs. Since the initial description of linear ablation lines targeting ventricular scar, many different approaches to substrate-based VT ablation have been developed. Strategies can broadly be divided into three categories: 1) targeting abnormal electrograms, 2) anatomical targeting of conduction channels between areas of myocardial scar, and 3) targeting areas of slow and/or decremental conduction, identified with “functional” substrate mapping techniques. This review summarises contemporary substrate-based ablation strategies, along with their strengths and weaknesses.

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1. Introduction

Ventricular tachycardia (VT) ablation has been repeatedly shown to be superior to medical therapy for reducing VT recurrence in the setting of structural heart disease [1–3]. However, mapping VT circuits can prove challenging due to non-inducibility, tachycardia irregularity and poor haemodynamic tolerance [4]. Substrate-based methods have subsequently been developed as an approach to complement activation and entrainment mapping. The standard model for re-entrant VT in the setting of structural heart disease is a re-entrant circuit through an electrically insulated channel [5]. Additionally, slow conduction within the channels is required in order to facilitate re-entry [6]. Typically, these channels occur within areas of scar or between scar and anatomical boundaries, such as valve annuli. In principle, substrate-based approaches aim to ablate the channels that serve as the substrate for

VT propagation without the requirement to map them in VT (Fig. 1).

The first description of substrate-based VT ablation was by Marchlinski et al. in 2000, whereby linear endocardial lesions extending from dense scar to normal myocardium proved to be an effective strategy in controlling unmappable VT [7]. Since then, multiple approaches to substrate-based VT ablation have been described [8–15]. Substrate-based ablation has been shown to reduce rates of VT recurrence and hospitalization but, like all VT ablation trials, has failed to demonstrate a mortality benefit [16]. As such, a substrate-based approach, with or without complementary activation/entrainment mapping, is considered the gold standard when performing a VT ablation [17]. There are, however, many different methods by which a substrate-based ablation can be performed. In this report we will review the current techniques used for substrate-based VT ablation and discuss their benefits and pitfalls.

2. Anatomical substrate ablation

Anatomical substrate ablation focusses primarily on visualising the channels within scar and targeting ablation to these areas.

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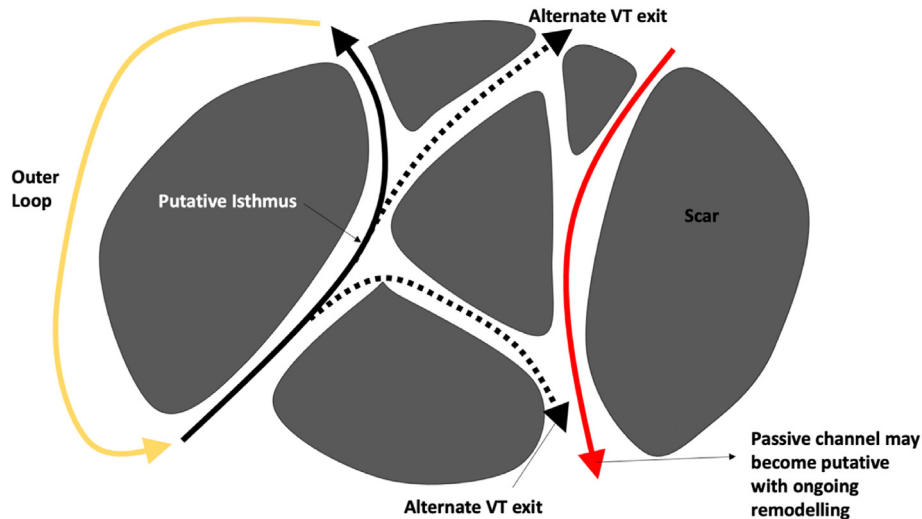


Fig. 1. Schematic of Scar-Related VT Channels. Putative VT isthmus shown in solid black arrow. Focal ablation to part of this circuit may terminate VT but allow for different VT circuits to form via alternate exits from the scar (black interrupted arrows). Non-putative channels in the scar may be present (red arrow) and are not targeted as part of a clinical VT ablation. However, with ongoing remodelling over time, these channels may precipitate re-entry. Ablation of all channels, not just putative channels, likely explains the better outcomes with substrate-based approaches.

Whilst they may identify channels of surviving myocardium within scar, they provide no information about the functional properties of these channels.

2.1. Voltage mapping

The voltage at any given site typically reflects the size of functionally viable myocardium at that site. Large amounts of myocardium in thick, healthy tissue produce large local voltages, whereas a small amount of diseased tissue may record low voltage signals and areas of transmural scar register hardly any signal at all. Voltage mapping is typically the term used to describe visualisation of EGM voltages projected on to the electroanatomical map. During an endocardial procedure, bipolar voltage is typically used to examine subendocardial substrate, whereas unipolar voltage provides a better assessment of transmural and epicardial scar [18].

Based on studies of patients with structurally normal hearts, a bipolar voltage of >1.5 mV is generally considered normal when mapping with a 3.5–4 mm tip catheter with a 1 mm ring electrode and 2 mm electrode spacing [19,20]. Historically, a lower value of <0.5 mV has been used to denote dense scar, although abnormal EGMs are often seen in these areas [21]. Areas of higher voltages bordered by areas of lower voltages are considered to be surrogates of myocardial channels traversing areas of scar and are therefore targeted with ablation [12]. To adequately visualise channels using this method, the lower threshold for dense scar must often be lowered to ≤ 0.2 mV (Fig. 2). Performing a substrate-based ablation using this strategy has been shown to be effective, with 77% of patients VT free at 17 ± 11 months [12].

Alternatively, voltage mapping can be used to define the extent of scar in order to perform a core isolation procedure. In this method, a circular set of ablation regions are delivered around scar area to surround isthmus sites, defined with either entrainment or pace-mapping [14]. Where VT is non-inducible, areas of dense scar (<0.5 mV) are isolated. This circular line of ablation transects channels as they enter and exit the scar, preventing them from sustaining re-entry. Core isolation is considered successful when the area surrounded by the lesion set is unable to be captured using a pacing output of 20 mA from ≥ 3 sites (exit block). Marchlinski et al. described core isolation in 44 patients, in whom core isolation

was achieved in 37. In this group, core isolation led to a better VT-free survival [14].

2.2. Limitations of voltage mapping

One of the major limitations of voltage mapping is the difficulty in determining the optimal threshold settings to visualise scar. Firstly, there are many factors that can alter the bipolar voltage of the endocardial electrogram. Electrode size, interelectrode spacing, wavefront directionality, catheter orientation, conduction velocity, gap junction disarray and anisotropy are all factors that may influence voltage mapping [22]. Secondly, there is no standardised minimum or maximum voltage requirement for a putative VT channel [23,24]. The voltage thresholds must be manually adjusted on a case-by-case basis to visualise channels within scar, which ultimately serves to be a highly subjective process (Fig. 2).

2.2.1. Electrode size and interelectrode spacing

Larger electrode size and/or larger electrode spacing typically produce lower bipolar voltages at heterogenous scar sites, as they have insufficient resolution and record activity over a large area. Conversely, smaller electrode size may record higher voltage due to small areas of surviving myocardium at the same site [22]. Multipolar catheters with smaller electrode size (typically 1 mm electrode size, 2–3 mm spacing) compared with ablation catheters (typically 3.5–4 mm tip length, 1.3–2.5 mm proximal electrode size, 1–2.5 mm spacing) offer the ability to generate high resolution maps quickly and are widely used in clinical practice [25]. An important caveat is that these multipolar catheters do not provide contact force information, and poor contact with the myocardial surface produces spuriously lower voltages [26]. More recently, very small electrode size with narrow interelectrode spacing has been shown to be superior in identifying viable myocardium compared with the electrode size and spacing of contemporary multipolar catheters [27].

2.2.2. Wavefront direction and omnipolar mapping

Parallel propagation of the wavefront in relation to an electrode pair typically produces larger voltages compared to a wavefront travelling perpendicular to an electrode pair [27]. Simultaneous

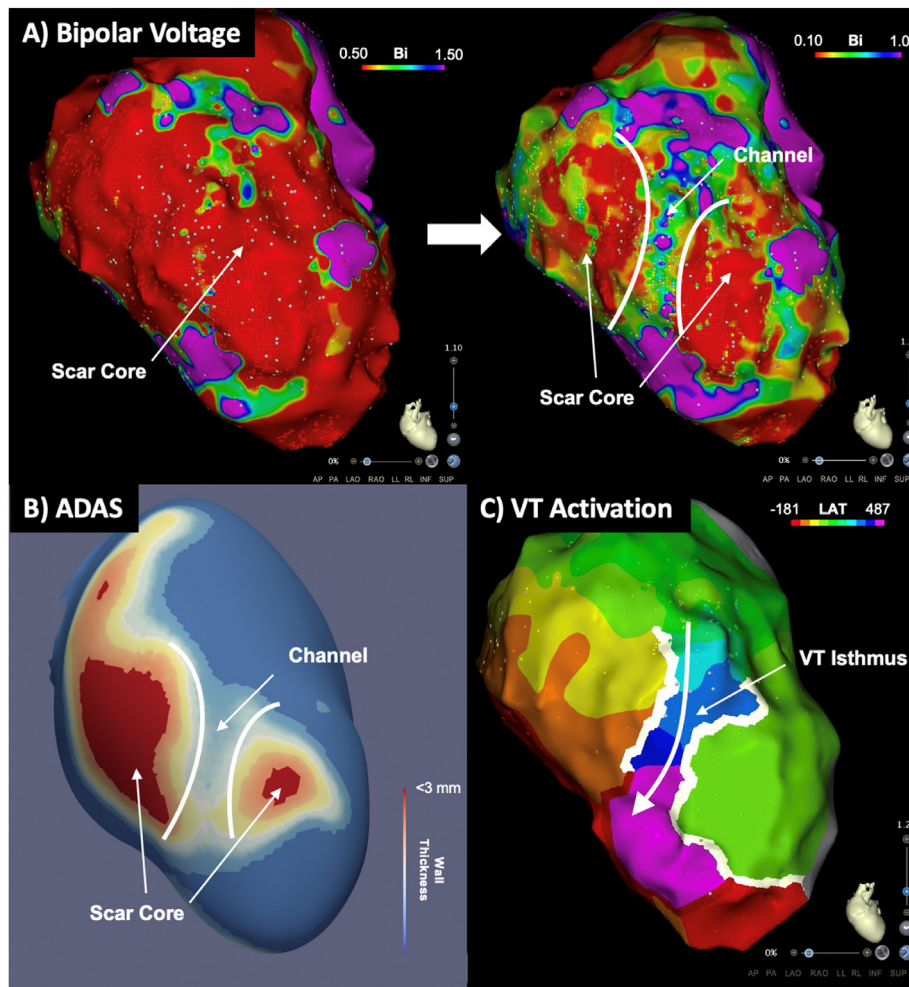


Fig. 2. Anatomical-Based Substrate Ablation. 72-year-old male with ischaemic cardiomyopathy from previous anteroseptal infarct. **Panel A:** Voltage mapping using traditional range of 0.5–1.5 mV shows a large area of scar core over the anteroseptum with no definite channel. Adjusting the voltage window to 0.1–1.0 mV reveals a channel between two areas of dense scar that was not seen using the traditional cutoff values. **Panel B:** A pre-procedural cardiac CT with ADAS processing demonstrates a border-zone channel between two areas of scar core at the mid septum. **Panel C:** Activation map of the clinical VT, demonstrating conduction through the conducting channel identified with both ADAS and voltage mapping. ADAS = automated detection of arrhythmogenic substrate, VT = ventricular tachycardia.

recordings from orthogonal electrode pairs have shown that the wavefront direction can result in a >50% difference in the bipolar voltage amplitude, with differences more pronounced in areas of higher voltages [27,28]. Omnipolar mapping catheters, such as the HD Grid (Abbott, St Paul, MN) and Optrell (Biosense Webster, Diamond Bar, CA) catheters, offer a novel solution to this issue, as the 'grid' of electrode spacing creates a network of electrode pairs with multiple different bipole directions. When the catheter is stationary, the effect of catheter orientation is negated using an omnipolar catheter. However, in the clinical setting where the mapping catheter is often moving and collecting EGMs at multiple angles, the directional dependence of bipolar voltage is minimal [29].

3. Electrogram-based substrate ablation

3.1. Late potentials

Late potentials (LPs) are typically defined as isolated potentials occurring after the QRS offset, although variation in LP definition exists [30]. LPs are considered to result from late activation of local myocardium, potentially within a putative channel [31]. Targeting LPs for ablation has been shown to be an effective strategy for

treating unmappable VT[32]. When targeting LPs as part of a substrate-based approach, abolition of LPs with ablation can be used as an endpoint in cases where VT is difficult to induce [33]. LPs are identifiable in 97% of cases, and where complete abolition of LPs is achieved, the recurrence rate of VT may be <10% [8,9].

3.1.1. Limitations of LP mapping

There are limitations that need to be considered in an LP-guided strategy (Fig. 3). Although sites with LPs during substrate mapping often participate in re-entrant circuits, many sites of re-entry do not demonstrate LPs [34]. Whilst LPs may provide a reasonable target for ablation, their overall sensitivity (16–30%) and positive predictive value (30–36%) is limited [21,35]. This may lead to suboptimal targeting of ablation and important physiological substrate being missed. Additionally, the specificity of LPs may only be moderate (68–90%), leading to unnecessary ablation of passive areas and prolonged procedural times [21,35].

3.2. Local abnormal ventricular activity

Local abnormal ventricular activity (LAVA) is defined as sharp, high-frequency ventricular potentials, possibly of low amplitude,

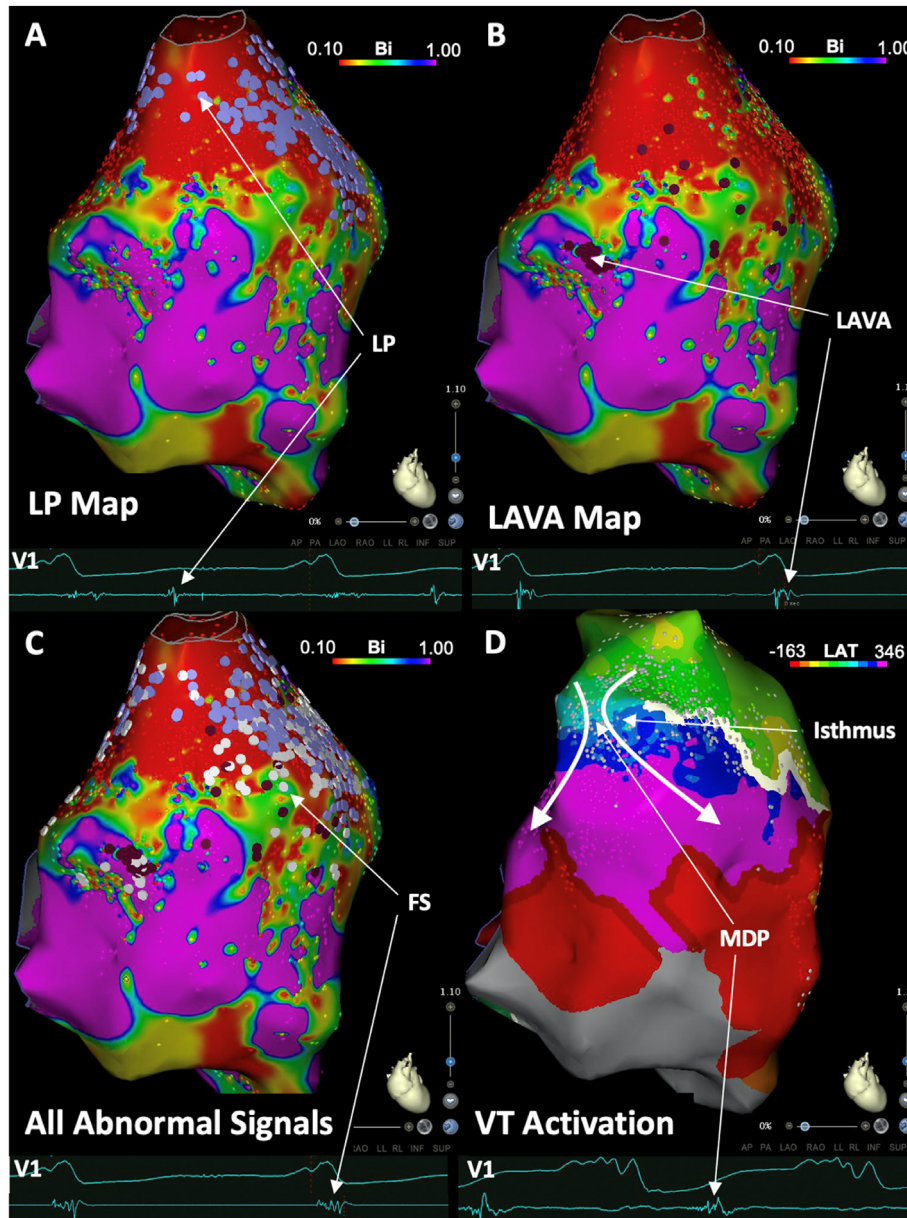


Fig. 3. EGM-Based Substrate Ablation. 54-year-old with sarcoidosis and VT originating from the RV free wall. **Panel A:** Voltage mapping demonstrates extensive scar over the RV free wall with no clear channel. LPs have been individually tagged (blue). LPs can be seen over an extensive area, predominantly within the scar area. **Panel B:** LAVAs have been individually tagged (burgundy). LAVA distribution here is primarily within scar border-zones. **Panel C:** All abnormal signals have been tagged (blue = LP, burgundy = LAVA, white = fractionated and double potentials). Abnormal signals cover virtually the entire region of abnormal voltage; substrate omogenization in this instance would require extensive ablation. **Panel D:** Mapped VT circuit. Critical isthmus site occurs in an area of very low voltage (<0.1 mV). All EGM types are found in this area, although the PPV for each type across the entire map is low. LP = late potential, LAVA = local abnormal ventricular activation, FS = fractionated signal, MDP = mid-diastolic potential, VT = ventricular tachycardia.

that are distinct from the far-field ventricular electrogram and occurs at any time during or after the far-field ventricular electrogram in substrate mapping [10]. LAVA are considered to be indicative of local activation of pathological tissue. In the initial description by Jais et al., LAVA were seen in 95.7% of patients, and LAVA-guided ablation resulted in elimination of LAVA in 70.1% of cases [10]. Successful LAVA elimination is associated with a reduction in VT recurrence and death during long term follow up [10,36]. VT-free survival rates of 61% at 5 years have been reported amongst patients who had successful elimination of LAVA at substrate ablation [36].

Additional techniques have been developed to aid the identification of LAVA during substrate mapping. Pacing from alternate

sites, or with a shortly coupled S2, may create delay between the far-field and high-frequency LAVA(37). LAVA may also be identified during local ectopy, where near-field activity occurs earlier than the far-field potential [37]. One proposed strength of the LAVA-guided method is that it also provides targets in areas of normal voltage that may otherwise be missed, although it has been shown that most LAVAs are observed within areas of low voltage [38]. Subsequent studies have confirmed a high specificity (86% & 89%) for LAVAs predicting critical sites for VT re-entry, although reported a low sensitivity (32 & 19%) and positive predictive value (PPV; 14% and 19%) [21,35]. Whilst LAVA offer an attractive ablation target, their lack of PPV means they should not be the sole focus of a substrate-based ablation approach (Fig. 3).

3.3. Scar homogenisation

Scar homogenisation refers to an approach where all 'abnormal' electrograms, including fractionated and delayed potentials, are targeted [11]. In this approach, any signal with >3 deflections, amplitude <1.5 mV, or a duration of >70 ms is ablated. The aim of scar homogenisation is to eliminate any signal that may represent a potential channel within the scar. This approach renders the scar area electrically inert and 'homogenised'. Limited activation mapping is generally indicated to identify the culprit scar, although this is not mandatory if VT is not inducible or not haemodynamically tolerated. Acute ablation endpoints include a) elimination of all abnormal potentials, or b) loss of local capture despite high output pacing (20 mA output at 10 ms pulse width) [11,39]. The rationale behind scar homogenisation is that culprit scar may harbour multiple channels, and that focal ablation of only the putative channel may allow other channels to facilitate VT over time with ongoing remodelling (Fig. 1). Scar homogenisation targets all channels and prevents these alternate circuits from developing [40].

In the initial description, scar homogenisation was compared with limited substrate ablation in consecutive patients. Scar homogenisation was associated with a significantly lower ventricular arrhythmia recurrence rate [11]. Importantly, ablation was performed from both the endocardium and epicardium in 33% of the scar homogenisation group. In a subsequent randomised trial, the VISTA study by Di Biase et al. evaluated substrate homogenisation versus targeted ablation of stable clinical VT circuits [40]. At 12-month follow-up, 15.5% of the substrate homogenisation group had a recurrence of VT compared with 48.3% in the clinical VT ablation group. These striking results have resulted in substrate homogenisation being widely adopted as a strategy in substrate-based ablation.

One limitation of the substrate homogenisation approach is that it relies on bipolar voltage and local fractionation, which are typically features of substrate located at the mapped surface. For example, intramural or epicardial scar may not demonstrate abnormal signals or low voltage on the endocardium. For this reason, performing substrate ablation from both the endocardium and epicardium has been demonstrated to improve VT-free survival at 5 years compared to an endocardial-only approach [41].

4. Pace-mapping approaches

4.1. Pace-mapping

Pace-mapping (PM) involves pacing different areas of the VT substrate to elicit a paced morphology that matches the clinical VT morphology. PM deep within the scar may identify areas of slow-conduction by demonstrating a long stimulus-QRS interval, although bystander channels may also demonstrate this phenomenon [42]. Putative channels within scar can be traced by identifying areas that have an identical paced QRS morphology but varying stimulus-QRS intervals (Fig. 4) [43]. These channels can then be targeted for ablation, with high rates of acute success in rendering clinical VTs noninducible using this strategy reported [43]. PM from an area may result in varying morphologies, due to multiple different exits from the channel, or may result in VT induction. These features are suggestive of a critical site and should prompt ablation to the area [44].

4.2. Pacing-defined channels

Although all substrate-based approaches aim to ablate channels within scar, the term 'scar dechanneling' is often used to refer to a method described by Soejima et al. [45]. In this approach, PM using

a high output (10 mA at 2 ms pulse width) within low voltage areas was used to define channels within electrically unexcitable scar. These areas of unexcitable scar were marked on voltage maps, with channels of surviving tissue between areas of unexcitable scar subsequently identified. Entrainment-proven VT isthmus channels occurred adjacent to these areas of unexcitable scar in all cases, and ablation lines joining unexcitable scar areas together resulted in VT noninducibility in 71% of cases.

4.3. Pace-Mapping Correlation Maps

Modern mapping systems allow for the visualisation of PM correlation on the electroanatomical surface. De Chillou et al. have described how these maps can be used to identify a VT isthmus, which can then be targeted for successful ablation [13]. PM from a VT exit site will often produce a morphology that is a good match to the VT(13). Likewise, pacing deeper within the VT channel will produce a good match provided the paced wavefront exits the channel in the same fashion as the VT. However, PM further into the channel often results in the wavefront exiting in the opposite direction, resulting in an abrupt change in the PM coefficient within the VT isthmus (Fig. 5, Central Illustration). Conversely, PM in the outer loop demonstrates a gradually worsening coefficient as the pacing site becomes further away from the VT exit site [46]. This method has been shown to identify VT circuits with a high degree of accuracy and is a useful tool for defining culprit channels in nonsustained VT(13).

4.4. Limitations of pace-mapping

There are several factors that influence PM morphology to be considered. First, the size of the virtual bipole generated during PM determines the amount of myocardium that is captured. Pacing at high outputs may result in far field capture of myocardium, altering the wavefront(s) and producing an inaccurate morphology [47]. Conversely, pacing at an output that is too low may fail to capture the local myocardium, creating a false impression of inexcitable scar. Second, areas of functional block may be present during substrate mapping but not VT, and vice versa. It may be therefore impossible to achieve an accurate PM from within a channel during substrate mapping, as these areas of functional block change the wavefront propagation [47]. Third, pacing-rate dependent properties may affect the PM morphology. Rate-dependent discontinuity of local myocardial bundles and conduction block influences local propagation and PM morphology [48]. For this reason, it is generally recommended that PM be performed at the tachycardiac cycle length [49]. Lastly, inadvertent anodal capture of the proximal electrode can lead to a 'fused' QRS morphology that is a composite of capture from both the distal and proximal electrodes. Due to these limitations, up to 70% of critical re-entry sites, identified with entrainment or termination of VT with ablation, do not demonstrate a PM that resembles the VT morphology [42].

5. Functional substrate mapping

Functional substrate mapping typically refers to methods that identify the underlying conduction properties of the tissue. In the latest refinement of substrate mapping the functional aspects of the substrate are further assessed by simply converting the local activation time (LAT) map into an isochronal map, creating a simplistic conduction velocity map. Areas of isochronal crowding act as surrogates of slowed conduction. By using alternate mapping methods or stressing the substrate with pacing manoeuvres, areas of pathological slow conduction may be identified [50,51].

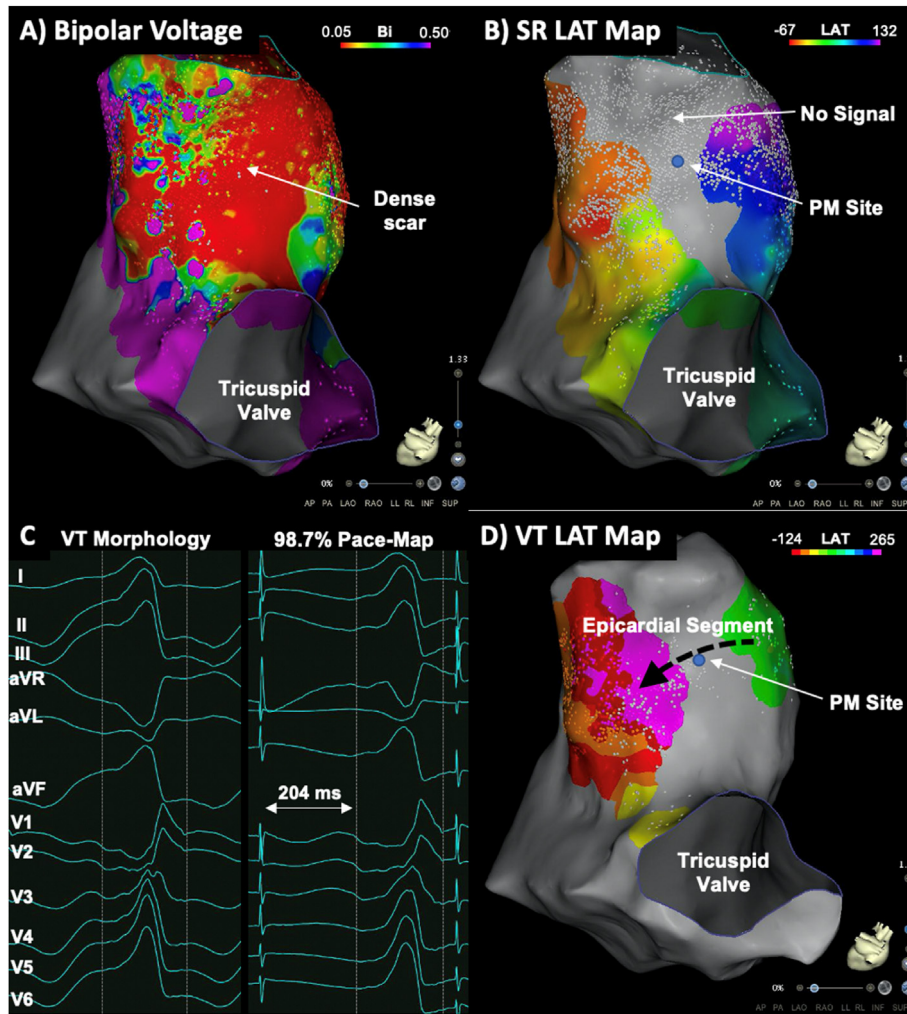


Fig. 4. Pace-Mapping-Based Substrate Ablation. 53-year-old male with tetralogy of Fallot and previous VT ablation, with line from superior tricuspid annulus to posterior pulmonary valve. **Panel A:** Bipolar voltage map demonstrating very low voltage (<0.05 mV) in the area of previous ablation. **Panel B:** No local signals area seen in the area of previous ablation. Given the clinical VT morphology was similar to VT ablated in the original procedure, a pace-mapping approach was undertaken. Pace-mapping at high output (20 mA at 10 ms pulse width) along the previous ablation line was performed. A single site of capture was identified (blue tag). **Panel C:** Pace-mapping shows a long stim-QRS (>200 ms) with an excellent (98.7%) morphology map to the clinical VT. **Panel D:** VT activation mapping reveals no local signals in the area of interest. However, ablation at the site of pace-mapping rendered the VT non-inducible. In this instance, pace-mapping at high-out likely captured an epicardial component of the circuit that could not be mapped endocardially.

5.1. Isochronal Latest Activation Mapping

Isochronal Latest Activation Mapping (ILAM) is a method by which the chamber of interest is mapped using a consistent wavefront. Each electrogram is annotated to the offset of the local electrogram (i.e. the latest activation), as this is thought to represent areas with long and fractionated signals more accurately [52]. LAT maps are then divided into isochrones with the same unit of time, with areas of isochronal crowding representing slow conduction (Fig. 6). In the description by Aziz et al., eight isochrones were used with ≥ 3 isochrones within a 1 cm area used to define a ‘deceleration zone (DZ)’. Primary DZs were then identified for ablation, defined as the areas with 1) the greatest extent of isochronal crowding, 2) later activation within the ventricular window, or 3) closest PM match for the targeted morphology, or PM demonstrating multiple exit site phenomenon [53]. Using this method to identify and ablate critical zones within the substrate, 70% of patients had no VT recurrence at 12 ± 10 months of follow-up [53]. Whilst isochronal crowding may be seen at areas of LPs, an LP-based focuses on a point-by-point interpretation of the electrogram. ILAM, however, requires a full activation map to identify

DZs and form an ablation strategy. Interestingly, the primary DZs do not typically localise to the areas of latest activation, suggesting that the sites of slow conduction are functionally more important than areas of absolute late activation [53].

5.2. Multiple wavefront mapping

Diseased ventricular tissue can demonstrate anisotropic properties and may only manifest pathological slow conduction when activated from certain wavefronts. In a multicenter study, Anter et al. examined patients with infarct-related VT by mapping the LV using three different wavefronts: 1) in sinus rhythm, 2) paced from the RV, and 3) paced from the lateral LV[54]. The cumulative areas of activation slowing, defined as the sum of all regions with activation times of >40 ms per 10 mm, were targeted for ablation. The areas of slow conduction were found to be dependent on the wavefront, with only $66 \pm 8\%$ of the total area of activation slowing identified in sinus rhythm mapping. By targeting areas that demonstrated conduction slowing in all wavefronts, 83.5% of patients were VT free after 3.6 years follow up [54].

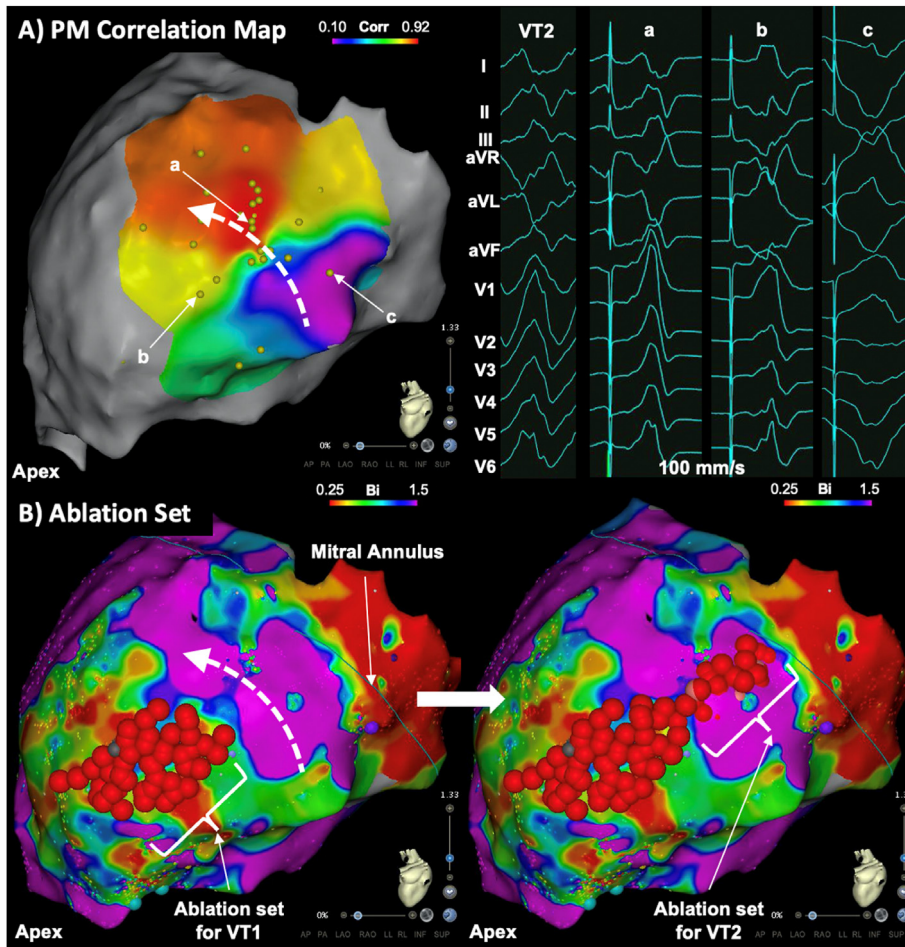


Fig. 5. Pace-Mapping Correlation Map. 28-year-old with desmin cardiomyopathy. Following ablation of clinical VT (VT1), VT2 was easily inducible but not haemodynamically tolerated. **Panel A:** A Pace-mapping demonstrated an acute transition from excellent correlation (a) to poor correlation (c), consistent with an isthmus channel (white interrupted arrow). **Panel B:** The channel identified with pace-map correlation was localised between the mitral annulus and the initial ablation set. Extending the ablation set to join the mitral annulus rendered VT2 noninducible. LAT = local activation time, PM = pace-map, VT = ventricular tachycardia.

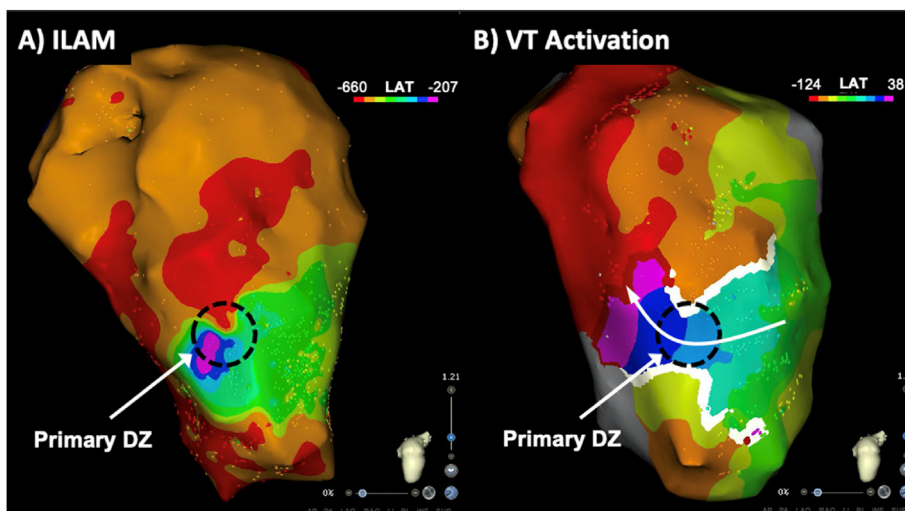


Fig. 6. ILAM-Based Substrate Ablation. 76-year-old with ischaemic cardiomyopathy. Endocardial VT ablation was performed, revealing a common isthmus at the mid-apical septum. **Panel A:** ILAM demonstrates a primary deceleration zone (maximum isochronal crowding) at the mid-apical septum. **Panel B:** VT activation mapping demonstrates the primary deceleration zone corresponds to the mid-isthmus. Ablation in this area rendered the VT non-inducible.

5.3. Decrement evoked potentials

Decrement evoked potentials (DEEPs) are potentials within the substrate that delay with a decremental extrastimulus. Jackson et al. created DEEP maps by performing a pacing train at 600 ms followed by an extrastimulus delivered at 20 ms above the ventricular effective refractory period [50]. This was performed on any LP or fractionated potential that was identified during substrate mapping. If the identified potential delayed with a decremental extrastimulus, it was annotated as a DEEP. If the potential blocked, then the extrastimulus was repeated with a longer coupling interval. DEEPs displayed a sensitivity of $50 \pm 23\%$ and a specificity of $43 \pm 23\%$ for identifying the VT isthmus. Potentials that demonstrated the greatest decrement had a higher specificity ($95 \pm 1\%$) but lower sensitivity ($29 \pm 10\%$) [50]. In a prospective evaluation, using the DEEP mapping approach to target ablation in patients with ischaemic cardiomyopathy rendered VT noninducible in the acute setting in 80% of patients [55].

5.4. Evoked delayed potential mapping

Similar to DEEP mapping, evoked delayed potential (EDP) mapping uses pacing to elicit abnormal potentials, or 'hidden' substrate. In this technique, signals are analysed during sinus rhythm, RV pacing at 500 ms, and during the application of a single RV extrastimulus delivered at 50 ms above the ventricular effective refractory period. This is performed over areas of scar identified using imaging data. Low voltage (<1.5 mV) local potentials that delay >10 ms or block in response to RV extrastimuli are considered EDPs. Using an ablation strategy that specifically targets EDP, de Riva et al. reported VT-free survival in 89% of patients at 1 year [56]. This was significantly higher than the 1-year VT-free survival in a historical comparison group (73%; $P < 0.05$), although this finding should be interpreted with caution as the ablation strategy was heterogeneous in the comparison group and the study was not randomised [56].

5.5. Hidden slow conduction analysis

Acosta et al. have also described a method to identify 'hidden' substrate [57]. Here, extrastimuli were delivered in attempt to manifest hidden slow conduction (HSC). Bipolar EGMs with >3 deflections and a duration of <133 ms were considered as potential sites of HSC. At these sites, double or triple ventricular extrastimuli were delivered. If a local potential manifest as a delayed component with extrastimuli, this was annotated as HSC. Ablation was performed targeting areas of HSC and conduction channel entrances. At a follow-up of 2 years, patients undergoing ablation using the HSC method had a higher VT free survival (75.7%) compared to a historical control group of standard VT ablation undergoing a scar dechanneling technique (58.8%; $P < 0.05$) [57].

5.6. Limitations of DEEP, EDP, HSAC mapping

One major limitation of the DEEP, EDP and HSC mapping approaches is that they are time consuming. Srinivasan et al. developed a method by in which sensed short-coupled ventricular extras were delivered from the RV apex during substrate mapping to invoke ventricular conduction delay [51]. The sensed ventricular extra was delivered every fifth beat at 20 ms above the ventricular effective refractory period. Two maps were created: 1) a traditional ventricular activation map in sinus rhythm, and 2) a map of potentials recorded with sensed extrastimulus. Ablation was then targeted to 1) critical areas identified with entrainment, 2) areas with a $>96\%$ PM coefficient, and 3) areas with LPs and LAVAs as

identified using the sensed extrastimulus mapping. Using this strategy, 90% of patients were free from device therapies at median follow-up of 12 months [51].

6. Cardiac imaging-guided ablation

6.1. Imaging-defined substrate

Integrating information on the structural VT substrate, defined by cardiac imaging modalities, has been shown to reduce procedure time and improve safety in ablation procedures [58]. Intracardiac echocardiography (ICE) is now in widespread use and can be integrated with modern mapping systems to define ventricular anatomy and myocardial scar. Myocardium that is thinned, akinetic, or has abnormal echo density can be delineated as scar, and has good correlation to scar defined by EAM, multidetector CT (MDCT) and cardiac MRI (CMR) [59]. The degree of echo density can also be used to differentiate scar core from border zone areas [60]. However, ICE is less effective in detailed scar characterisation than MDCT and CMR(58).

There have been multiple studies evaluating the correlation of scar defined by CMR and EAM[61, 62]. The results have been variable, with some showing mismatch between the two modalities, particularly in the identification of scar border zones [63]. Regardless, it has been consistently shown that putative VT isthmuses frequently occur in CMR-defined scar [64,65]. CMR has been used to identify substrate for ablation with varying degrees of success. CMR features providing potential targets for ablation include scar transmural, areas of scar border zone, and the core scar-scar border zone junction [66].

Multidetector computed tomography (MDCT) has a significantly higher spatial resolution compared with cardiac MRI (CMR). MDCT can be used to define scar using wall thinning, hypoattenuation (a result of fatty metaplasia), decreased perfusion, and hyperattenuation [67,68]. MDCT-defined scar correlates well with EAM-defined scar in the setting of ischaemic cardiomyopathy but is less robust in non-ischaemic cardiomyopathy [69]. It has been repeatedly shown that putative VT substrate is located within or adjacent to MDCT-defined scar [70,71]. In addition to scar, MDCT has the added benefit of defining detailed cardiac anatomy, including coronary arteries and epicardial fat, which may be important when planning an ablation [58].

Nuclear imaging techniques may provide incremental diagnostic information in patients with VT and can be useful when planning an ablation strategy. Areas of viable myocardium may be distinguished from inert scar with positron emission tomography (PET) scanning [72]. In patients with otherwise unexplained cardiomyopathies and VT, PET may demonstrate an inflammatory aetiology, such as sarcoidosis, in up to 50% of patients [73]. Combined PET/CT images may also be integrated into EAM systems to help target substrate ablation. Critical isthmuses have been shown to be located within or adjacent to PET-defined scar [74]. PET/CT has also been used to identify channels of metabolically viable tissue within scar that are not identified with voltage mapping [75]. The major limitation of PET is that it lacks anatomical detail, and generally requires integration with either CT or MRI.

6.2. Limitations of imaging-based techniques

Imperfect image integration remains an unsolved issue. No standardized approach to merging images is available, with various methods described. Registration error is typically in the range of 3–5 mm even in highly regimented studies [76]. A factor that may further limit image integration is the change in anatomy that can occur between scan and procedure. Chamber volume and

orientation of the heart are subject to change and may result in poor co-registration of imaging data with mapping data during a procedure [77].

A significant limitation of CMR is the low spatial resolution. A 3-T CMR can have a maximum voxel resolution of 1.4 mm³ [78]. Conducting channels measuring <0.2 mm have been described, suggesting that CMR may miss some critical isthmuses [79]. Whilst MDCT has a much higher resolution (<0.4 mm voxel size), the requirement for radiation and poorer tissue characterization compared to CMR remain limitations [80]. Additionally, many patients requiring VT ablation have an ICD in situ. In some cases, these devices are not MRI-compatible. In other cases, they generate significant artifact on both MRI and CT that may limit image quality.

6.3. Proprietary segmentation software

6.3.1. InHeart

InHeart software analyses either CT or CMR images to create digitally rendered 3D cardiac models with segmentation of important anatomic features such as wall thinning, epicardial fat,

phrenic nerves and coronary arteries. In a small series, identifying conduction channels based on wall thickness using the InHeart software detected the putative VT isthmus in 100% of cases [81]. Integrating the InHeart software has been shown to reduce ablation times in VT ablation, with randomized studies to evaluate clinical outcomes ongoing [82].

6.3.2. ADAS

Automatic Detection of Arrhythmogenic Substrate (ADAS) software has been developed for the processing of cardiac imaging to aid VT ablation and is now commercially available. This software uses either MDCT or CMR generate ventricular scar maps [76]. These maps depict potential conduction channels of preserved myocardium within dense scar, so-called ‘border-zone corridors’, that can be identified either manually or automatically by the software [83]. The maps can be exported and merged to modern electroanatomical mapping systems to help target ablation (Fig. 3).

Multiple studies have attempted to refine substrate-based procedures by integrating CMR with ADAS processing to target the ablation strategy [15,76,83,84]. In a non-randomised prospective

Table 1
Studies investigating different methods for substrate-based VT ablation.

Ablation Method	Study	Number of Patients	Endpoint	Endpoint Achieved	Ablation Amount	Follow Up	VT Free Survival at Follow Up
Linear Ablation	Marchlinski et al. 2000[7]	16 (9 ICM, 7 NICM)	Acute Noninducibility	47%	59 ± 34 lesions	8 months (median)	75%
	Soejima et al. 2001[92]	40 (all ICM)	Acute Noninducibility	58%	21 ± 10 lesions	21 ± 6 months	62.5%
LP Ablation	Vergara et al. 2012[8]	50 (36 ICM and 14 NICM)	LP Elimination	90%	14 ± 6 lesions	13.4 ± 4.0 months	80%
	Arenal et al. 2013[9]	59 (all ICM)	LP Elimination	78%	11 ± 5 min	17 ± 11 months	77%
LAVA	Jais et al. 2012 [10]	70 (56 CM and 14 NICM)	LAVA Elimination and noninducibility	70%	23 ± 11 min	22 months (median)	44.3%
	Wolf et al. 2018 [36]	159 (all ICM)	LAVA Elimination and noninducibility	64%	36 ± 20 min	47 months (median)	55%
Scar Homogenisation	Di Biase et al. 2012[11]	43 (all ICM)	Elimination of all abnormal potentials	Not reported	74 ± 21 min	25 ± 10 months	81%
	Di Biase et al. 2015[40]	58 (all ICM)	Elimination of all abnormal potentials	Not reported	68 ± 21 min	12 months	84.5%
Scar Homogenisation: Endocardial + Epicardial Voltage Map Scar Dechanneling	Mohanty et al. 2022[41]	70 (all ICM)	Noninducibility of monomorphic VT	100%	67.5 ± 24.9 min	60 months	81.4%
Pacing-defined Scar Dechanneling	Arenal et al. 2004[12]	26 (all ICM)	Ablation of conduction channels identified with voltage mapping	77%	14 ± 8 lesions	17 ± 11 months	77%
	Soejima et al. 2002[45]	14 (all ICM)	Ablation of conduction channels identified with pacemapping	100%	24 ± 10 lesions	6 ± 4 months	71%
Pace-Mapping Correlation Map	de Chillou et al. 2014[13]	10	Termination of VT; transection of the isthmus	100%	10 ± 9 min	65 ± 6 months	70%
Core Isolation	Tzou et al. 2015 [14]	44 (32 ICM and 12 NICM)	Isolation of dense scar regions with exit block	84%	111 ± 91 lesions	18 ± 9 months	86%
Imaging-Based Scar Dechanneling	Andreu et al. 2017[15]	54 (37 ICM and 17 NICM)	Ablation of channels identified with CMR-aided EAM	84%	19 ± 12 min	20 ± 19 months	81.5%
	Soto-Iglesias et al. 2020[83]	28 (23 ICM, 5 NICM)	CMR-guided ablation of channels (without complementary EAM)	96%	15 ± 8 min	12 months	96%
ILAM	Irie et al. 2015 [52]	10	Clinical VT noninducibility	100%		6 ± 1 months	80%
	Aziz et al. 2019 [53]	120 (60 ICM, 60 NICM)	Clinical VT noninducibility	98%	29 (21–38) minutes	12 ± 10 months	70%
DEEP	Porta-Sanchez et al.[55]	20 (all ICM)	VT noninducibility	80%	31 ± 21 min	6 months	75%
EDP	de Riva et al. 2018[56]	60 (all ICM)	VT noninducibility	90%	15 (10–21) minutes	12 months	89%
HSC	Acosta et al. 2020[57]	70 (44 ICM, 26 NICM)	VT noninducibility	85.7%	16 (8–23) minutes	24 months	75.7%
Sensed Protocol Mapping	Srinivasan et al. 2020[51]	30 (all ICM)	VT noninducibility	97%	32 min	12 months (median)	90% ^a
Multiple Wavefront Mapping to Identify Re-entry Vulnerable Zones	Anter et al. 2020[54]	85 (all ICM)	VT noninducibility	Not reported	28 ± 12 min	43 months (median)	80% ^a

^a Free of device therapy for VT. LAVA = local abnormal ventricular activation, LP = late potential, EAM = electroanatomical mapping, DEEP = decremental evoked potentials, EDP = evoked decremental potentials, ILAM = isochronal latest activation mapping. Ablation time is reported as mean ± standard deviation or median (interquartile range).

Table 2
Studies comparing substrate-based VT ablation with conventional strategies.

Study	Design	Ablation Approach	VT-Free Survival	Comparison Group	VT-Free Survival	Follow-up	Results
Volkmer et al. 2006[31]	Single Center, Retrospective, Case-control	LP Ablation (25 patients)	54%	Mapping and ablation of clinical VT (22 patients)	60%	25 ± 13 months	No significant difference in VT recurrence
Ventura et al. 2007[93]	Single-center, Prospective, Cohort	Pace-mapping (14 patients)	57%	Mapping and ablation of clinical VT (16 patients)	75%	14 ± 6 months	No significant difference in VT recurrence
Di Biase et al. 2012[11]	Multicenter, Prospective, Cohort	Scar homogenisation (43 patients)	81%	Limited substrate ablation (49 patients)	53%	25 ± 10 months	Scar homogenisation significantly improved VT-free survival (P < 0.01)
Di Biase et al. 2015[40]	Multicenter, Prospective, Randomised	Scar homogenisation (58 patients)	84.5%	Mapping and ablation of clinical VT (60 patients)	51.7%	12 months	Scar homogenisation significantly improved VT-free survival (P < 0.01)
Fernandez-Armenta et al. 2016 [94]	Single Center, Prospective, Randomised	Scar dechanneling (24 patients)	58.3%	Mapping and ablation of clinical VT followed by scar dechanneling (24 patients)	66.7%	22 ± 14 months	No significant difference between groups
Andreu et al. 2017[15]	Single Center, Prospective, Cohort	CMR-aided scar dechanneling (54 patients)	81.5%	EAM-guided scar dechanneling (105 patients)	56.2%	20 ± 19 months	CMR-aided group had a significantly lower VT recurrence rate (P < 0.01)
de Riva et al. 2018[56]	Single Center, Prospective, Cohort	EDP-targeted substrate ablation. (60 patients)	89%	Historical cohort (standard substrate ablation) (90 patients)	73%	1 year	Patients with 'hidden' substrate identified with EDP mapping had a significantly lower VT recurrence at 1 year (P < 0.04)
Soto-Iglesias 2020[83]	Multicenter, Prospective, Cohort	CMR-guided dechanneling (28 patients)	96%	EAM-guided scar dechanneling (28 patients)	75%	12 months	CMR-guided and CMR-aided ablation groups had lower VT recurrence than the no CMR group (P < 0.02)
Acosta et al. 2020	Multicenter, Prospective, Cohort	HSC-guided scar dechanneling (70 patients)	75.7%	Historical control group (scar dechanneling) (68 patients)	58.8%	2 years	HSC-based approach was superior to historical control group (P < 0.05).

pilot study, CMR with ADAS was used to define continuous corridors of surviving myocardium surrounded by scar core connecting 2 areas of healthy tissue. In a subset of patients, ablation was targeted to these CMR-defined channels without acquisition of any EAM. When contrasted to groups where either no CMR or a hybrid approach of EAM + CMR was used, the CMR-guided group had lower procedural and fluoroscopy times. The CMR-guided group also had significantly improved VT-free survival compared to the group without CMR imaging, although there was no difference with the group who underwent a hybrid approach of EAM + CMR(83).

7. Investigational approaches

Several other approaches have been described but have not been adequately evaluated prospectively and should not yet be used in clinical practice. Hattori et al. identified rotational wavefronts to effectively locate conduction around the end of lines of block [85]. These areas of rotational activation were seen at critical VT sites, defined by PM or termination with ablation, in 70% of the VTs investigated. Rossi et al. created novel maps of EGM duration [86]. In all cases, the areas with long EGM duration in substrate mapping harboured the site of longest EGM duration in VT. In turn, the site with the longest EGM in VT was the site of VT termination in 92% of cases. However, the areas of long EGM duration during substrate mapping were large ($8.9 \pm 5 \text{ cm}^2$), limiting the potential of this method to focus ablation. Several studies have also used signal frequency analysis to aid identification of critical VT substrate sites with reasonable success rates, although the feasibility of performing this in real-time has yet to be investigated [87,88]. Finally, conduction velocity mapping has shown that slow conduction is a highly sensitive predictor of critical sites, although current automated conduction velocity mapping algorithms are not optimised for substrate mapping [89].

An intriguing emerging technology is computational modelling

based on cardiac imaging. Multimodality imaging provides detailed and patient-specific data on ventricular geometry and scar architecture. By incorporating this data into biophysical cardiac models, arrhythmia mechanisms and putative channels can be identified using a virtual electrophysiological study [90]. Several small proof-of-concept reports have suggested this image-based modelling may be used to predict VT circuits and future arrhythmic events [91]. However, this technology is currently experimental only, as it is not yet widely available and has not been prospectively validated.

8. A hybrid approach to substrate-based VT ablation

There are many ways to approach a substrate-based VT ablation, but not every method is possible in every patient. For example, a PM approach is not feasible where the VT is noninducible at the outset, and critically unwell patients may not tolerate the haemodynamic stress and long procedure times associated with DEEP and EDP protocols. Ultimately, a skilled electrophysiologist needs to be familiar with many techniques in order to adapt to each case as required.

A common approach is to start with a multipolar catheter to map the chamber of interest in a stable rhythm, identifying areas of scar and tagging abnormal potentials. LAT should be annotated to the latest activation in order to identify deceleration zones. PM is performed during the initial collection of data, which can be used to define electrically unexcitable scar. Once the substrate is defined, induction of VT is performed. Even if nonsustained or not haemodynamically tolerated, the limited points will often direct the operator to the area of scar likely to be the culprit. Additionally, previously collected PM points will provide a PM coefficient map to reference to. Even if the VT is stable and mappable, a substrate-based ablation should be performed after termination of the arrhythmia due to the improved outcomes associated with these approaches (see Tables 1 and 2).

9. Conclusion

Substrate-based ablation for treatment of VT is the gold standard and has been shown to be superior to targeted ablation of the clinical VT. Despite this, long term recurrence rates remain sub-optimal. Whilst advances in functional substrate mapping techniques have served to target ablation, many of these techniques have not been prospectively evaluated in a randomised fashion. A skilled electrophysiologist must be familiar with multiple approaches to tailor ablation to patient-specific factors.

Declaration of competing interest

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