Epicardial substrate mapping for ventricular tachycardia ablation in patients with non-ischaemic cardiomyopathy: a new algorithm to differentiate between scar and viable myocardium developed by simultaneous integration of computed tomography and contrast-enhanced magnetic resonance imaging

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Received 11 June 2012; revised 6 September 2012; accepted 17 October 2012; online publish-ahead-of-print 15 November 2012

Aims

During epicardial electroanatomical mapping (EAM), it is difficult to differentiate between fibrosis and fat, as both exhibit attenuated bipolar voltage (BV). The purpose of this study was to assess whether unipolar voltage (UV), BV, and electrogram characteristics (EC) can distinguish fibrosis from viable myocardium and fat during epicardial EAM for ventricular tachycardia (VT) ablation in non-ischaemic cardiomyopathy (NICM).

Methods and results

Ten NICM patients (7 males, 56 ± 13 years) with VT underwent epicardial EAM with real-time integration of computed tomography-derived epicardial fat and contrast-enhanced MRI-derived scar. Bipolar voltage (filtered 30–400 Hz), UV (filtered 1–240 Hz), and EC (duration and morphology) were correlated with the presence of fat and scar. At sites devoid of fat, the optimal cutoff values to differentiate between scar and myocardium were 1.81 mV for BV and 7.95 mV for UV. Bipolar voltage, UV, and electrogram duration >50 ms distinguished scar from myocardium in areas covered with <2.8 mm fat (all P < 0.001), but not ≥ 2.8 mm fat. In contrast, electrogram morphology-characteristics could also detect scar covered with ≥ 2.8 mm fat (P = 0.001). A newly developed three-step algorithm combining electrogram morphology, duration, and UV could correctly identify scar with a sensitivity of 75%. Unipolar voltage but not BV could detect intramural scar in the absence of fat.

Conclusions

Both BV ≤ 1.81 mV and UV ≤ 7.95 mV are useful for detection of scar during epicardial EAM, in the absence of ≥ 2.8 mm fat. However, EC can be used to detect scar covered with fat. A newly developed algorithm combining UV and EC can differentiate between scar and viable myocardium. Unipolar voltage but not BV could detect intramural scar.

Keywords

Ventricular tachycardia • Ablation • Image integration • Magnetic resonance imaging • Computed tomography

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doi:10.1093/eurheartj/ehs382
Introduction

The substrate for ventricular tachycardia (VT) in patients with left ventricular (LV) non-ischaemic cardiomyopathy (NICM) is frequently located intramurally or epicardially and may require an epicardial ablation approach. Since the majority of induced VTs are haemodynamically unstable, substrate mapping is indispensable for successful ablation. Epicardial substrate mapping is however challenging. First, it may be difficult to differentiate between scar and epicardial fat, since both exhibit attenuated bipolar electrogram amplitudes. Secondly, even in the absence of epicardial fat, scar may be difficult to detect if located intramural.

Electrogram characteristics (EC) have been proposed to distinguish scar from epicardial fat since long electrogram duration, fragmented electrograms, and late potentials indicate slow conduction typical for inhomogeneous scar. However, subtle bipolar electrogram abnormalities such as low-amplitude late potentials may be reduced to noise level by the interposition of epicardial fat. Unipolar voltage (UV) has been demonstrated to have a larger field of view, which may allow detection of scar covered by fat and intramural scar.

Computed tomography (CT) and contrast-enhanced magnetic resonance imaging (CE-MRI) are considered gold standards for delineation of fat and fibrosis. Prior studies have demonstrated the feasibility and accuracy of integration of CT-derived epicardial fat and CE-MRI-derived fibrosis with electroanatomical maps (EAM). By integrating both CT- and CE-MRI-derived data during substrate mapping, gold standards for the presence of fat and fibrosis become available.

The purpose of this study was to (i) establish BV and UV cutoff values for scar detection during epicardial EAM, (ii) assess whether voltages and EC can distinguish scar from viable myocardium in the presence of fat, (iii) develop an algorithm that differentiates between scar and viable myocardium, and (iv) to determine whether the epicardial area of interest containing ablation target sites can be delineated using voltage or EC.

Methods

Patients

The study population consisted of 10 out of 11 consecutive patients with NICM referred for combined endocardial and epicardial VT ablation, with integration of both CT-derived epicardial fat and CE-MRI-derived scar information. One patient was excluded because of imaging artefacts causing non-interpretable CE-MRI image data. Coronary artery disease was excluded by coronary angiography in all patients. Seven patients underwent combined endocardial and epicardial VT ablation after endocardial ablation failure which was presumed to be due to an epicardial VT exit site based on the lack of early epicardial activation during VT and/or an endocardial substrate for VT. In the remaining three patients, an epicardial VT exit site was suspected based on the 12-lead ECG morphology of the clinical VT.

Six patients with idiopathic ventricular arrhythmias (VA) who underwent endocardial and epicardial EAM with CT integration served as controls for voltages and EC. Structural heart disease was excluded by echocardiography and CT in six patients (100%), by coronary angiography in five patients (83%), and by MRI in four patients (67%). All six patients underwent combined endocardial and epicardial ablation after endocardial ablation failure and an endocardial activation pattern consistent with an epicardial site of origin.

All patients were treated according to the clinical protocol and provided informed consent.

Computed tomography acquisition and processing

Before the procedure, electrocardiogram-gated cardiac CT imaging was performed with intravenous iodinated contrast agent either on a 64-detector row helical scanner or a 320-detector row volumetric scanner (Toshiba Medical Systems, Otawara, Japan). Using in-house developed software (Mass, V2009-EXP LKEB, Leiden, The Netherlands), the endocardial, epicardial, and pericardial contours were manually traced on short-axis reformatted CT slices (0.5 × 0.5 mm resolution, 2 mm thickness, 2 mm inter-slice gap) to create 3D meshes (Figure 1). Fat thickness was computed by calculating the distance between epicardial and pericardial contours and the vertices of the epicardial 3D mesh were colour coded for fat thickness. Subsequently, the original CT data and the meshes were imported into the mapping system (CARTO XP®, Biosense Webster, Inc., Diamond Bar, CA, USA). Using CARTOMerge (IPE) software, which enables integration of multiple data sets, the ventricles, aorta, and coronary arteries were segmented and merged with the 3D meshes.

Contrast-enhanced magnetic resonance imaging acquisition and processing

Contrast-enhanced MRI was performed on a 1.5T Gyroscan ACS-NT/Intera MR system (Philips Medical Systems, Best, The Netherlands). A standardized protocol was followed, including a black-blood turbo spin-echo sequence for the proximal aorta. Contrast-enhanced images were acquired 15 min after bolus injection of gadolinium. The heart was imaged in one breath-hold with 20–24 imaging levels (dependent on heart size) in short-axis views.

The images were post-processed as described previously. The centreline of the proximal coronary arteries was manually defined in the black-blood spin-echo image data and the aortic, endocardial, and epicardial contours were semi-automatically detected on the short-axis views. The contours were converted into 3D meshes (Mass research software, Figure 1). Myocardial tissue with ≥ 35% of maximal signal intensity was considered scar. The vertices of the LV endocardial and epicardial meshes were colour coded with scar transmurality for the inner and outer half of the wall, respectively. All meshes were imported into the CARTO system using CARTOMerge (IPE) software.

Electrophysiological evaluation

Anti-arrhythmic drugs were discontinued for ≥ 5 half-lives with the exception of amiodarone (n = 1). Programmed electrical stimulation was performed under conscious sedation (three drive cycle lengths (600, 500, and 400 ms), one to three ventricular extrastimuli (≥ 200 ms) from two right ventricular (RV) sites and burst pacing (CL ≥ 200 ms), repeated with isoproterenol (2–10 μg/min when necessary). A positive endpoint for stimulation was the induction of sustained monomorphic VT lasting > 30 s or requiring termination because of haemodynamic compromise.

Electroanatomical mapping, real-time image integration, and ablation

Pericardial access was obtained through a subxyphoid puncture followed by intravenous heparin administration. Electroanatomical mapping was performed using a 3.5 mm irrigated-tip catheter with a 2 mm ring electrode and a 1 mm interelectrode spacing (Navistar...
Figure 1  Processing and integration of CT and contrast-enhanced MRI. Step 1: epicardial fat meshes and 3D scar reconstructions were created from the short-axis computed tomography and contrast-enhanced magnetic resonance imaging slices. Step 2: before the procedure, the computed tomography was segmented and all meshes were imported into the mapping system. Step 3: during the procedure, computed tomography- and contrast-enhanced magnetic resonance imaging-derived images were integrated with the electroanatomical map [displayed as a mesh to better visualize the scar distribution (right)]. Step 4: after the procedure, points were projected on the corresponding short-axis computed tomography slices and the 3D scar reconstruction to determine fat thickness and the presence of underlying scar. Contrast-enhanced magnetic resonance imaging denotes contrast-enhanced magnetic resonance imaging; LAD, left anterior descending; LM, left main; LV, left ventricle; RCA, right coronary artery; RV, right ventricle.
ThermoCool, Biosense Webster, Inc., Diamond Bar, CA, USA) and the CARTO® system. Electrograms were filtered at 30–400 Hz (bipolar) and 1–240 Hz (unipolar). Limited EAM of the aortic root was performed and the left main coronary artery position, confirmed by undiluted contrast injection through the mapping catheter, was tagged on the map. Secondly, an endocardial map of the LV was created using a retrograde approach via the aorta. An RV map was created if indicated. Computed tomography-derived images were visually aligned with the EAM using the left main landmark to overcome rotation errors. The LV surfaces were automatically aligned using CARTO-Merge software and the mean surface registration error was calculated.

Contrast-enhanced magnetic resonance imaging-derived images were visually aligned with the EAM using the left main landmark. Then, the LV surfaces were aligned with the translation tool until the lowest mean surface registration error was reached.

After image registration, epicardial EAM of the target area was performed. Endocardial and epicardial ablation target sites were identified based on activation mapping and entrainment mapping for stable VT, and substrate mapping (EC and pace-mapping) for unstable VT. Radio-frequency energy was applied at 30–45 W (maximum temperature 45 °C, flow 20–30 mL/min, 60 s) for endocardial sites and up to 50 W (flow 20 mL/min) for epicardial sites.

Electrogram analysis

All bipolar electrograms were displayed at the same gain (reference calliper 0.20 mV, Figure 2) and categorized as normal (≤4 sharp spikes) or abnormal (>4 sharp spikes). The latter were subdivided into the following morphologies: double potentials (amplitude ratio ≤ 1.5), continuously fragmented electrograms [amplitude/duration (mV/ms) ratio ≤ 0.05], late potentials (inscribing after QRS and separated by an isoelectric segment > 20 ms), or other abnormal morphologies (>4 spikes but none of the previous; Figure 2). In addition, electrogram duration was measured from the first to the last sharp spike and categorized into four predefined categories: ≤50 ms, 51–60 ms, 61–70 ms, or >70 ms.

Post-procedural reverse registration of electroanatomical maps with both computed tomography and contrast-enhanced magnetic resonance imaging

After the procedure, all points were superimposed on the corresponding short-axis CT slice using the reversed registration matrix and point coordinates (Mass research software). The epicardial fat thickness was calculated for each point and categorized as 0.0 mm, 0.1–2.7 mm, or ≥2.8 mm. Sites with 0.0 mm fat were analysed separately to assess the impact of scar on EAM parameters in the absence of fat. The 2.8 mm cutoff has been demonstrated to separate low (<1.5 mV) from normal bipolar voltage (BV). All points were also superimposed on a 3D reconstruction of the CE-MRI, which was created using the short-axis slices (MATLAB software, version 2009b). Centred around each mapping point that was projected on the LV epicardial surface, a 5 mm diameter transmural cylinder was created and divided into three layers of equal thickness. Points with late enhancement (LE) in the endocardial 1/3 or 2/3 were categorized as endocardial scar, those with LE only in the intramural layer as intramural scar, those with LE in the epicardial 1/3 or 2/3 as epicardial scar, and points with LE in all three layers as transmural scar. All LV epicardial ablation target sites with a ≥11/12 pacemap were evaluated for voltages, EC, and the presence of LE.

Endomyocardial biopsy

After ablation, when indicated by current guidelines, endomyocardial biopsy was performed (six patients, interventricular septum (n = 4) and/or apicolateral LV (n = 3)). Tissue was fixed in 4% formaldehyde. After embedding the tissue in paraffin, cross-sections were cut at 4 μm and stained for collagen content by Picro-sirius Red staining. Nuclei were counterstained with Mayer’s haematoxylin. High-resolution images were taken by microscopy and collagen content was quantified as a percentage of the total biopsy surface using dedicated software (ImageJ, National Institutes of Health, USA). The amount and pattern...
of fibrosis (compact and/or interstitial) were compared with CE-MRI and EAM findings.

**Statistical analysis**

Categorical variables are displayed as number (percentage) and continuous variables as mean ± SD or median (interquartile range). Data were analysed using the χ²-test, Fisher’s exact test, Mann–Whitney U–test, or Kruskal–Wallis test when appropriate. Receiver-operating characteristic curve analysis was performed to determine the optimal cutoff values of bipolar and UV for detection of scar, which were defined as the values maximizing the sum of sensitivity and specificity. The area under the curve (AUC) was calculated to evaluate the accuracy of the mapping parameters. To create an algorithm for differentiation between scar and viable myocardium, independent predictors of scar were identified using multivariable logistic regression analysis and backward stepwise selection (inclusion dependent predictors of scar were identified using multivariable logistic regression analysis and backward stepwise selection). McNemar’s test was used to compare the sensitivity and specificity for the different steps of the algorithm. All analyses were performed with SPSS v18.0 (SPSS Inc., Chicago, IL, USA). All P-values were two-sided and a P-value of < 0.05 was considered significant.

**Results**

**Patients**

Ten patients with NICM (seven males, 56 ± 13 years) and six patients with idiopathic VA (five males, 55 ± 19 years) were studied. Baseline characteristics are summarized in Table 1. Mapping of the LV [NICM mean 110 ± 66 points (median 102, min 33–max 254), idiopathic mean 50 ± 27 points (median 50, min 21–max 90)] and epicardium [NICM mean 137 ± 78 points (median 138, min 55–max 247), idiopathic mean 80 ± 51 points (median 81, min 28–max 164)] was performed focusing on the area of interest based on the 12-lead ECG of spontaneous and induced VA.

Image integration was successfully performed in all patients (CT surface registration error 2.0 ± 0.3 mm in NICM patients and 3.5 ± 1.8 mm in patients with idiopathic VA; CE-MRI surface registration error 3.2 ± 0.4 mm) (Figure 3).

**Fat and epicardial voltages**

Of 1374 epicardial mapping points acquired in patients with NICM, 476 (35%) points were projected on the RV and excluded. Epicardial fat thickness was 0.0 mm at 423 (47%) epicardial LV sites, 0.1–2.7 mm at 296 (33%) sites, and ≥ 2.8 mm at 179 (20%) sites. Late enhancement on MRI was present at 558 (62%) points and no LE at 340 (38%). In patients with idiopathic VA, 268 points were analysed. Epicardial fat thickness was 0.0 mm fat at 37 (14%) epicardial LV sites, 0.1–2.7 mm at 48 (18%) sites, and ≥ 2.8 mm at 183 (68%) sites. Both bipolar and unipolar electrogram amplitudes at sites without LE were attenuated by fat in NICM (P < 0.001, Figure 4A and B) and controls (P < 0.001, data not shown).

**Bipolar and unipolar voltages: scar vs. viable myocardium**

Bipolar voltage and UV in areas without scar on CE-MRI or fat on CT were similar in NICM patients and controls (Figure 4A and B). In patients with NICM, cutoff values of 1.81 mV for BV (AUC 0.73, sensitivity 59% and specificity 78%) and 7.95 mV for UV (AUC 0.79, sensitivity 80% and specificity 72%) could best differentiate between the absence and presence of scar in areas devoid of fat. In areas covered by ≥ 2.8 mm fat, neither bipolar nor UV could differentiate between the absence or presence of scar. A summary of the value of EAM parameters for the identification of scar is provided in Table 2.

**Electrogram characteristics: scar vs. viable myocardium**

In NICM patients, electrograms were prolonged (>50 ms) at 263 (47%) sites with scar, when compared with only 45 (13%) sites without evidence of scar on CE-MRI (P < 0.001). Electrograms at scar sites with < 2.8 mm fat were more often prolonged (>50 ms) than electrograms at scar sites with ≥2.8 mm fat (50 vs. 36%, P = 0.02, Figure 5A and B).

The electrogram morphology at sites with scar was categorized as normal in 173 (31%), double-equal in 61 (11%), fragmented in 57 (10%), late potential in 22 (4%), and other abnormal morphologies in 245 (44%) points. The double-equal, fragmented, and late potential morphologies were unaffected by fat thickness (P = 0.90), while the other abnormal electrogram morphologies were affected by fat thickness (P < 0.001, Figure 5A and B, Table 2).

**Algorithm for differentiation between scar and viable myocardium**

The variables that were independently associated with scar by multivariable logistic regression analysis were electrogram

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**Table 1** Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients with NICM (n = 10)</th>
<th>Patients without SHD (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>7 (70%)</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>56 ± 13</td>
<td>55 ± 19</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25 ± 4</td>
<td>28 ± 5</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>39 ± 13</td>
<td>56 ± 7</td>
</tr>
<tr>
<td>LV end-diastolic volume, mL</td>
<td>243 ± 99</td>
<td>112 ± 33</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>3 (30%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>1 (10%)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 60 mL/min</td>
<td>2 (20%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>Atrial flutter / fibrillation (%)</td>
<td>1 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>PVC (%)</td>
<td>0</td>
<td>5 (83%)</td>
</tr>
<tr>
<td>VT (%)</td>
<td>10 (100%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

LV, left ventricular; NICM, non-ischaemic cardiomyopathy; PVC, premature ventricular contraction; SHD, structural heart disease; VT, ventricular tachycardia.

**Figure 3**

**Figure 4A**

**Figure 5A**

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Figure 3 Example of simultaneous computed tomography and contrast-enhanced magnetic resonance imaging integration during epicardial electroanatomical mapping. Substrate mapping demonstrates low voltage areas consistent with epicardial fat, scar, or both. Late potentials were detected at the basal left ventricular low-voltage area, while an apparently healthy but attenuated electrogram was found at the interventricular groove. Integrated computed tomography-derived fat meshes demonstrate that the interventricular groove and the right ventricular are covered by thick fat layers, possibly explaining the attenuated electrogram amplitudes. The late potentials were caused by a basal scar, which was identified by the integrated contrast-enhanced magnetic resonance imaging-derived scar mesh. PA, pulmonary artery. Other abbreviations as in Figure 1.
morphology, electrogram duration, and UV, but not BV. The three independently associated variables were used to create a three-step algorithm, which is displayed in Figure 6.

The complete algorithm had an overall sensitivity of 75%. The sensitivity was 83% in areas covered with <2.8 mm fat, which decreased to 42% in the presence of ≥2.8 mm fat (Table 2). However, in contrast to bipolar and UV, the algorithm maintained a high specificity in areas covered with ≥2.8 mm fat.

Using the complete algorithm, 84% of transmural, 73% of epicardial, and 64% of intramural scar sites could be identified, when compared with only 36% of endocardial scar sites.

**Bipolar and unipolar voltages, electrogram characteristics: scar type**

To determine the accuracy of bipolar and UV for detection of different types of scar, sites covered by ≥2.8 mm fat were excluded. Both BV and UV were reduced in the presence of epicardial and transmural scar (all P < 0.001, Figure 4C and D), but only UV was affected by intramural scar (P < 0.001). Sites with transmural scar more often had prolonged (>50 ms) and morphologically abnormal electrograms than sites with epicardial, intramural, or endocardial scar (all P < 0.001, Figure 5C and D). Epicardial scar in turn resulted in more prolonged (>50 ms) electrograms than intramural (P = 0.007) or endocardial scar.
Late potentials were only observed at sites with transmural scar.

**Ablation target sites**

A total of 40 VTs were induced (cycle length 310 ± 77 ms). A ≥ 11/12 pacemap could be produced for 17 VTs (43%). At 9 of these 17 sites (53%), diastolic potentials were identified during VT and at 4 (24%) VT slowed and terminated during ablation. Eight (47%) target sites were located at the LV epicardium, 3 (18%) in the LV, 3 (18%) in the aortic root, 2 (12%) at the epicardial RV outflow tract, and 1 (6%) at the RV side of the interventricular septum. At all LV epicardial target sites, BV was < 1.81 mV, UV ≤ 7.95 mV, electrogram duration > 50 ms, and electrogram morphology abnormal (five late potential, one fragmented, two other abnormal). Late enhancement was present at all LV epicardial target sites (six transmural, one subepicardial, one intramural). Six of eight VTs (75%) were not inducible after ablation. One VT could not be abolished presumably due to a deep intramural circuit (intramural LE on MRI) and another due to interposition of a coronary artery and > 10 mm epicardial fat.

**Histology**

Endomyocardial biopsy from the interventricular septum was performed in four patients (three specimens each) distant from areas with LE on MRI. In three patients, voltages and electrograms were normal at the biopsy site, while both interstitial and limited compact fibrosis were found in all three patients (2, 13, and 16% of surface). None of the biopsy sites corresponded to an area of LE.

**Discussion**

The present study is the first to compare voltage maps, EC, fat, and scar by integration of both CT and CE-MRI with epicardial EAM. In addition, the distribution and amount of fibrosis as identified by histology were also compared with EAM and CE-MRI. The main findings can be summarized as follows: (i) BV ≤ 1.81 mV and UV ≤ 7.95 mV are the optimal cutoff values for identification of scar during epicardial EAM of areas devoid of fat, (ii) EC, but not bipolar or UVs, can detect scar covered by fat, (iii) the proposed algorithm can be applied to differentiate between scar and viable myocardium, and (iv) UV can be used to identify intramural scar.

**Bipolar and unipolar voltages, scar, and fat**

In the current study, epicardial bipolar and unipolar cutoff values for detection of scar were determined based on CT and CE-MRI. In a prior study by Cano et al.,2 normal epicardial BV values were assessed by excluding a 1.5 cm wide area along the course of the coronary arteries and the atroventricular groove. Thick fat layers often found in other areas13 may explain the reported lower BV cutoff value of 1.0 mV. In another study, CT-derived fat was integrated with EAM, but a gold standard for the presence of scar was lacking.5 The currently presented cutoff values of 1.81 mV for BV and 7.95 mV for UV are likely to be more accurate since detailed information on fat and scar was available.

It has been postulated that having a larger 'field of view', UV could detect scar covered by fat, thereby compensating for the

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**Table 2** Diagnostic performance of electroanatomical mapping parameters to detect scar for areas with <2.8 mm fat and ≥ 2.8 mm fat

<table>
<thead>
<tr>
<th>Fat thickness (mm)</th>
<th>AUC*</th>
<th>PPV</th>
<th>NPV</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2.8</td>
<td></td>
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<tr>
<td>≥ 2.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar voltage ≤ 1.8 mV</td>
<td>0.73</td>
<td>0.57</td>
<td>78%</td>
<td>58%</td>
<td>53%</td>
</tr>
<tr>
<td>Unipolar voltage ≤ 7.95 mV</td>
<td>0.78</td>
<td>0.58</td>
<td>80%</td>
<td>60%</td>
<td>64%</td>
</tr>
<tr>
<td>Electrogram duration &gt; 50 ms</td>
<td>0.70</td>
<td>0.58</td>
<td>89%</td>
<td>69%</td>
<td>50%</td>
</tr>
<tr>
<td>Electrogram morphology: any abnormal</td>
<td>–</td>
<td>–</td>
<td>80%</td>
<td>69%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Algorithm

Step 1: electrogram morphology: only double, fragmented, late potential

Steps 1+2: as above, OR duration > 50 ms†

Steps 1 + 2 + 3: as above, OR unipolar voltage ≤ 7.95 mV‡

*Parameters are analysed as a continuous variable.
†Overall sensitivity and specificity compared with previous step by McNemar’s test, P < 0.001. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.
limitation of BV mapping. However, in the NICM population, UV could not differentiate between the presence or absence of scar at sites with ≥2.8 mm fat, suggesting a limited field of view.

**Electrogram characteristics, scar, and fat**

Prolonged bipolar electrograms with an abnormal morphology are likely to indicate slow conduction in inhomogeneous scar, perhaps related to VT. Since bipolar electrogram amplitudes are attenuated by epicardial fat, low amplitude components such as late potentials may be reduced to noise level. In this study, both CT-derived fat and CE-MRI-derived scar information were integrated, which for the first time allowed evaluation of the value of different EAM parameters. Electrograms were prolonged at only 47% of sites with LE, suggesting that CE-MRI and EAM may provide complementary information, with CE-MRI more accurately delineating (intramural) fibrosis and EAM providing functional information. Importantly, double-equal, fragmented, and late potentials were not affected by fat and almost exclusively detected in scar areas, whereas other (more subtle) abnormal electrogram morphologies were affected by fat and also frequently found in non-scar areas. Subtle electrogram abnormalities may be caused by small amounts of fibrosis not detected by CE-MRI, as was found in the biopsy specimens. Late potentials may indicate the presence of slow conduction caused by large amounts of scar, which is supported by the presence of transmural scar at all sites with late potentials.

**Algorithm**

If CE-MRI is not available, the proposed easy-to-apply three-step algorithm may be used to improve the accuracy of scar delineation.
during epicardial EAM. In areas with $\geq 2.8$ mm fat (as delineated by CT, which can be acquired irrespective of prior device implantation), only the first and second step should be used to maintain specificity, whereas the third step may be used for sites with $<2.8$ mm fat (on average 80% of mapping sites). When CT scans are not available, steps 1 and 2 of the algorithm can be used, although with lower sensitivity. When only the electrogram morphology (any abnormal) is applied, the sensitivity is acceptable and the specificity is unaffected by fat thickness.

Voltage mapping and scar type

In the current study, for the first time, it is demonstrated that epicardial UV can be used to identify intramural scar. However, due to the limited field of view UVs cannot be used to detect subendocardial scar. Previously, Hutchinson et al. demonstrated that 61% of endocardial low UV areas ($\leq 8.27$ mV) overlapped with epicardial low BV areas. This may, however, also be explained by epicardial scar extending towards the endocardium. Further studies are needed to assess the exact ‘field of view’.

Ablation target sites

Since extensive epicardial EAM is time-consuming, it may be preferable to map the area of interest only. Importantly, all target sites were projected on areas with transmural LE on MRI, suggesting that CE-MRI may be used to delineate the area of interest. The combination of all EAM parameters may be used when CE-MRI is not available.

Histology

Histology is the true gold standard to detect, quantify, and characterize fibrosis, but its results, unlike CE-MRI, are not readily available during the procedure. Biopsy specimens revealed both interstitial and compact fibrosis in the majority of cases, although LE on MRI was only found remote from these areas. These findings may explain why EC were frequently abnormal even in the absence of LE on MRI. Interstitial fibrosis and small amounts of compact fibrosis not detected by CE-MRI may cause electrogram abnormalities, as activation fronts curve around lines of block created by such strands of fibrosis. This is an important finding when considering CE-MRI as a gold standard for detection of fibrosis in NICM. Whether areas of fibrosis not detectable on CE-MRI are related to VT needs further evaluation.

Limitations

This study only analysed mapping points that were projected on the LV epicardium and therefore, our findings do not apply to the RV epicardium. In addition, our findings only apply to the commonly used 3.5 mm tip catheters with a 2 mm ring electrode and a 1 mm interelectrode spacing. Although low voltage may have been caused by poor contact, this was unlikely as pericardial effusions were absent and the irrigant was removed frequently. One patient with an electroanatomical small basolateral scar not clearly visible on CE-MRI due to imaging artefacts was excluded illustrating that CE-MRI and EAM may still be used in a complementary manner.

It should be noted that obtaining pre-procedural CT scans requires pre-procedural planning and is associated with radiation exposure. However, CT-derived coronary anatomy may also reduce the number of contrast injections before epicardial ablation and thus, reduce the radiation exposure during the procedure.

The relatively small number of mapping points, particularly in patients with idiopathic VA, may have limited the accuracy of the maps. The number of controls was small due to the fact that epicardial ablation is not required in the majority of patients with
idiopathic VA. The number of NICM patients studied was also small because implanted devices frequently impeded CE-MRI acquisition. For patients in whom CE-MRI is not available during the procedure, we provide tools to distinguish scar from viable myocardium and fat.9

Clinical implications
Substrate mapping is of key importance during epicardial VT ablation since activation mapping cannot be performed in the majority of VTs. However, during epicardial EAM, it may be difficult to distinguish scar from fat, as both are associated with attenuated bipolar electrogram amplitudes. Moreover, even in the absence of epicardial fat, scars may be difficult to detect if located intramurally. The current study provides insight into the value of different epicardial EAM parameters for detection of scar in patients with NICM. Our findings have important implications when EAM is performed at areas covered by ≥2.8 mm fat, such as the basal LV13 which is often affected in patients with NICM.3,15 In addition, epicardial UV mapping may be particularly useful for detection of intramural scars, which are common in patients with NICM1 and cannot reliably be detected based on BV and EC alone.

Magnetic resonance imaging is limited by the presence of devices and even if safe, it is significantly hampered by artefacts.8 Computed tomography is, however, available in all patients and may be important not only to prove, but also to exclude the presence of epicardial fat. The combination of CT, UV mapping, and EC is likely to improve the accuracy of epicardial substrate mapping, which is important for successful catheter ablation of VT.

Conclusion
Bipolar voltage ≤1.81 mV and UV ≤7.95 mV are the optimal cutoff values to differentiate between scar and viable myocardium during epicardial EAM, but both are attenuated by epicardial fat. Specific electrogram morphologies are not affected by fat, but can identify only one quarter of all scar sites. The proposed easy-to-use algorithm allows more accurate differentiation between scar and viable myocardium during epicardial EAM. Unipolar voltage, but not BV can be used to identify intramural scar.

Supplementary material
Supplementary material is available at European Heart Journal online.

Funding
Carine F.B. H.T. is supported by the Netherlands Heart Society (grant no: 2008B074).

Conflict of interest: the Department of Cardiology receives unrestricted research grants from Boston Scientific, Medtronic and Biotronik.

References