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Advancement in cardiac imaging for treatment of ventricular arrhythmias in structural heart disease

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Over the last decades, substrate-based approaches to ventricular tachycardia (VT) ablation have evolved into an important therapeutic option for patients with various structural heart diseases (SHD) and unmappable VT. The well-recognized limitations of conventional electroanatomical mapping (EAM) to delineate the complex 3D architecture of scar, and the potential capability of advanced cardiac imaging technologies to provide adjunctive information, have stimulated electrophysiologists to evaluate the role of imaging to improve safety and efficacy of catheter ablation. In this review, we summarize the histological differences between SHD aetiologies related to monomorphic sustained VT and the currently available data on the histological validation of cardiac imaging modalities and EAM to delineate scar and the arrhythmogenic substrate. We review the current evidence of the value provided by cardiac imaging to facilitate VT ablation and to ultimately improve outcome.

Keywords

Ventricular tachycardia • Cardiac magnetic resonance • Computed tomography • Catheter ablation • Fibrosis • Histology

Introduction

Over the last decades interventional treatment for monomorphic sustained ventricular tachycardia (MSVT) has evolved into an important therapeutic option for patients with structural heart disease (SHD) and scar-related VT.¹ Various image modalities, including cardiac magnetic resonance (CMR), computed tomography (CT), nuclear imaging and intracardiac echocardiography (ICE) have been used to facilitate catheter ablation in conjunction with electroanatomical mapping (EAM). Cardiac imaging has the potential advantage to non-invasively delineate the arrhythmogenic substrate with a higher degree of precision than EAM. Real-time imaging and accurate image integration may pave the way for the precise application of new energy sources and non-invasive ablative radiation. Real-time imaging may also allow for monitoring of lesion formation to optimize acute procedural endpoints. However, to further improve and to responsibly use cardiac imaging in substrate-based ablation, knowledge

of the substrate for MSVT in various SHD, and the capability of image modalities to visualize this substrate, is crucial.

This review will summarize the histological differences between SHD aetiologies related to MSVT and evaluate the histological validation of cardiac imaging modalities and EAM to delineate both scar and the arrhythmogenic substrate. To this end, we use 'scar' to refer to any pathological fibrosis and 'substrate' to refer to specific areas related to MSVT. We review the current evidence of the value provided by imaging and discuss possible future uses of cardiac imaging in the interventional treatment of MSVT. We performed a systematic search in medical databases using multiple complex search terms, reviewed all cross-references to relevant articles, and reviewed all published literature from research groups who contribute to the field. However, due to the complexity of the subject material, our approach did not fulfil the systematic review criteria as outlined by PRISMA.²

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The histology of scar in structural heart disease associated with monomorphic sustained ventricular tachycardia

Monomorphic sustained ventricular tachycardia occur in SHD patients of varying aetiologies, including, but not limited to, ischaemic cardiomyopathy (ICM), arrhythmogenic right ventricular cardiomyopathy (ARVC), hypertrophic cardiomyopathy (HCM), and dilated cardiomyopathy (DCM).¹ The latter encompasses a wide range of aetiologies including inflammatory diseases (e.g. cardiac sarcoidosis and post-myocarditis), and various genetic causes (Lamin A/C (LMNA) mutation being the most widely recognized).³ Different genetic and acquired insults may result in different degrees of cell injury, different repair mechanisms and different amounts, patterns, and architectures of fibrosis (Figures 1 and 2). As shown, the histological characteristics of scar vary significantly depending upon the aetiology. These variations may impact on both the resulting substrate and the ability of cardiac imaging to delineate it.

Cardiac imaging to delineate scar and their validation using histology as the gold standard

Late gadolinium-enhanced (LGE)-CMR has become the preferred imaging technique to delineate scar. Binary approaches categorize tissue into scar vs. normal myocardium based on either the maximal

signal intensity (SI) of affected regions or on the SI of healthy remote myocardium.^{39,40} Methods using three categories (dense fibrosis/scar core, moderate fibrosis/scar border zone, and healthy myocardium) based on two SI thresholds, are referred to as ternary methods.^{41–43} Importantly, there is no agreement on the optimal method and the optimal thresholds to quantify scar core and border zone, and different methods and thresholds will significantly affect the diagnostic yield of LGE-CMR (Figure 3). Cardiac T1 mapping, T2 mapping, and diffusion-weighted imaging (DWI) are other promising techniques allowing assessment of the extracellular volume fraction as a potential measure of diffuse fibrosis, myocardial oedema and fibre orientation, respectively.^{44,45}

Computed tomography has a significantly higher spatial resolution, even if compared to modern isotropic 3D LGE-CMR. However, a drawback is the unfavourable signal-to-noise ratio with suboptimal results, particularly for chronic scars. Furthermore, the doses of highly concentrated iodine-based contrast agents used in animals to achieve acceptable results are much higher than those used in clinical practice.⁴⁶

Nuclear imaging, including positron emission tomography (PET) and single-photon emission tomography (SPECT) can distinguish non-viable scar, viable hibernating scar, and healthy myocardium by changes in metabolism and/or perfusion, but are hampered by a poor resolution.⁴⁷

Intracardiac echocardiography has been used to delineate scar based on wall-thinning, wall motion abnormalities,⁴⁸ and occasionally the heterogeneity in SI.⁴⁹

Although widely used, different cardiac image modalities have not been histologically validated for most aetiologies, as summarized in Table 1 and visualized in Figure 1. Briefly, in ICM LGE-CMR (both binary and ternary methods),^{4,39,40,50,51} contrast-enhanced

| Aetiology | Histology of scar | Imaging of scar validated by histology | | | EAVM of scar validated by histology | Comparison between EAVM of scar and imaging | | | Histology of substrate ^a | Imaging of substrate ^a validated by histology | Detection of substrate ^a by imaging | | |
|---------------------|-------------------|--|----|-----|-------------------------------------|---|----|-----|-------------------------------------|--|--|----|-----|
| | | CMR | CT | ICE | | CMR | CT | ICE | | | CMR | CT | ICE |
| ICM | | | | | | | | | | | | | |
| ARVC | | | | | | | | | | | | | |
| HCM | | | | | | | | | | | | | |
| DCM | | | | | | | | | | | | | |
| Cardiac sarcoidosis | | | | | | | | | | | | | |
| Postmyocarditis | | | | | | | | | | | | | |
| LMNA-mutation | | | | | | | | | | | | | |

Human studies (n>10) Human studies (n≤10) Animal studies No data available

Figure 1 Overview of the available evidence on invasive and non-invasive methods of scar delineation in different aetiologies related to monomorphic sustained tachycardia. ^aAs determined by conventional methods (e.g. activation mapping, entrainment mapping, termination sites). ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; CT, computed tomography; DCM, dilated cardiomyopathy; EAVM, electroanatomical voltage mapping; HCM, hypertrophic cardiomyopathy; ICE, intracardiac echocardiography; ICM, ischaemic cardiomyopathy.

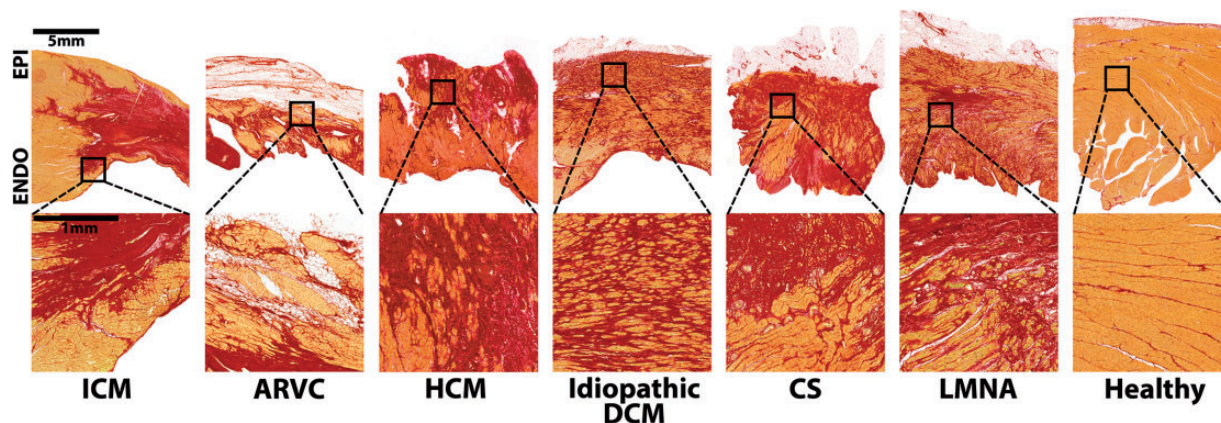


Figure 2 Examples of scar pattern in different aetiologies of structural heart disease. Stained with sirius red (fibrosis stains red, viable myocardium yellow). Ischaemic cardiomyopathy (ICM): compact scar extending from the subendocardium to the epicardium with sparing of the endocardial rim. Along the border, viable myocardium is interspersed by fibrous tissue.^{4–10} Arrhythmogenic right ventricular cardiomyopathy (ARVC): genetic disease,^{11,12} characterized by fibrofatty replacement of myocytes starting at the subepicardium,^{13–16} most frequently affecting the right ventricle with biventricular disease in approximately half of the cases, whilst the septum is rarely involved.^{13,17} Hypertrophic cardiomyopathy (HCM): autosomal dominant inherited disease,^{18,19} characterized by myocyte hypertrophy and disarray, starting at the subendocardium^{19–21} with interstitial collagen expansion, leading to interstitial fibrosis, preferentially involving the septum, followed by the lateral and apical left ventricular wall.^{19,21} Small vessel involvement may cause myocardial ischaemia and replacement fibrosis.¹⁹ Idiopathic dilated cardiomyopathy (DCM): highly variable scar pattern, including subendocardial, subepicardial, mid-wall, and transmural patterns; patchy or diffuse architectures are most frequently seen.^{22–28} Here, an example of diffuse fibrosis extending transmurally is given. Cardiac sarcoidosis: demarcated areas of irregular non-necrotising granulomas leading to patchy fibrosis,^{29–32} mainly affecting the left ventricle and the septum, followed by the right ventricle.^{29–31} LMNA-mutation: one example of a patient with dominant, but not exclusively, mid-myocardial (predominantly interstitial) fibrosis, primarily involving the basal septum, the conduction system, and the posterior left ventricular wall.^{33–36} Healthy control: minimal interstitial fibrosis between bundles of myocardium. Post-myocarditis (not shown): heterogeneous disease,³⁷ histologically defined by an inflammatory infiltrate with necrosis, leading to fibrosis.³⁸

CT,^{53–55} nuclear imaging,^{40,56–58,113} and ICE⁵⁹ have been histologically validated to identify compact scar in animal models—and occasionally in small human cohorts.^{56–58} However, although less compact architectures of fibrosis are detectable in humans *in vivo* in non-ischaemic aetiologies, their accurate delineation is still limited, and data comparing imaging with full heart histology are sparse, hampered by the lack of animal models. In ARVC and *post-myocarditis*, histological validation of CMR is based solely on three explanted or post-mortem hearts.^{76,77,107–109} In HCM, the total amount of fibrosis in human septal myectomy specimens correlated to LGE on CMR, using a binary method.⁸⁹

In a mixed cohort of DCM patients a higher cut-off value (6SD instead of the commonly used 2SD) has been proposed to delineate scar on LGE-CMR.⁹³ However, in a patient with DCM and a more complex scar pattern, we could demonstrate that the application of different LGE scar delineation methods (both binary and ternary) resulted in markedly different estimates of scar location and size, and none of the methods were able to delineate diffuse fibrosis as identified on histology (Figure 3). Other techniques, such as T1 mapping⁹³ and DWI⁹⁸ may be able to identify diffuse interstitial fibrosis, a pattern which is more frequently observed in DCM. In cardiac sarcoidosis and LMNA-mutated patients, imaging has not been validated by histology.

In conclusion, imaging is able to delineate compact scar, but currently applied binary or ternary methods to quantify and delineate

fibrosis may not reflect the complex architecture of fibrosis as observed in different aetiologies.

Validation of electroanatomical voltage mapping to delineate scar using histology as the gold standard

Electroanatomical voltage mapping (EAVM) is considered the gold standard in electrophysiology for invasive scar identification. Areas of low bipolar voltages (BV) <1.5 mV recorded with large tip electrodes (3.5–4.0 mm) are usually considered scar. However, bipolar electrogram amplitudes depend on electrode size and spacing, orientation of the catheter, and wavefront propagation. Therefore, new technologies, such as multielectrode mapping with small electrodes and omnipolar electrogram recordings may improve near field resolution and may allow orientation independent voltage mapping.^{65,114} Endocardial unipolar voltages (UV) <8.27 mV may be able to detect intramural or epicardial scar.¹¹⁵ It should be pointed out, however, that these cut-off values have not been validated against histology in all aetiologies. Most of the data are extrapolated from patients with ICM (Table 1 and Figure 1). In animal models of ICM areas of BV <1 mV⁵⁹ or BV <1.5 mV correlated well with areas of scar as

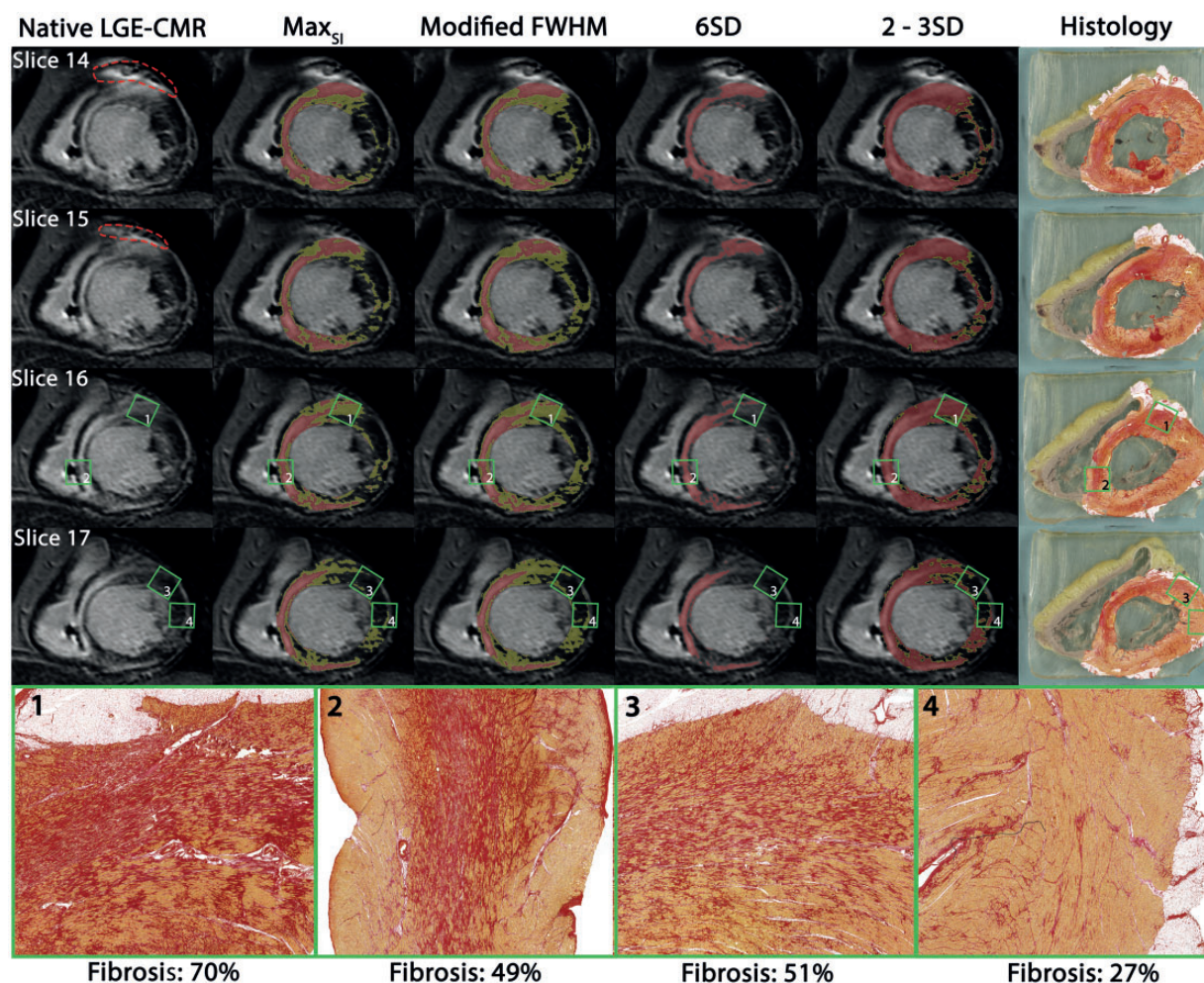


Figure 3 Reprinted with permission from EHJ.²² Different scar delineation techniques applied in dilated cardiomyopathy: different LGE-CMR scar delineation methods applied to one patient with DCM with corresponding histology. Red dotted line: ICD artefact. Red: scar core. Yellow: scar border zone according to different methods. Green squares: locations of high-resolution histology inserts from non-ablation locations. Areas of dense mid-septal fibrosis surrounded by viable myocardium corresponded well with areas of LGE on CMR (insert 2). Despite high quantity, less well delineated fibrosis (insert 1) was only identified as core scar when using the 2-3SD method; as border zone when using the SI_{max} or modified full width at half maximum method. Despite comprising more than 50% fibrosis, a diffuse pattern was not detected on LGE-CMR irrespective of method used (insert 3). CMR, cardiac magnetic resonance; FWHM, full width at half maximum; LGE, late gadolinium enhancement; SD, standard deviation.

identified by gross pathology, both endocardially and epicardially.^{60,61} In dogs, an inverse relation existed between average BV amplitude and extent of scar transmural.⁶² A case study of a patient with MSVT showed a good correlation between the area of scar on EAVM (<0.5 mV) and post-mortem scar size.⁶³ In another case report, areas with BV <0.5 mV on EAVM corresponded to areas with $>80\%$ fibrosis, whilst regions with BV >1.5 mV corresponded to $<20\%$ fibrosis in post-mortem biopsies.⁶⁴

In an ARVC patient, a correlation was found between low endocardial BV (<1.5 mV) areas and gross pathological abnormalities in the explanted heart if scar transmural exceeded 60%.⁷⁹ Others reported a good correlation between low endocardial BV areas and fibrofatty replacement identified on endomyocardial biopsy, although the transmural and size of scar was not quantified in the

biopsy.⁸⁰⁻⁸² In a small series of three ARVC patients, endomyocardial biopsies taken from areas with UV <5.5 mV and BV >1.5 mV showed fibrofatty replacement on histology; implying that endocardial UV amplitudes may be more sensitive to scar in ARVC than endocardial BV amplitudes.⁸³

Recently, post-mortem and post-transplant whole human heart histology from patients with DCM was used to validate EAVM. A linear relationship between the amount of viable myocardium and both BV and UV could be demonstrated, but no singular voltage cut-off value, which identifies pathological amounts of fibrosis, could be found.²² In a doxorubicin cardiomyopathy sheep model dividing the left ventricle into nine segments, a cut-off of 7.5 mV for UV and 2.7 mV for endocardial BV mapping was proposed to distinguish between segments containing $<5\%$ fibrosis and $>10\%$ fibrosis, with

modest sensitivity and specificity.⁹⁹ Electroanatomical voltage mapping has not been histologically validated in HCM, cardiac sarcoidosis, post-myocarditis, or LMNA-mutated patients.

Although EAVM is frequently used as the gold standard to delineate scar, it is poorly validated against the true gold standard (histology) in most aetiologies. Similar to the imaging modalities, currently applied binary or ternary voltage cut-off values to delineate (heterogeneous) scars are unlikely to reflect the complex histology.

Comparison between cardiac imaging and electroanatomical voltage mapping to delineate scar

As human histological data to validate either EAVM or imaging are sparse, the two indirect methods for scar delineation are frequently used to 'validate' each other (Table 1 and Figure 1).

In ICM, LGE-CMR scar delineation methods have been compared to EAVM data. In animal infarct studies, LGE-CMR scar core correlated well with $BV < 0.5$ mV and scar core and border zone together corresponded to $BV < 1.5$ mV, when using the 3SD methods for scar delineation.¹¹⁶ In humans, 60% of SI_{max} on LGE-CMR yielded the highest correlation to distinguish scar core (< 0.5 mV) and border zone (0.5 – 1.5 mV) on EAVM.⁷⁰ Dense ($SI \geq 50\%$ of SI_{max}), transmural scars corresponded well with $BV < 1.5$ mV; however, this cut-off could not accurately detect non-transmural, small subepicardial scar, nor transmural border zone (SI 35–50% of SI_{max}).⁴³ Several studies have shown a moderate correlation between areas of wall-thinning (< 5 mm) on contrast-enhanced CT and low voltages ($BV < 1.5$ mV).^{68,69,71,72} A few studies have compared nuclear imaging to EAVM in ICM. $BV < 0.5$ mV could be predicted by PET with 89% sensitivity using a threshold of 50% metabolic activity to define scar.⁷³ When PET-CT data were integrated with EAVM, the surface area of $BV < 0.9$ mV correlated best with the PET-defined scar (uptake $< 50\%$).⁷⁴ Of interest, integrating FDG-PET-CT with EAVM revealed metabolically active channels within EAVM scar ($BV < 0.5$ mV).⁷³ Electroanatomical voltage mapping findings have also been compared to areas of cardiac denervation using ^{123}I -MIBG-SPECT. The area of EAVM scar ($BV < 0.5$ mV) was 2.5 times smaller than ^{123}I -MIBG-denervated areas, whereas the EAVM border zone (BV 0.5 – 1.5 mV) was similar to the ^{123}I -MIBG transition zone.⁷⁵

Akinetic and thinned areas on ICE corresponded with electroanatomical low BV areas in a pig infarct model (< 2 mV)⁵⁹ and in a series of 15 patients after myocardial infarction (< 1.5 mV).⁴⁸ Of interest, in a mixed cohort of 22 patients (10 ICM, 12 DCM), 83 myocardial segments were analysed by ICE and EAVM. Low BV areas (< 0.5 mV) showed significantly higher ICE derived SI (mean pixel SI unit) compared to areas with border zone voltages (0.5 – 1.5 mV) and normal myocardium areas, whereas EAVM border zone areas showed higher SI heterogeneity on ICE (SD of SI).⁴⁹

In ARVC, both wall motion abnormalities and LGE on CMR have been compared with EAVM data. A good correlation between dyskinetic regions on CMR and low BV areas (< 1.5 mV) has been reported.^{84,85} However, reports on the association between LGE-CMR and EAVM in ARVC are conflicting. Two studies report a poor association, with an underestimation of scar size on LGE-CMR

compared to areas of $BV < 1.5$ mV, especially when low BV areas comprised $< 20\%$ of the right ventricle.^{80,86} Another study reported a strong correlation between LGE-CMR and low voltage areas.⁸⁵ Intramyocardial right ventricular fat infiltration derived from CMR was poorly associated with low voltage areas.⁸⁵ In contrast, CT-derived intramyocardial fat and EAVM showed a good association in ARVC. A high agreement between right ventricular fat on CT (< 10 HU) and epicardial $BV < 1.0$ mV⁸⁷ or < 1.5 mV^{69,88} or endocardial $UV < 5.5$ mV has been reported.^{87,88} The association was weaker for endocardial BVs,^{69,87,88} probably due to the dominant subepicardial involvement in ARVC.^{13,83}

In HCM, comparison between EAVM and imaging data has not been reported.

In DCM different BV and UV EAVM cut-off values to detect LGE-CMR derived scar have been suggested, likely due to differently applied algorithms in heterogeneous and small patient populations. The best endocardial cut-off values to detect LGE-CMR derived scar defined as $SI \geq 30\%$ of SI_{max} were $BV < 2.04$ mV and $UV < 8.01$ mV, respectively.¹⁰³ Using the same CMR method, epicardial voltage mapping with cut-offs of $BV < 1.81$ mV and $UV < 7.95$ mV could delineate LGE-CMR derived scar in areas devoid of epicardial fat.¹⁰² In a heterogeneous group of patients (10 DCM and 5 cardiac sarcoidosis), endocardial $BV < 1.78$ mV and $UV < 5.64$ mV were able to identify areas of LGE ($> 6SD$ above remote myocardium).¹⁰¹ In another heterogeneous series (11 DCM and 4 cardiac sarcoidosis), endocardial cut-off values of $BV < 1.55$ mV and $UV < 6.78$ mV were reported to identify scar on LGE-CMR (full width at half maximum method).¹⁰⁰ There is little data on contrast-enhanced CT findings in DCM with contradictory reports regarding the relationship between (rarely observed) wall thinning (< 5 mm) and low voltage areas.^{68,69,71,104} One study reported a poor (13%) agreement between wall-thinning and endocardial $BV < 1.5$ mV,⁶⁹ whilst another reported an agreement of 63%.^{68,104} Delayed enhancement on CT could predict low voltage areas ($BV < 1.5$ mV and $UV < 8.0$ mV) with a sensitivity of 78% in a heterogeneous series of 19 patients with DCM.⁷¹ There is sparse data comparing ICE and EAVM in DCM. In a small and pre-selected series of 18 patients with DCM and increased echogenicity of the mid/subepicardial lateral wall on ICE, echogenic areas corresponded to epicardial BV areas < 1.0 mV.¹⁰⁵

With regard to the more specific DCM-aetiologies, one cardiac sarcoidosis report suggested a good correlation between areas of active inflammation by PET-CT and low voltage zones.¹⁰⁶ In patients with presumed post-myocarditis subepicardial LGE on CMR showed a reasonable overlap of 76–83% with epicardial $BV < 1.5$ mV areas.^{68,110,111} Using CT data, the agreement between wall-thinning (< 5 mm) and $BV < 1.5$ mV was 29% for the endocardium, but 80% for the epicardium in 11 patients, likely due to the dominant subepicardial involvement in post-myocarditis.¹⁰⁴ In a LMNA patient, a case report showed good correlation between EAVM and LGE-CMR.¹¹²

Although most reports showed a good correlation between EAVM-derived scar delineation based on BV and cardiac imaging for transmural post-infarct scars, there are inconsistent data concerning non-transmural and non-ischæmic scars. LGE-CMR seems to be superior to EAVM in detecting localized fibrosis in humans with DCM, at least if a single voltage cut-off value is applied, regardless of the variation in wall thickness.²² In contrast, in ARVC, EAVM seems to be currently superior to any image modality in detecting right ventricular

Table 1 Histological validation of imaging^a and electroanatomical voltage mapping and comparison between imaging and electroanatomical voltage mapping to delineate scar in different aetiologies related to monomorphic sustained ventricular tachycardia

| Aetiology ^a | Imaging of scar validated by histology | EAVM of scar histology validated by histology | Comparison between EAVM of scar and imaging |
|------------------------|--|---|---|
| ICM | CMR—animal studies: <ul style="list-style-type: none">LGE (binary): Good correlation between LGE areas and large histological scars ($n = 24, 18, 10, 12$)^{39,40,50,51}LGE (binary): 100% of scars with >25% transmural were detected by LGE-CMR, compared to 88% of smaller, subendocardial scars ($n = 12$)⁴⁰LGE (ternary): Good correlation between both <i>ex vivo</i> LGE and histological SC and BZ ($n = 5$)⁴Post-contrast T1 (ternary): Good correlation between <i>ex vivo</i> T1 mapping and histological SC and BZ ($n = 5$)⁵²DWI (ternary): Good correlation between <i>ex vivo</i> DWI and histological SC and BZ ($n = 5$)⁴ CT—animal studies: <ul style="list-style-type: none">Contrast (binary): Good correlation between scar size on CT and histology ($n = 17, 15, 8$)^{53–55}Contrast (ternary): CT underestimated scar compared to LGE-CMR, CT overestimated scar compared to pathology ($n = 15$)⁵⁴ Nuclear imaging—human studies: <ul style="list-style-type: none">PET-CT: both PET-perfusion (¹³N-ammonia) and PET-metabolism (¹⁸FDG) correlated well with gross pathology in transplanted hearts ($n = 3$)⁵⁶PET-CT: perfusion/metabolism mismatched areas contained viable cells, whereas areas with reduced perfusion and metabolism showed extensive fibrosis in transmural biopsies ($n = 33$)⁵⁷SPECT: ^{99m}Tc-sestamibi correlated well with histological myocardial fibrosis in transplanted hearts ($n = 15$)⁵⁸ | Animal studies: <ul style="list-style-type: none">Low bipolar voltage areas (<1.5 or <1 mV) correlate well with histological scar at gross pathology both endocardially and epicardially ($n = 7, 22, 13$)^{59–61}An inverse relationship existed between average BV amplitude and extent of scar transmural ($n = 13$)⁶²All fractionated electrograms are located within areas of scar ($n = 7$)⁵⁹ Human studies: <ul style="list-style-type: none">Scar on EAVM (<0.5 mV) correlated well with post-mortem gross pathology ($n = 1$)⁶³BV < 0.5 mV corresponded to >80% fibrosis, whilst BV > 1.5 mV corresponded to <20% fibrosis at post-mortem histology ($n = 1$)⁶⁴ | CMR—animal studies: <ul style="list-style-type: none">LGE (binary): No significant difference between scar volume on CMR vs. BV < 1.5 mV irrespective of catheter used ($n = 11$)⁶⁵LGE (ternary, MCLE): SC on CMR correlates well with areas of BV < 0.5 mV. BZ on CMR correlates well with BV 0.5–1.5 mV ($n = 5$)⁶⁶DWI (ternary): Good correlation between percentage SC area delineated by CMR and EAVM ($n = 6$)⁶⁷ CMR—human studies: <ul style="list-style-type: none">LGE (binary): BV < 1.5 mV overlap with areas of LGE on endocardial surface in two studies (91 ± 8% and 69 ± 17%, respectively) ($n = 3, 26$)^{68,69} and with areas of LGE on epicardial surface (73 ± 7%) ($n = 26$)⁶⁹LGE (ternary): 60% of SI_{max} yielded the highest correlation between EAVM (SC < 0.5 mV, BZ: 0.5–1.5 mV) and LGE-CMR ($n = 10$)⁷⁰LGE (ternary): Dense ($SI \geq 50\%$ of SI_{max}), transmural, thin walled scars correlates well with BV < 1.5 mV. BV < 1.5 mV cannot accurately detect non-transmural, small subepicardial scar or infarct gray-zone (BZ = SI 35%–50% of SI_{max}) ($n = 15$).⁴³ Contrast-enhanced CT—animal studies: <ul style="list-style-type: none">Good agreement between contrast-enhanced dual energy CT and BV < 1.5 mV (91% agreement, kappa 0.69) ($n = 8$)⁵⁵ |

Continued

Table 1 Continued

| Aetiology ^a | Imaging of scar validated by histology | EAVM of scar histology validated by histology | Comparison between EAVM of scar and imaging |
|------------------------|--|---|--|
| ARVC | <p>ICE—animal studies:</p> <ul style="list-style-type: none"> Infarct size determined by ICE (akinesia) had a good correlation with scar on gross pathology (<i>n</i> = 7)⁵⁹ | | <p>Contrast-enhanced CT—human studies:</p> <ul style="list-style-type: none"> Contrast (binary): Low voltage (BV < 1.5 mV and UV < 8.0 mV) could be identified by delayed enhancement with a sensitivity of 78% and specificity of 86% (<i>n</i> = 23)⁷¹ Wall-thinning (<5 mm): BV < 1.5 mV is moderately correlated to wall-thinning,^{68,69,72} with agreement 66±14% on endocardium and 60 ± 13% on epicardium in largest cohort (<i>n</i> = 59)⁶⁹ <p>Nuclear imaging—human studies:</p> <ul style="list-style-type: none"> PET-CT: BV < 0.5 mV can be predicted by PET with 89% sensitivity using a threshold of 50% metabolic activity (<i>n</i> = 14)⁷³ PET-CT: Surface area of BV < 0.9 mV correlated best with PET-defined scar (uptake <50%) (<i>n</i> = 19)⁷⁴ PET-CT: PET revealed metabolically active channels within EAM-scar (BV < 0.5 mV) (<i>n</i> = 10)⁷³ SPECT: area of BV < 0.5 mV was 2.5 times smaller than ¹²³I-MIBG-denervated areas, whereas BV 0.5–1.5 mV was similar to the ¹²³I-MIBG transition zone (<i>n</i> = 15)⁷⁵ <p>ICE—animal studies:</p> <ul style="list-style-type: none"> Good correlation between BV < 2 mV and aknetic and thinned areas on ICE (<i>n</i> = 7)⁵⁹ <p>ICE—human studies:</p> <ul style="list-style-type: none"> BV < 1.5 mV correlated with akinesia and wall-thinning on ICE in 87% of segments (<i>n</i> = 15)⁴⁸ Low-voltage areas (BV < 0.5 mV) have higher SI on ICE than BZ voltages (0.5–1.5 mV) Normal voltage areas (>1.5 mV) have lower SI than BZ voltages (10 ICM, 12 DCM)⁴⁹ |
| | <p>CMR—human studies:</p> <ul style="list-style-type: none"> Good side-to-side correlation between non-contrast hyperenhancement and fat infiltration on histological examination of explanted or post-mortem hearts (<i>n</i> = 3)^{76,77} | <p>Human studies:</p> <ul style="list-style-type: none"> BV < 1.5 mV correlates well with grooves pathological abnormalities if scar transmurality exceeds > 60% of the wall thickness (<i>n</i> = 1)⁷⁹ Fibrofatty replacement on EMB and BV are well correlated,^{80–82} although | <p>CMR—human studies:</p> <ul style="list-style-type: none"> Native CMR: Good side-to-side correlation between low voltage (<1.5 mV) and dyskinesia (<i>n</i> = 1, 17). Intramyocardial fat was poorly associated with low voltage (<i>n</i> = 17)^{84,85} LGE (binary): LGE underestimates scar compared to EAVM, especially when scar involves <20% of the RV area (<i>n</i> = 18 and <i>n</i> = 23)^{80,86} |

Continued

Table 1 Continued

| Aetiology ^a | Imaging of scar validated by histology | EAVM of scar histology validated by histology | Comparison between EAVM of scar and imaging |
|------------------------|---|--|---|
| HCM | <p>CT:</p> <ul style="list-style-type: none"> Non-contrast CT could not identify fibrofatty replacement in autopsied patients ($n = 4$)⁷⁸ <p>CMR—human studies:</p> <ul style="list-style-type: none"> LGE (binary): LGE reflects the total amount of fibrosis in myectomy specimen ($n = 29$)⁸⁹ LGE (binary): If the degree of collagen increases, the likelihood of LGE also increases, especially if there is >15% collagen in a segment ($n = 1$)⁹⁰ | <p>transmurality and size of scar was not quantified in EMB^{81,82}</p> <ul style="list-style-type: none"> EMB taken from areas with UV < 5.5 mV and BV > 1.5 mV showed fibrofatty replacement on histology ($n = 3$)⁸³ | <ul style="list-style-type: none"> LGE (binary): strong correlation between LGE and low-voltage areas⁸⁵ <p>Contrast-enhanced CT:</p> <ul style="list-style-type: none"> Intramyocardial fat: High agreement between low voltage and fat (HU < -10) with endocardial unipolar (<5.5 mV) or epicardial BV (<1.0 mV⁸⁷ or <1.5 mV^{69,88}) or endocardial UV < 5.5 mV^{87,88} in the RV ($n = 14$⁸⁷, $n = 16$,⁸⁸ and $n = 19$⁶⁹) Intramyocardial fat: Lower agreement between endocardial bipolar low voltage (<1.5 mV) and fat (HU < -10) ($n = 16$,⁸⁸ $n = 14$,⁸⁷ and $n = 19$⁶⁹) |
| | Unknown | Unknown | Unknown |
| DCM | <p>CMR—animal studies:</p> <ul style="list-style-type: none"> Post-contrast T1: T1 was able to identify interstitial fibrosis ($n = 11$)⁹¹ | <p>Human studies:</p> <ul style="list-style-type: none"> Linear relationship between amount of viable myocardium and both UV and BV. No singular cut-off value can be found which identifies pathological amounts of fibrosis ($n = 8$)²² | <p>CMR—human studies:</p> <ul style="list-style-type: none"> LGE (binary, FWHM): LGE generated cut-off value to detect scar of BV < 1.55 mV and UV < 6.78 mV ($n = 11$ DCM, 4 cardiac sarcoidosis)¹⁰⁰ LGE (binary, 6SD): LGE generated a cut-off value of BV < 1.78 mV and UV < 5.64 mV ($n = 10$ DCM, 5 cardiac sarcoidosis)¹⁰¹ LGE (binary): Epicardial cut-offs of BV < 1.81 mV and UV < 7.95 mV correspond to LGE (SI \geq 35% of SI_{max}) in areas devoid of fat ($n = 10$)¹⁰² |

Continued

Table 1 Continued

| Aetiology ^a | Imaging of scar validated by histology | EAVM of scar histology validated by histology | Comparison between EAVM of scar and imaging |
|--|---|--|---|
| <ul style="list-style-type: none"> LGE (ternary): 59% overlap between BV < 1.5 mV and areas of LGE on endocardial surface (n = 1).⁶⁸ The agreement between epicardial BV < 1.5 mV and LGE was 32 ± 12% (n = 9)⁶⁹ LGE (ternary): Endocardial cut-off values of BV < 2.04 mV and UV < 8.01 mV correspond to areas of LGE (SI ≥ 35% of SI_{max}) (n = 19)¹⁰³ | <p>CMR—human studies (whole heart histology):</p> <ul style="list-style-type: none"> LGE (binary): Mid-wall LGE on CMR is confirmed as mid-wall fibrosis on histology (n = 7)⁹² LGE (binary): LGE (6SD) correlated to the total amount of fibrosis in transplanted hearts (n = 11)⁹³ LGE (binary and ternary): different scar delineation methods resulted in markedly different estimates of scar location and size. No method was able to delineate diffuse fibrosis (n = 1)²² LGE has good side-to-side correlation with fibrosis in an explanted heart (n = 1)⁹⁴ Post-contrast T1: Excellent agreement between T1 and diffuse fibrosis (n = 11)⁹³ | <p>Animal studies:</p> <ul style="list-style-type: none"> UV 7.5 mV and BV 2.7 mV could distinguish segments with <5% fibrosis from segments with >10% fibrosis (n = 12) with 77% and 76% sensitivity and specificity for UV respectively and 54% and 76% sensitivity and specificity for BV, respectively⁹⁹ | <p>Contrast-enhanced CT:</p> <ul style="list-style-type: none"> Wall thinning: agreement between BV < 1.5 mV and wall thinning (<5 mm) was 40% on the endocardium and 38% on the epicardium (n = 4)¹⁰⁴ Wall thinning: BV < 1.5 mV agreed with wall-thinning (<5 mm) in 13 ± 16% on endocardium and 23 ± 21% on epicardium (n = 22)⁶⁹ Wall thinning: BV < 1.5 mV matched with wall-thinning (<5 mm) with overlap of 63 ± 21% (n = 3)⁶⁸ Contrast (binary): Low-voltage areas (BV < 1.5 mV, UV < 8.0 mV) can be predicted by delayed enhancement with a sensitivity of 78% and specificity of 91% (n = 19)⁷¹ |
| <p>CMR—human studies (EMB):</p> <ul style="list-style-type: none"> LGE (binary): LGE is poorly related to collagen volume fraction (n = 22)⁹⁵ (n = 14)⁹⁶ Post-contrast T1: extracellular volume on T1 mapping has a moderate (n = 36)⁹⁶ to strong (n = 24)⁹⁷ correlation with collagen volume fraction DWI: Correlation exists between diffusivity and percentage of fibrosis on histology in LVAD core biopsies (n = 14)⁹⁸ <p>CT: Unknown</p> <p>ICE: Unknown</p> | ICE: | <ul style="list-style-type: none"> In pre-selected patients with DCM and increased echogenicity of the mid/subepicardial lateral wall on ICE, echogenic areas corresponded to epicardial BV < 1.0 mV (n = 18)¹⁰⁵ | Continued |

Table 1 Continued

| Aetiology ^a | Imaging of scar validated by histology | EAVM of scar histology validated by histology | Comparison between EAVM of scar and imaging |
|-------------------------|---|---|---|
| Inflammatory | Unknown | Unknown | Nuclear imaging: <ul style="list-style-type: none">• PET-CT: good correlation between areas of active inflammation by PET-CT and low-voltage zones (n = 1)¹⁰⁶ CMR—human studies: <ul style="list-style-type: none">• LGE: epicardial BV < 1.5 mV had an overlap of 76–83% with subepicardial LGE (n = 7,¹¹⁰ n = 2,⁶⁸ and n = 19¹¹¹) Contrast-enhanced CT—human studies: <ul style="list-style-type: none">• The agreement between BV < 1.5 mV and wall-thinning (5 mm) was 29% for the endocardium and 80% for the epicardium (n = 11)¹⁰⁴• Overlap between wall-thinning (<5 mm) and epicardial low voltage (BV < 1.5 mV) was 55% (n = 7)¹¹⁰ |
| Cardiac sarcoidosis | Unknown | Unknown | CMR—human studies: <ul style="list-style-type: none">• LGE (binary): LGE corresponded to BV < 1.5 mV and a good pacemap was in this segment (n = 1)¹¹² |
| Post-myocarditis | CMR—human studies (whole heart histology): <ul style="list-style-type: none">• LGE: Good side-to-side correlation between LGE and fibrosis on whole heart histology (n = 3)^{107–109} | Unknown | |
| Inherited LMNA-mutation | Unknown | Unknown | |

^aStudies including mixed aetiologies which did not provide separate analyses were not included in this table.

ARVC, arrhythmogenic right ventricular cardiomyopathy; BV, bipolar voltage; BZ, border zone; CMR, cardiac magnetic resonance; CT, computed tomography; DCM, dilated cardiomyopathy; DWI, diffusion-weighted imaging; EAM, electro-anatomical mapping; EAVM, electroanatomic voltage mapping; EMB, endomyocardial biopsy; FWHM, full width at half maximum; HCM, hypertrophic cardiomyopathy; HU, Hounsfield unit; ICE, intracardiac echocardiography; ICM, ischaemic cardiomyopathy; LGE, late gadolinium enhancement; LVAD, left ventricular assist device; MCLE, multicontrast late enhancement; PET, positron emission tomography; RV, right ventricle; SC, scar core; SD, standard deviation; SI, signal intensity; SPECT, single-photon emission tomography; UV, unipolar voltage.

involvement (Table 1). Whether functional image modalities provide supplementary information to EAVM that might be important for interventional VT treatment, requires further studies.

The arrhythmogenic substrate for monomorphic sustained ventricular tachycardia

Scar in SHD is not the same as the substrate for MSVT. The presumed dominant mechanism for MSVT in patients with SHD is myocardial re-entry facilitated by slow conduction and areas of fixed or functional conduction block. The only human histological data on MSVT isthmuses come from activation mapping and histological examination of the diastolic pathway in infarcted, explanted, Langendorff-perfused hearts from patients who underwent heart transplantation.^{5,6} Branching and merging surviving myocardial bundles, with a range in diameter from that of a single cell to a few millimetres, separated by collagenous septa, provided the histological substrate for slow conduction during VT, typically located in the subendocardium. The smallest described widths of a diastolic pathway of fast VT with a short diastolic interval traversing the infarct, was $\sim 250\ \mu\text{m}$.⁵ There are no human or animal model data on the specific histological characteristics of the arrhythmogenic substrate for MSVT in non-ischaemic aetiologies (Figure 1).

Activation mapping has evolved as the current clinical gold standard to identify the underlying mechanism and to localize the isthmus of macro-reentrant VT. It aims to localize low amplitude diastolic electrograms of surviving bundles. Although left ventricular assist devices may allow for activation mapping of poorly tolerated VT, detailed human data on entire re-entry circuits, particularly for non-ischaemic aetiologies, are meagre. In addition, focal MSVT mechanism have been reported in both ischaemic and non-ischaemic aetiologies.²³

Accordingly, substrate mapping has become an important strategy which relies on scar delineation based on voltages and, additionally, on the identification of electrograms potentially consistent with (delayed) activation of 'channels of surviving bundles' during stable rhythm. Poorly coupled, fractionated, split, and late potentials are considered as surrogate for VT substrate. Fractionated electrograms have been recorded from areas of scar (defined by histology) in animal infarct models.⁵⁹ In DCM, fragmented electrograms were related to fibrotic barriers in human explanted papillary muscles.¹¹⁷ Notably, the architecture of fibrosis was more important than its density to generate conduction disturbances.^{6,118}

More recently, broader definitions of abnormal electrograms [local abnormal ventricular activities (LAVA)] have been suggested.¹¹⁹ Local abnormal ventricular activities corresponded to areas of scar (on LGE-CMR and CT) in ICM^{68,69,72} and intramyocardial fat (on CT) in ARVC.^{69,88} The correlation between LAVA and scar in DCM is less favourable and inconsistent (overlap 29–72% on CT and 37–88% on LGE-CMR),^{68,69,104} and there is a paucity of data on the underlying tissue architecture and specificity and sensitivity of LAVAs for the critical VT substrate.

Of importance, high-resolution mapping data of VT circuits in a chronic anterior infarct animal model could demonstrate that the

isthmus of infarct-related circuits was formed by functional rather than fixed lines of block. Critical isthmus sites may therefore not be evident during sinus rhythm (SR) as they depend on pacing rate, coupling intervals, and vector of wavefront propagation.¹²⁰

Capability of cardiac imaging to detect the substrate of ventricular tachycardia

Human data comparing the histology of VT substrate with cardiac imaging are difficult to obtain (Figure 1). Therefore, most human studies have validated the ability of imaging to detect sites related to VT re-entry circuits against EAM data. The VT-related sites were usually identified by pacemapping during SR (electrophysiological surrogate for VT-related sites) and less frequently by the gold standard activation mapping, entrainment mapping, or VT-termination (Supplementary material online, Table S1). In some reports, the VT-related sites were defined using LAVAs as surrogates for potential VT substrate.^{68,69,72,121}

In three pig (ICM models) and 17 human studies, imaging was used to investigate myocardial tissue characteristics at sites with confirmed VT re-entry circuits or at sites with assumed VT substrate (Supplementary material online, Table S1). These studies included in total 274 ICM, 124 DCM, and 19 ARVC patients. However, the individual study populations were generally small (only five of the human studies comprised >20 patients^{69,71,122–124}), heterogeneous, and some patients were likely included in multiple reports from the same group.

Although several imaging modalities were evaluated, most studies used LGE-CMR (Supplementary material online, Table S1). The studies mainly employed 2D LGE-CMR with good in-plane resolution but 5–8 mm slice thickness. High-resolution isotropic 3D LGE-CMR was performed in humans by two research groups.^{68–70,122,123}

In general, the studies evaluated the spatial relationship between binary-defined scar on imaging and VT isthmuses (or surrogates thereof).^{43,47,68,69,71,72,101,102,116,125–127} A minority of the studies aimed to identify the more complex characterization of scar, such as delineation of scar core and border zone^{124,128–130} or provided data on scar pattern and transmuralty.^{101,124,131} The locations of scar (on imaging) and VT-related sites (on EAM) were either evaluated by image integration^{43,101,125,127–129,131} or by side-by-side comparison per cardiac segment.^{47,71,128} Moreover, different groups used different methods and thresholds to define scar (Supplementary material online, Table S1), making comparisons between the studies difficult.

Despite the limitations, the studies have consistently shown that, regardless of the aetiology and imaging modality used, virtually all VT-related sites, electrophysiological surrogates for VT sites (e.g. pace-mapping) or surrogates for potential VT substrate (e.g. LAVAs) were located within the scar or close to its border (Supplementary material online, Table S1).

Conflicting results have been reported regarding more specific scar characteristics at the VT-related sites as derived from LGE-CMR. While some authors found 71–100% of VT-related sites or surrogates in areas of dense scar (defined by >3SD or >50% of SI_{max} , respectively),^{128,130} others have observed clustering of VT-related sites (or their surrogates) around the border of the scar.^{47,72}

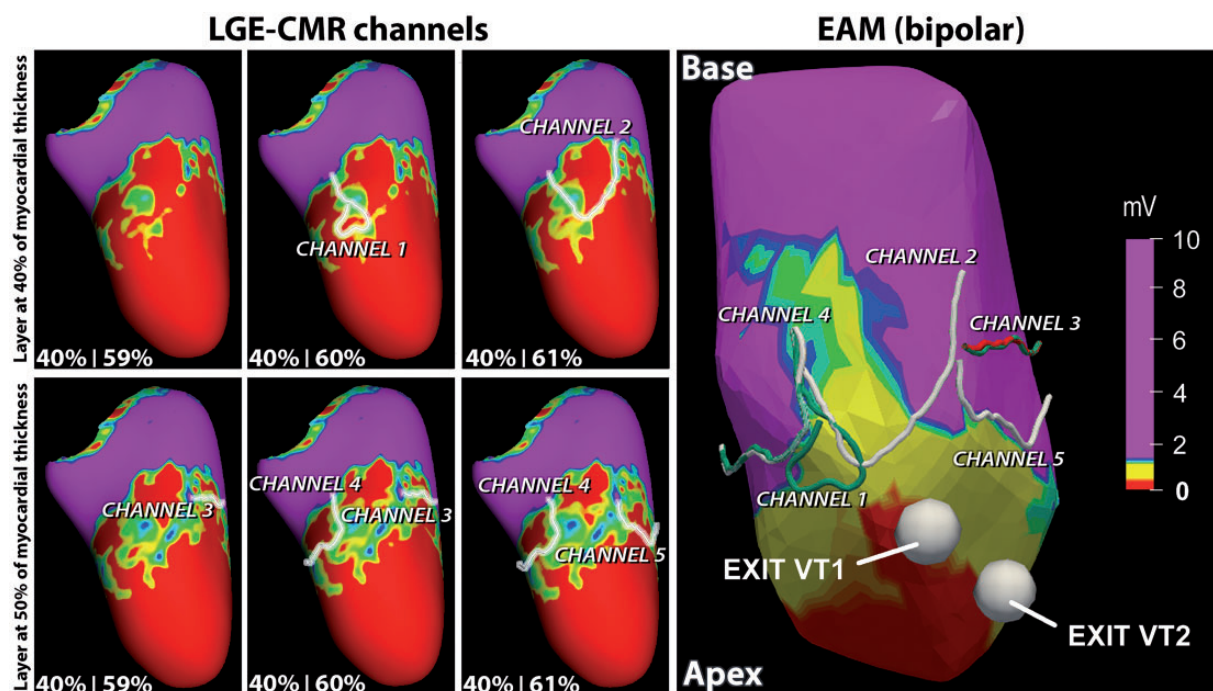


Figure 4 Impact of changes in scar delineation methods on LGE-CMR defined channels: a patient with anterior infarction. All images in modified superior view. Left: channels calculated by an automated algorithm.¹³³ The percentages represent arbitrary threshold definitions of scar border zone and scar core, respectively (as % of SI_{max}). A 1% change in the threshold definition resulted in a change of the number of channels (± 1) and their orientation within a layer, although the change in the extent of scar was visually almost indiscernible. Therefore, it is important to visualize the channels also in a 3D-reconstruction from multiple layers and to use electrogram data during ablation. Right: endocardial bipolar voltage map of the same patient. White spheres mark exits of two clinical VTs (identified by pacemapping and confirmed by non-inducibility of the VTs after ablation at these sites). It should be highlighted that this figure demonstrates only one case; the within-patient reproducibility and diagnostic accuracy of this promising technique for identification of VT substrate needs to be determined by a systematic study. CMR, cardiac magnetic resonance; EAM, electroanatomical mapping; LGE, late gadolinium enhancement; VT, ventricular tachycardia.

In contrast, two research groups have reported that 74–100% of VT-related sites were located in LGE derived border zone channels within dense scar.^{122,132} In both studies, LGE-derived border zone channels were first compared to channels with intermediate BV within low-voltage areas, referred to as conducting channels. Voltage channels were determined either by individually adapting the upper and lower voltage threshold for scar¹³² or by using standard, fixed BV thresholds.¹²² The LGE-CMR border zone channels were detected either on raw LGE-CMR images in two layers^{70,132} or on projected SI maps in five concentric layers (10%, 25%, 50%, 75%, and 90% of the wall thickness),^{122,123} with border zone defined as 40–60% and scar core as $>60\%$ SI of the SI_{max} .^{70,122,123} However, users were allowed, at their discretion, to adjust the SI thresholds by $\pm 5\%$.^{122,123} In this context, it is important to realize that even a minimal change in the definition of scar core and border zone can generate a different number and orientation of channels within a layer (Figure 4).

Despite the different SI methods and EAVM thresholds, the majority (81–100%) of EAVM conducting channels had a matching SI channel in orientation and involved left ventricular segment.^{70,122,123,132} However, not all matching channels were VT related and EAVM seemed to be still superior to LGE-CMR as 23 of 23 VT isthmus sites

were related to EAVM conducting channels compared to 17 of 23 sites to border zone channel on CMR.¹²²

There are limited studies that report on VT-related sites and LGE-CMR scar characteristics in DCM patients. Including VT isthmuses identified by activation mapping, entrainment and VT termination as the gold standard, we could demonstrate that all concealed entrainment sites, and 77% of VT termination sites were located in areas with $\geq 75\%$ scar transmural and in areas of transition from scar core ($SI \geq 50\%$ of SI_{max}) to border zone (SI 35–50% of SI_{max}).¹²⁴ These results were comparable between DCM and ICM patients. In contrast, in a heterogeneous group of DCM patients (5 cardiac sarcoidosis and 10 idiopathic DCM), 15 of 18 VT-related sites, identified mostly by pacemapping, occurred in scar (defined as $SI > 6$ SD above the mean SI of remote myocardium) with 25–75% transmural. Only one of the 18 VT-related sites occurred in transmural scar.¹⁰¹ These inconsistent results may be due to differently applied SI algorithm for scar delineation.

Functional imaging can provide additional information on metabolism, perfusion and innervation. Using ^{82}Rb -PET, 50% of VT exits were found in extensions of viable hibernating myocardium.¹³⁴ Of interest, ^{123}I -MIBG-SPECT showed that 36% of all ablation sites were

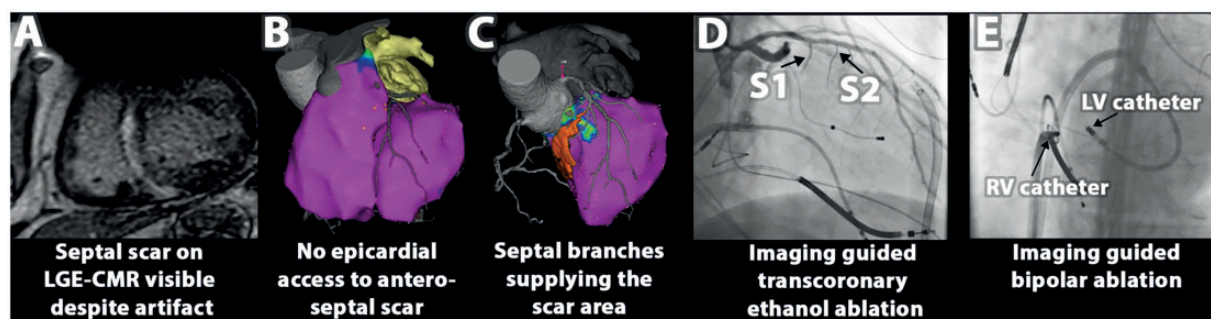


Figure 5 Example of multimodal image integration to facilitate bailout treatment strategies: (A) pre-procedural LGE-CMR shows septal scar, extending to left ventricular (LV) summit. (B) Integrated biventricular endocardial mapping (right ventricular (RV) and LV bipolar voltage maps, purple indicates normal bipolar voltage) confirms that the scar is not accessible through epicardial approach. (C) LV unipolar voltage mapping (purple indicates normal voltages) could not delineate the entire segmented scar (shown in orange), which was supplied by two septal branches (S1 and S2) as evident from CT/CMR image integration, allowing for transcoronary ethanol ablation (D) and imaging guided bipolar ablation between two ablation catheters located at the RV and LV site of the segmented scar (E). Bailout strategies reduced VT burden in this patient; after surgical resection patient has been entirely VT free. CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

in areas that had normal BV but abnormal sympathetic innervation.⁷⁵ Whether nuclear imaging provides complementary information on the arrhythmogenic substrate requires further studies.

In conclusion, there is unambiguous evidence that most VT-related sites arise from scar as detected by imaging. In this regard, LGE-CMR appears to be the superior and most studied modality. However, currently available *in vivo* imaging techniques seem to be insufficient to precisely delineate parts of the scar that are required to sustain MSVT.

Impact of cardiac imaging on outcome of ablation

The impact of pre-procedural imaging and/or real-time image integration on the outcome of VT ablation has not been evaluated in randomized trials. Nevertheless, small non-randomized studies suggest that imaging may have a valuable adjunctive role to conventional EAM-guided ablation (Supplementary material online, Table S2).

One group could demonstrate that pre-procedural evaluation of scar transmural in *ICM* patients may affect the choice of the most effective approach to ablation. Patients with a transmural scar [which was detected by LGE-CMR (56%), transthoracic echocardiography (51%), CT (28%), or SPECT (8%)] had fewer VT recurrences after ablation if they underwent first-line combined endo-epicardial ablation compared to endocardial ablation only.¹³⁵

Pre-procedural evaluation of scar may be even more valuable in *DCM* patients with a wide range of scar patterns and locations. In a retrospective analysis, a better acute outcome of VT ablation could be observed in *DCM* patients who underwent pre-procedural LGE-CMR and intraprocedural integration of the segmented scar, compared to patients without imaging.¹³⁶ In fact, the use of pre-procedural LGE-CMR was the only independent determinant of procedural success. The clinical benefit was attributed to the fact that knowledge of the location and pattern of the scar (which was intramural in 71% of the cases) resulted in a more

effective ablation strategy. The authors reported that imaging helped to reveal intramural scars in areas with normal BV and allowed for adaption of the ablation strategy accordingly; e.g. an epicardial approach for epicardial and free-wall intramural scars, a biventricular approach for septal intramural scars, and longer radiofrequency applications at higher power for intramural scars. However, neither a more frequent epicardial approach, nor differences in radiofrequency applications or mapping density were reported in the imaging group.¹³⁶

Two retrospective studies, which included predominantly *ICM* patients, reported an independent association between real-time integration of LGE-CMR and/or wall-thinning and long-term procedural success.^{121,133} In the first study, the strategy was to eliminate all LAVAs,¹²¹ in the second the strategy was to target slow conduction channels detected by EAM.¹³³ While image integration helped to identify areas of interest and facilitated substrate mapping, EAM characteristics were ultimately used to identify ablation targets.

In a recent report, long-term VT recurrence was compared between 11 *ICM/DCM* patients who underwent LGE-CMR image integration and 11 non-randomized controls without pre-procedural imaging.¹³⁷ In the imaging group, all low-voltage areas and all areas of LGE-CMR derived scar were targeted by ablation. The authors found, by Cox regression, significant association between the use of image integration and VT recurrence [HR 0.12 (95% CI 0.02–0.75) adjusted for five covariates], even though the rate of VT recurrence did not differ between the imaging and non-imaging group (7/11 vs. 9/11, $P = 0.4$). Details on the regression analysis were not provided.

To assess the true impact of cardiac imaging on procedural safety and efficacy, a prospective randomized trial is needed. Such a trial should include a comprehensive description of how cardiac imaging is implemented in the workflow of mapping and ablation and, additionally, time efficiency and cost effectiveness should be evaluated.^{138,139} Despite a lack of randomized, prospective data, there is increasing

evidence that multimodal imaging plays an important role in patients undergoing VT ablation.

Pre-procedural and intraprocedural multimodal imaging: practical considerations

Pre-procedural transthoracic echocardiography is recommended to evaluate cardiac and valvular function, and to exclude mobile intracavitary thrombi, although in this regard, CMR may be more accurate.^{1,140} Pre-procedural LGE-CMR and PET-CT can provide important insights in the potential underlying aetiology and disease activity (e.g. cardiac sarcoidosis), which may impact type and timing of intervention.^{141–143}

The most important information gained from pre-procedural LGE-CMR is the location and pattern of scar (Figures 5 and 6). Presence of a subepicardial, free-wall intramural, transmural, or inferolateral scar may justify a first-line endo-epicardial approach.^{87,102,131,135,144,145} Absence of such scar distribution may help prevent unnecessary epicardial access, thus avoiding an additional 4–7% risk of associated major complications.^{146,147}

Likewise, scar located in the recess of the mitral valve may be more easily reached by a retrograde rather than transseptal approach.¹⁴⁸ On the other hand, involvement of the interventricular septum may require a biventricular approach and additional ablation from the aortic root.^{69,102,136}

Real-time integration of imaging-derived scar at the beginning of the ablation procedure enables one to focus high-resolution EAM on scar areas harbouring potential VT substrate, which likely reduces procedure time (Figure 6).¹³³ Visualization of scar may also help to identify VT substrate in regions with 'normal' voltage,^{43,75} or reveal falsely low voltage due to poor catheter contact.⁴³ Intramural scar may require longer and more powerful radiofrequency applications or alternative technologies [e.g. bipolar ablation, transcoronary ethanol ablation (Figure 5), coil embolization, needle catheter, half saline irrigation, or gadolinium-facilitated radiofrequency ablation].^{136,149,150} Real-time integration of CT may be particularly helpful for epicardial VT ablation.¹⁰² Visualization of epicardial fat may help in interpretation of epicardial low voltage during mapping and in adaptation of radiofrequency energy during ablation (Figure 7). It has been shown that a layer of >2.8 mm of fat significantly attenuates BV^{102,152} and a layer of 7–10 mm of fat may prevent effective ablation by conventional techniques.^{152,153} Of note, a >4 mm thick layer of fat covers about 25% of epicardial surface, mainly located at the base of the ventricles, acute margin, and interventricular grooves—locations which are often targeted by ablation in patients with DCM.¹⁵³

Another virtue of CT is the ability to accurately visualize the coronary arteries and in 74–85% of the patients also the course of the left-sided phrenic nerve.^{153–155} Imaging and accurate integration of the coronary artery tree (Figure 8) can minimize coronary injections

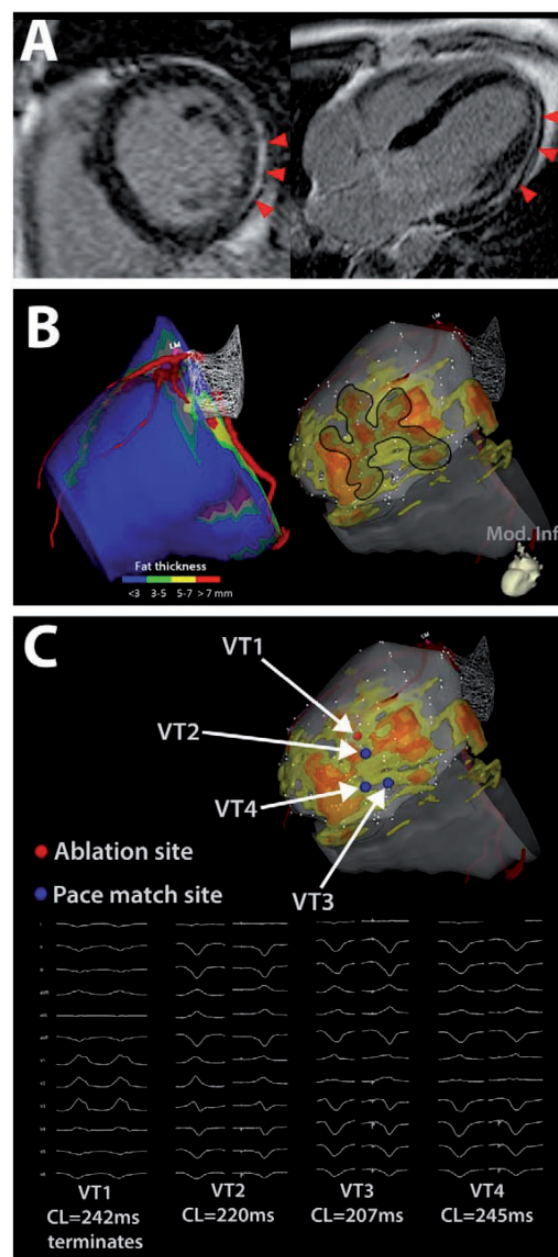


Figure 6 Use of multimodal image integration to facilitate epicardial ablation: (A) inferior-lateral intramural/subepicardial scar with localized ≥75% scar transmural identified on LGE-CMR pre-procedurally. (B) Multimodal image integration: left: no coronary arteries extending over area of interest nor significant epicardial fat layer (epicardial shell colour coded for fat thickness according to bar). Right: transition between scar core (orange) and border zone (yellow) and higher scar transmural shown with grey overlay. (C) High density mapping of area of interest (core-border zone transition, ≥75% scar transmural), all VT-related sites were located in or near the area of interest. CL, cycle length; VT, ventricular tachycardia.

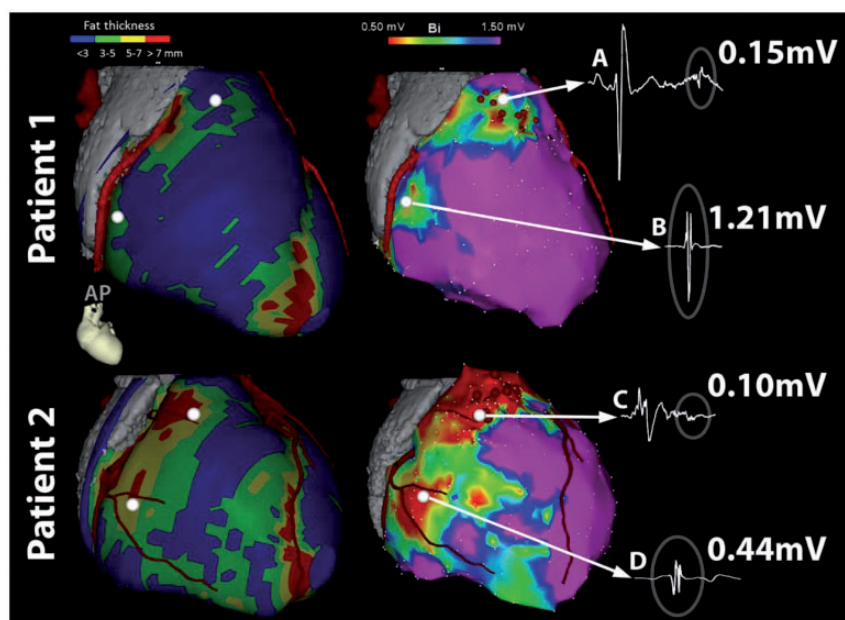


Figure 7 Modified from JACC, reprinted with permission.¹⁵¹ CT-Image integration used to visualize epicardial fat thickness for interpretation of epicardial BV: two endurance athletes with isolated epicardial scar in the anterior right ventricular outflow tract. Left: epicardial contours colour-coded for epicardial fat thickness according to bar, together with coronary arteries in a modified right anterior oblique view, right: epicardial bipolar voltage maps from the same two patients. Integration of epicardial fat images together with abnormal electrogram characteristics allows for classification of electrograms; (A) low-voltage electrogram with late potential in area without fat is due to scar (B) low voltage due to fat (C) low voltage, fragmented electrogram due to scar potentially attenuated due to fat (D) very low-voltage electrogram due to fat.

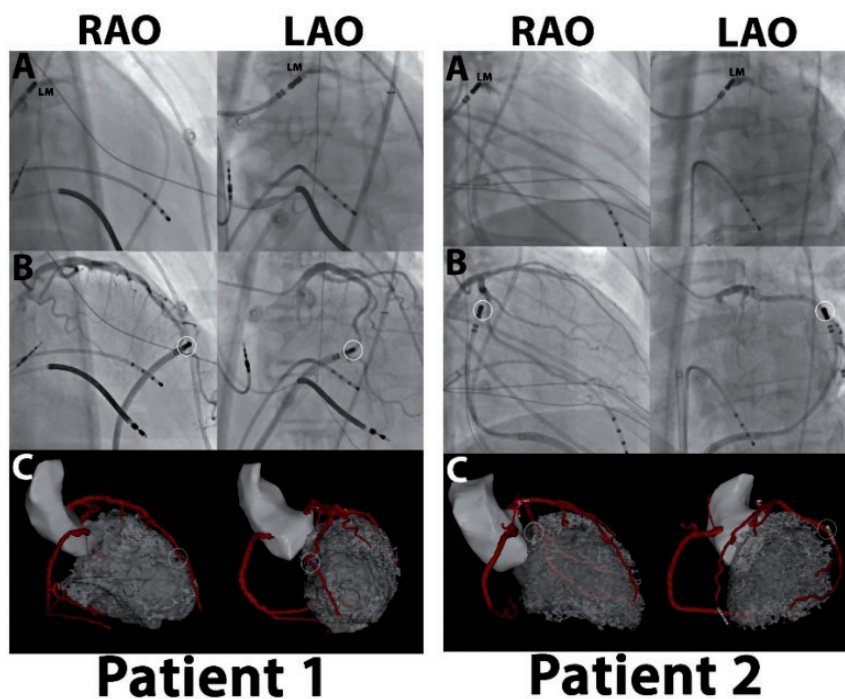


Figure 8 Evaluation of the image integration accuracy using the left main as single landmark: (A) left main (LM) position confirmed by contrast injection through irrigation port of ablation catheter. LM position tagged and used to align images. (B, C) Unique anatomical features used to confirm accuracy of integration. Catheter located epicardially next to curvature (Patient 1) or bifurcation (Patient 2), as seen on coronary angiography. Location of catheter as visualized on CARTO-software confirms location at same anatomical location relative to coronary anatomy without additional automatic or manual adaptation after single-landmark image integration. LAO, left anterior oblique; RAO, right anterior oblique.

during epicardial mapping/ablation, without concerns for coronary injury.¹⁵³ Whether visualization of the phrenic nerve by CT is sufficient to prevent nerve injury without confirming its position by high-output pacing has not yet been evaluated.

Intraprocedural guidance by ICE may be particularly helpful for ablating intracavitary structures with complex anatomy such as papillary muscles.¹⁵⁶ Intracardiac echocardiography may also be used to verify catheter contact and for real-time monitoring of lesion formation.¹⁵⁷

Workflow of image integration

Although there are many ways to integrate images with EAM data, there are basic principles common to all (Figure 9).^{75,101,121,124,130,133,134,137} The first step is extracting anatomical structures (e.g. chamber of interest with endocardial and epicardial contours, coronary arteries, venous structures, epicardial fat thickness, phrenic nerve) and tissue characteristics of interest (e.g. scar core, border zone, SI channel) by manual and semiautomated segmentation techniques. Segmentation of scar and specific tissue characteristics from LGE-CMR requires single SI thresholds. As outlined above, there is no consensus on the SI algorithm that should be used and small changes in scar definition impact segmentation results (Figures 3 and 4).

In the next step, the segmented structures are reconstructed and exported as 3D meshes (most commonly as .vtk files). Various quantitative and qualitative tissue characteristics—such as scar transmural, wall thickness, or averaged SI—can be colour-coded and projected on the surface of a 3D shell of the ventricles (Figure 9).⁴³ The term SI map refers to a 3D shell, colour-coded for SI of all voxels at a particular layer of the myocardium.¹³³ Registration of the image-derived 3D models (.vtk files) with EAM is usually done by landmark registration, which is followed by an automatic registration algorithm, and occasionally by manual correction. The technical aspects of the image registration and the achieved accuracies are described in detail elsewhere.¹⁵⁸ Typical reported registration error (the mean distance between the image mesh/surface and the EAM surface) is 2.0–4.8 mm.¹⁵⁸ However, a small registration error does not necessarily imply good registration accuracy, especially if an automated registration algorithm permits rotation.¹⁵⁹

We prefer a single-landmark registration, using the ostium of the left main coronary artery. The ostium can be readily visualized by injecting contrast dye through an open-irrigation tip ablation catheter (Figures 8 and 9). The 3D images are then usually only translated to the correct position, without the need for rotation. The accuracy of the registration during epicardial mapping can be verified by placing the tip of an ablation catheter on a distinct epicardial anatomical landmark which can be directly visualized by angiography. An example of such validation landmark is the bifurcation of a major branch of the left coronary artery (Figure 8).

After the procedure, the registration matrix used for the real-time image integration can be utilized to project exported EAM points on the original raw images (Figure 9). Such an approach provides a particularly productive framework for investigating the relationship between VT and complex scar characteristics.

Future perspectives

Image integration is routinely performed in only a few electrophysiology labs in the world. One of the reasons is the lack of a universal, user-friendly, yet user-adjustable software platform that would streamline the laborious process. Development of such a platform should be co-ordinated by a multicentre consensus. Moreover, to generate reproducible results, there is a need for standardization of definitions of tissue characteristics, such as scar core and border zone, which would ideally be histologically validated for ischaemic and non-ischaemic aetiologies.

Until recently, the presence of an implantable cardioverter-defibrillator (ICD) was considered to be a contraindication for CMR, thus excluding most patients undergoing VT ablation. However, emerging evidence indicated that CMR could be safely performed in most patients with current generation ICD.^{160,161} In addition, promising CMR techniques, such as wideband LGE-CMR, are evolving which minimize imaging artefacts caused by devices.¹⁶²

To overcome the limitations of performing CMR in patients with ICDs, there has also been rising interest in the detection of scar using CT. Promising CT techniques are being developed that will hopefully enable reliable delineation of myocardial scar. These techniques include delayed-enhancement CT and virtual monochromatic imaging.⁴⁶ Future CT scanners with dual energy sources will also likely reduce contrast load.⁴⁶

To improve imaging of the arrhythmogenic substrate there is a need for scanners with better spatial resolution. Current state-of-the-art navigator gated 3D LGE-CMR at 3T can generate continuous *in vivo* images with voxel resolution of $1.4 \times 1.4 \times 1.4$ mm.¹³³ Such resolution may be sufficient for quantification of a compact scar, but it is suboptimal for accurate visualization of the intricate architecture of fibrosis.⁵ Advanced cardiac T1 mapping techniques and accelerated diffusion-weighted CMR acquisition sequences together with improved post-processing techniques may allow detailed imaging of the diseased myocardium. Although DWI may provide unique information on structure and integrity of the myocardium, current acquisition times, and motion sensitivity require further improvements before being used in clinical practice.⁴⁵

One of the inherent limitations of integrating pre-acquired LGE images, are the potential changes that may occur between the image acquisition and ablation (e.g. due to change in volume load or heart rhythm). This limitation can be overcome by performing CMR directly in the electrophysiology lab. Real-time CMR enables direct tracking of catheters, avoids registration error, and provides feedback on lesion formation.^{163,164} Promising results from animal studies indicate that such real-time visualization of ablation lesions could be used in the future for titrating radiofrequency energy.¹⁶⁵

There are several other evolving technologies that might help in the future in personalized VT ablation, including body surface mapping and image-based arrhythmia modelling. A detailed description of these techniques is beyond the scope of this review, and we therefore refer to recent review articles.^{166,167}

Finally, for further development of imaging modalities for non-invasive identification of arrhythmogenic substrate, it is essential to improve our understanding of its complex ultrastructural and functional components. This will require close co-operation of basic research scientists, clinical electrophysiologists, and cardiovascular

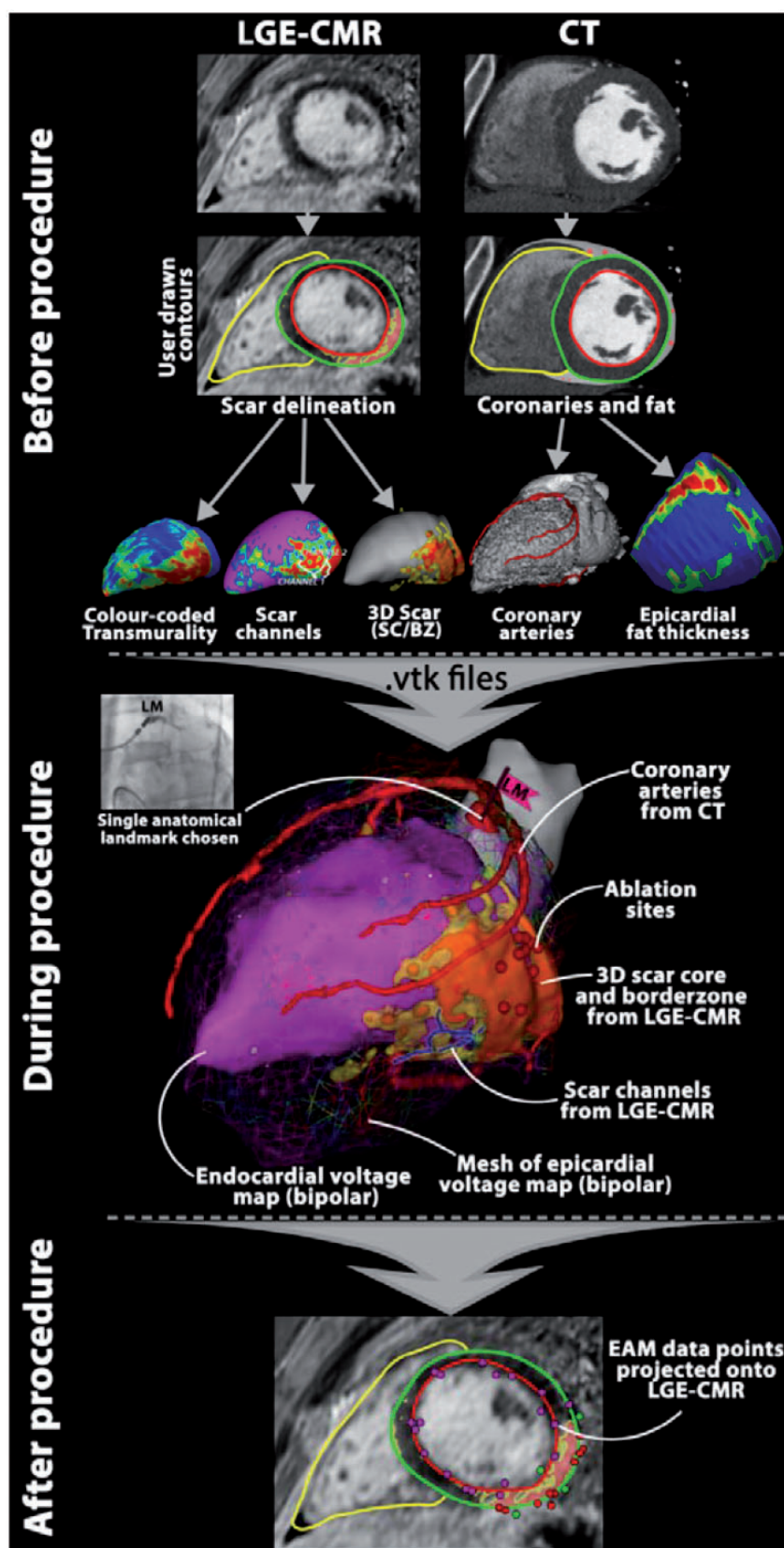


Figure 9 Example of workflow for image integration using CARTO® 3: see text for additional explanation. BZ, border zone; CMR, cardiac magnetic resonance; CT, computed tomography; EAM, electroanatomical mapping; LGE, late gadolinium enhancement; SC, scar core.

imaging specialists. It is also important to critically re-evaluate the capability of currently used imaging techniques. Concepts such as binary or ternary division of scar based on arbitrary cut-offs may be clinically appealing, but oversimplified.

Supplementary material

Supplementary material is available at *Europace* online.

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