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Chapter 4
Early reperfusion during acute myocardial infarction affects ventricular tachycardia characteristics and the chronic electroanatomical and histological substrate

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Abstract

Background: Reperfusion therapy during acute myocardial infarction (AMI) results in myocardial salvage and improved ventricular function but may also influence the arrhythmogenic substrate for ventricular tachycardia (VT). This study used electroanatomical (EA) mapping and infarct histology to assess the impact of reperfusion on the substrate and on VT characteristics late after AMI.

Methods and Results: The study population consisted of 36 patients (32 male, 63±15yr) referred for treatment of VT 13±9yrs after AMI. Fourteen patients with early reperfusion during AMI were compared with 22 non-reperfused patients. Spontaneous and induced VTs and the characteristics of EA voltagemaps were analyzed. Twenty-seven patients were treated by radiofrequency catheter ablation. Ten patients (non-reperfused 6) were treated by ventricular restoration with intraoperative cryoablation in 9. During surgery biopsies were obtained from the resected core of the infarct. VT cycle length of spontaneous and induced VTs was shorter in reperfused patients (reperfused 299±52/270±58ms, non-reperfused 378±77/362±74ms, p=0.01). An EA patchy scar pattern was present in 71% of reperfused and in 14% of non-reperfused patients (p=0.004). The proportion of EA dense scar was smaller in reperfused patients (24±18% vs. 45±21%, p=0.02). Histological assessment in 10 patients revealed thick layers of surviving myocardium in 75% of reperfused but in none of non-reperfused patients.

Conclusions: Scar size and pattern defined by EA mapping are different between VT patients with and without reperfusion during AMI. Less confluent EA scars match with thick layers of surviving myocardium on histology. Early reperfusion and less confluent electroanatomical scar are associated with faster VTs.
Introduction

Catheter ablation is an important therapeutic option for controlling recurrent ventricular tachycardia (VT) late after acute myocardial infarction (AMI). Mapping studies have shown that reentry circuit locations and VT characteristics vary greatly among patients and are influenced by the 3-dimensional geometry of infarcted areas. In animal models, the duration of coronary artery occlusion determines size, transmurality and geometry of myocardial fibrosis after AMI. Thus, it seems likely that early reperfusion, which has become the standard treatment of acute AMI will influence the nature of the VT substrate. Recently, methods have been developed to characterize the VT substrate based on bipolar electrogram characteristics during sinus or paced rhythm. These methods have been applied to ablation of VTs that are not stable for mapping during VT, targeting the substrate with linear radiofrequency lesions at the electrophysiological scar borderzone. Animal studies to validate this substrate based ablation approach were performed in a chronically occluded infarct related artery (IRA) model resulting in a homogeneous dense scar surrounded by a small scar borderzone.

We hypothesized that early reperfusion during AMI results in smaller and less homogeneous scars on electroanatomical voltage maps and faster spontaneous and inducible VT as compared to non-reperfused patients late after MI. To further evaluate the effect of early reperfusion on the VT substrate the results of electroanatomical voltage maps were compared with infarct histology according to the reperfusion strategy in a subgroup of patients undergoing cardiac surgery.

Methods

Patient population

The population comprised of 36 consecutive patients late after AMI referred for catheter ablation or surgical treatment of sustained monomorphic VT without contraindications for LV mapping and without evidence of reversible ischemia. Clinical evaluation consisted of careful history taking regarding the reperfusion strategy during the index myocardial infarction and consecutive ischemic events, arrhythmias and symptoms of heart failure. All patients underwent echocardiography, coronary angiography and nuclear myocardial perfusion imaging to detect ischemia. The results, including the functional status, the presence of a left ventricular (LV) aneurysm, concomitant valvular disease and residual coronary artery disease were evaluated by a team of cardiologists, electrophysiologists and cardiothoracic surgeons according to the institutional protocol. Patients with significant coronary artery stenosis and reversible ischemia on nuclear perfusion imaging, or with a mobile LV thrombus or with NYHA heart failure class IV symptoms were excluded from the study.
Patients presenting with symptoms of heart failure and a dilated or aneurysmatic LV after anterior AMI were considered candidates for a combined surgical approach of ventricular restoration comprising of an endoventricular circular patch plasty and intraoperative VT ablation. In the remaining patients radiofrequency catheter ablation (RFCA) was offered.

**Coronary Angiography**

All available coronary angiograms obtained during and after the index AMI were reviewed by an interventional cardiologist to assess the effect of the early reperfusion strategy. Based on these results patients were classified as either acutely reperfused with documented open IRA or as not-reperfused. The TIMI (thrombolysis in myocardial infarction) scoring system was used to determine the patency of the infarct related artery (IRA). Patients were considered reperfused when TIMI 3 flow grade was present after reperfusion therapy.

**Electrophysiological evaluation**

After informed consent all patients underwent electrophysiological evaluation including electrical programmed stimulation (EPS) and LV electroanatomical (EA) voltage mapping. Studies were performed in the post absorptive, non-sedated state. Antiarrhythmic drugs were discontinued for 5 half-lives, with the exception of amiodarone which was continued in 14 patients. The EPS-protocol consisted of 3 drive-cycle lengths (600, 500 and 400ms) and ≤3 ventricular extrastimuli from 2 right ventricular sites and burst pacing. 12-lead ECGs and intracardiac electrograms were recorded simultaneously with a 48-channel acquisition system (Cardio-Lab 4.1; Prucka Engineering, Houston, TX, USA). The positive endpoint of EPS was reproducible induction of a sustained monomorphic VT lasting ≥30s or requiring termination because of hemodynamic compromise. When catheter ablation was performed the entire protocol was repeated until all inducible VTs were eliminated or until the procedure was classified as ablation failure in the judgment of the physician. Sinus rhythm (SR) EA voltage mapping (CARTO XP EP system Biosense Webster Inc, Diamond Bar, CA, USA) of the LV was performed with a 3.5mm tip quadrupolar mapping catheter, interelectrode spacing 2-5-2mm (NaviStar ThermoCooled, Biosense Webster Inc, Diamond Bar, CA, USA) by a retrograde aortic approach. Bipolar voltage maps with a spatial resolution of <15mm were created. Electrical scar in the IRA provided area was defined by voltage criteria. Electrogram amplitudes ≤0.5mV were defined as dense scar, voltages >0.5mV and ≤1.5mV as scar borderzone and a ‘patchy pattern’ of EA scar as ≥2 low voltage areas separated by areas of preserved voltage (>1.5mV). For each map the surface of the total scar, the scar borderzone and the dense scar were measured using software provided with the CARTO system.

VT was defined as IRA related if the reentry circuit isthmus site was located within the area supplied by the IRA. A reentry circuit isthmus site was defined by either activation and entrainment mapping for tolerated VT or by pace-mapping (≥11/12 lead match between VT QRS and paced QRS morphology and a Stimulus-to-QRS interval (S-QRS) >40ms) in
patients with poorly tolerated VTs or who were scheduled for operation. In the latter, the potential reentry circuit isthmus site was marked by a single RF application to facilitate ablation during surgery.

Ablation

RFCA was performed at isthmus sites during VT for stable VTs and during SR for unstable VTs with an open irrigated tip catheter. Radiofrequency power was applied to a maximum of 50W, provided that the temperature recorded from the electrode remained below 50°C for 60sec. All inducible monomorphic VTs were targeted and RF energy was applied, if a potential isthmus site could be identified.

Cryoablation concomitant to surgery was performed using a Surgifrost® cryoprobe (Cryocath, Montreal Canada). Overlapping applications, up to -150 °C during 90 sec, were applied to the endocardial scar border as identified by the surgeon. The epicardial surface was inspected for the extent of the scar, identified as a white discoloration of the muscular tissue. After opening of the left ventricle the endocardial surface was inspected for the extent of the scar. Next, the thickness of the left ventricular wall was assessed by palpation: a distinction between the normal thickness of the LV wall and the scar can be identified in every patient. In most patients the border at which the ventricular wall changes thickness coincides with the endocardial extent of the visible scar, except for the septal extension. The area for endocardial cryoablation was based on visible extension of the scar tissue or, in rare cases where no visual identification was possible, on the change in wall thickness. Care was taken that the VT reentry circuit isthmus site marked during catheter mapping was included in the ablation line. The encircling cryoablation line coincided with the suture line of encircling endoventricular patch plasty performed after ablation. VTs with a morphology corresponding to 12-lead surface ECG documentation of a spontaneous VT were considered clinical and VTs with a CL corresponding the CL of a VT documented in the ICD as presumptive clinical VT. Complete ablation success was defined as the absence of any inducible monomorphic VT after the ablation procedure. Partial success was defined as successful ablation of one or more clinical/presumptive clinical VT, but other VT remained inducible; and ablation failure was defined by continued inducibility of the clinical/presumptive clinical VT. Acute success was tested immediately after RFCA in patients who underwent catheter ablation and during a second EPS before hospital discharge in patients who underwent surgery.

Histological assessment

In patients treated with surgical ablation and/or ventricular restoration transmural biopsies were taken from the removed central part of the LV scar and were systematically assessed by a pathologist blinded to clinical history and mapping findings. Routine H&E stains were performed on 5 µm formalin-fixed paraffin embedded (FFPE) sections. All sections were
analyzed for the presence and distribution of myocardial fibrosis. Assessment included visual scoring for density, location (predominance of subendocardial or subepicardial fibrosis) and extent of fibrosis and evaluation of the maximum percentage of transmurality. The identified area of most extensive fibrosis was further morphometrically analyzed for total wall thickness, thickness of the remaining viable myocardium and the ratio of remaining myocardium thickness to total wall thickness. In addition, the spatial relation between viable myocardium and fibrous tissue was assessed and scored for each section and compared to the EA mapping results of the core infarct region.

**Statistical Analysis**

Continuous variables are expressed as mean±SD, and categorical variables as frequency(%). Mann Whitney U-test and Fishers Exact test were used to compare data when appropriate. Mean VTCL was compared after first averaging the VTCL of individual patients and subsequently perform analysis. All statistical analyses were performed with SPSS software (version 16 SPSS Inc., Chicago, Illinois). For all tests a p-value ≤0.05 was considered significant.

**Results**

**Baseline criteria**

The 36 patients (63±15yr, 32 male) were referred for treatment of VT 13±9 years after AMI. Fourteen (38%) patients had undergone acute reperfusion therapy. Reperfusion was achieved by PCI in 8 patients and thrombolysis in 5. In one patient with an occluded LAD collateral flow to the IRA (Rentrop grade 3) was present at the time of acute infarction. This was considered spontaneous reperfusion of the infarcted area. The time from onset of symptoms to presentation was available in 12 patients. All patients were admitted within 6 hours after onset of symptoms. The median symptom-onset to presentation time was 2 hours and 45 minutes (interquartile range 1h – 5h40min). The median estimated time to needle or time to balloon was 45min (interquartile range 36min – 1h) and 1h (interquartile range 30min – 2h), respectively resulting in a median symptom onset to balloon/needle time of 3h30min (interquartile range 2h6min – 6h6min). Twenty-two patients did not undergo early reperfusion therapy. Twenty-two (60%) had anterior wall infarction, 11 (31%) inferior wall infarction, 2 (6%) posterior wall infarction and 3 (8%) had more than one infarct location. In these 3 patients the IRA were the left anterior descending (LAD) and right coronary artery (RCA); one patient underwent successful thrombolysis of the LAD and RCA subsequently and was classified as reperfused patient. The remaining two had chronic occlusion of the LAD and RCA and were classified as non-reperfused patients. At referral the IRA was patent in all patients who had undergone early reperfusion and occluded in 17 non-reperfused
patients. In 5 non-reperfused patients the IRA was patent due to late PCI in 4 and late spontaneous reperfusion in 1.

After evaluation 9 (25%) patients were offered a combined approach of surgical ventricular restoration and intraoperative VT ablation. In one patient surgical ventricular restoration without cryoablation was performed after initial catheter ablation. The baseline characteristics of the patients are summarized in table 1.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All n=36</th>
<th>Reperfused n=14</th>
<th>Non-Reperfused n=22</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>32(89)</td>
<td>13(93)</td>
<td>19(86)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age (year)</td>
<td>63±15</td>
<td>60±11</td>
<td>65±16</td>
<td>0.05</td>
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<tr>
<td>Diabetes</td>
<td>5(14)</td>
<td>1(7)</td>
<td>4(18)</td>
<td>0.6</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>3(8)</td>
<td>2(14)</td>
<td>1(5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Time after AMI (year)</td>
<td>13±9</td>
<td>8±5</td>
<td>16±10</td>
<td>0.01</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td>22(60)</td>
<td>10(71)</td>
<td>11(50)</td>
<td>0.3</td>
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<tr>
<td>Inferior AMI</td>
<td>11(31)</td>
<td>3(21)</td>
<td>8(36)</td>
<td>0.5</td>
</tr>
<tr>
<td>Posterior AMI</td>
<td>2(6)</td>
<td>0</td>
<td>2(9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Multiple AMI</td>
<td>3(8)</td>
<td>1(7)</td>
<td>2(9)</td>
<td>1.0</td>
</tr>
<tr>
<td>Late PCI of IRA</td>
<td>8(22)</td>
<td>4(29)</td>
<td>5(23)</td>
<td>0.7</td>
</tr>
<tr>
<td>Late CABG of IRA</td>
<td>9(25)</td>
<td>1(7)</td>
<td>8(36)</td>
<td>0.06</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21(58)</td>
<td>9(64)</td>
<td>12(55)</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>9(25)</td>
<td>3(21)</td>
<td>6(27)</td>
<td>0.8</td>
</tr>
<tr>
<td>3</td>
<td>6(17)</td>
<td>2(14)</td>
<td>4(18)</td>
<td>0.8</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>30±13</td>
<td>33±16</td>
<td>28±11</td>
<td>0.5</td>
</tr>
<tr>
<td>Anterior aneurysm</td>
<td>18(40)</td>
<td>7(50)</td>
<td>11(50)</td>
<td>1.0</td>
</tr>
<tr>
<td>LV hypertrophy</td>
<td>3(8)</td>
<td>0</td>
<td>3(14)</td>
<td>0.3</td>
</tr>
<tr>
<td>Failed AAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>16(44)</td>
<td>4(29)</td>
<td>12(55)</td>
<td>0.2</td>
</tr>
<tr>
<td>Sotalol</td>
<td>10(28)</td>
<td>4(29)</td>
<td>6(27)</td>
<td>1.0</td>
</tr>
<tr>
<td>Class I</td>
<td>4(11)</td>
<td>1(7)</td>
<td>3(14)</td>
<td>1.0</td>
</tr>
<tr>
<td>B-Blocker</td>
<td>29(81)</td>
<td>11(79)</td>
<td>18(82)</td>
<td>1.0</td>
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</tbody>
</table>
Spontaneous VT
Fifty-five different spontaneous VT were registered during 4.7±5 months preceding referral. The number of different VT did not differ between reperfused and non-reperfused patients (1.4±1.3 versus 1.7±1.1, p=0.4). Twenty VTs were documented on 12-lead surface ECGs and 35 on local electrograms stored in the ICD. In the latter group a difference in VTCL of >30ms was considered as different VT. The VTCL was significantly shorter in reperfused patients as compared to non-reperfused patients (299±52ms vs. 378±77ms, p=0.01) (figure 1). To correct for the effect of antiarrhythmic drugs and specifically of amiodarone on VTCL, the mean CL of VTs registered without any AAD and without amiodarone were compared. There was a non-significant tendency to a shorter VTCL without AAD and a significant shorter VTCL without amiodarone in reperfused compared to non-reperfused patients (table 1).

Electrophysiological evaluation
VT was inducible in all patients with a total of 80 different induced VTs. The CL of the first induced VT (the positive endpoint of EPS) was significantly shorter in reperfused patients (278±80ms versus 391±109ms, p=0.002). A similar difference was found for the mean VTCL (270±58 vs. 362±74, p=0.001) (figure 1).
In 71% of reperfused patients fast VTs with a CL<250ms were inducible compared to 23% non-reperfused patients (p=0.003). After exclusion of patients on amiodarone during EPS the induced VTCL remained significantly shorter in reperfused patients (254±51ms vs. 334±65ms, p=0.006).

**Electroanatomical mapping**

LV voltage mapping was performed with a mean number of 214±43 mapping points. The total scar surface area (bipolar voltage<1.5mV) was comparable in reperfused and non-reperfused patients (65±48cm² vs. 85±46cm²). However, the surface area of dense scar (bipolar voltage<0.5mV) and the percentage of dense scar in relation to total scar was significantly smaller in the reperfused group (reperfused 21±25 cm² and 24±18% vs. non-reperfused 42±32 cm² and 45±21%, p=0.02 and p=0.002 respectively).

A patchy scar pattern in the IRA related area was found in 13(36%) patients. Ten of 14 reperfused patients (71%) had a patchy pattern but only 3 (14%) non-reperfused (p=0.001) (figure 2).

In patients who underwent primary PCI the differences as compared to non-reperfused patients were even more pronounced. In these patients the average CL of clinical and induced VTs was 270±23ms and 239±24ms, respectively (figure 1). The average absolute surface area of dense scar was 11±12cm², the mean percentage of dense scar was 14±12% and 7(88%) had a patchy scar pattern.

**Figure 1.** The median and interquartile range for spontaneous (panel A) and induced (panel B) VTCL are displayed for reperfused vs. non-reperfused patients vs. patients after PCI, for patients with a patchy vs. patients without a patchy pattern of electroanatomical scar and for patients with and without amiodarone treatment. CL indicates cycle length; EP electrophysiological study; PCI, percutaneous coronary intervention; VT, ventricular tachycardia.
Figure 2. Left ventricular electroanatomical voltagemaps of six patients. Bipolar voltages are color coded according to the colorbar. Voltages <1.5mV were considered abnormal. The 3 maps on the left hand side are obtained in reperfused patients and the 3 on the right in non-reperfused patients. The scar pattern is patchy in reperfused and homogeneous in non-reperfused patients. (for figure in color see page: 255)
The targeted reentry circuit sites of VT were located within the scar area supplied by the IRA in 33 patients. In 3 patients no reentry circuit isthmus side could be identified based on the above defined criteria. However, the VT QRS morphology was compatible with an exit site located in the area supplied by the IRA.

The results of the electrophysiological evaluation are summarized in table 2.

### Table 2. EPS and electroanatomical mapping

<table>
<thead>
<tr>
<th></th>
<th>All (n=36)</th>
<th>Reperfused (n=14)</th>
<th>Non-Reperfused (n=22)</th>
<th>p=</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induced VT at EPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number distinct VT</td>
<td>2.3±1.6</td>
<td>2.1±1.7</td>
<td>2.5±1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>CL first induced VT (ms)</td>
<td>347±112</td>
<td>278±80</td>
<td>391±109</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean CL (ms)</td>
<td>326±81</td>
<td>270±58</td>
<td>362±74</td>
<td>0.001</td>
</tr>
<tr>
<td>Shortest CL (ms)</td>
<td>290±62</td>
<td>251±37</td>
<td>314±63</td>
<td>0.001</td>
</tr>
<tr>
<td>Longest CL (ms)</td>
<td>363±117</td>
<td>292±90</td>
<td>409±112</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean CL without AAD (ms)</td>
<td>297±70</td>
<td>254±51</td>
<td>334±65</td>
<td>0.006</td>
</tr>
<tr>
<td>Points voltagemap</td>
<td>214±43</td>
<td>220±44</td>
<td>211±56</td>
<td>0.6</td>
</tr>
<tr>
<td>Surface area map (cm²)</td>
<td>244±55</td>
<td>249±55</td>
<td>242±55</td>
<td>0.7</td>
</tr>
<tr>
<td>Surface area scar (cm²)</td>
<td>77±47</td>
<td>65±48</td>
<td>85±46</td>
<td>0.2</td>
</tr>
<tr>
<td>Surface area dense scar (cm²)</td>
<td>35±32</td>
<td>21±25</td>
<td>42±21</td>
<td>0.02</td>
</tr>
<tr>
<td>Surface area borderzone (cm²)</td>
<td>43±24</td>
<td>44±29</td>
<td>42±21</td>
<td>0.8</td>
</tr>
<tr>
<td>Borderzone % of scar</td>
<td>62±22</td>
<td>76±17</td>
<td>54±21</td>
<td>0.002</td>
</tr>
<tr>
<td>Patchy pattern of scar</td>
<td>13(36)</td>
<td>10(71)</td>
<td>3(14)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CL indicates cycle length; EPS, electrical programmed stimulation; VT, ventricular tachycardia; AAD, antiarrhythmic drugs. Data are expressed as frequency (%) or mean±SD.

### Ablation

Catheter ablation was performed in 24/27 patients. In 3 patients, all after early reperfusion with non-tolerated VT (average CL 227±7ms) and a patchy scar pattern no potential VT isthmus site could be identified. In 2 non-reperfused patients epicardial catheter ablation was performed after endocardial ablation failure, which was successful in one. In none of the reperfused patients an epicardial ablation approach was considered appropriate. No procedure related complications were observed.

Ten patients were treated by surgery after electrophysiological evaluation. Nine patients (reperfused 3 (21%), non-reperfused 6 (27%)) were treated by surgical cryoablation and surgical ventricular restoration. One patient underwent surgical ventricular restoration without cryoablation after catheter ablation. There was one peri-operative death due to
heart failure. One patient refused post-operative EPS. Outcome after ablation did not differ between reperfused and non-reperfused patients (table 3).

### Histological assessment

Histological assessment was performed in the subpopulation of 10 patients undergoing a surgical intervention (reperfused 4, non-reperfused 6). In all non-reperfused patients focal, transmural fibrosis was found; in contrast 3/4 patients with early reperfusion had only non-transmural fibrosis (Figure 3A+B). The average wall thickness of the infarcted area was 1.4±0.7mm. In reperfused patients the average wall thickness was significantly thicker than in non-reperfused patients (2.0±0.6 mm versus 1.0±0.5mm, p=0.03, Figure 3C). The average thickness of viable myocardium even in the most severely fibrotic area was 1.0±0.8 mm in reperfused patients, translating to a ratio of viable myocardium to total wall thickness of 0.5±0.3. In the patients (4 reperfused, 1 non-reperfused) with a patchy pattern of EA scar the average wall thickness was thicker than in patients with a homogeneous EA scar (1.9±0.5mm vs. 0.8±0.2mm, p=0.01). The extent to which viable myocytes were interspersed with fibrosis was categorized (figure 4). Five dominant histological patterns were identified: (A) Contiguous areas of viable myocardium, (B) small confluent areas of fibrosis surrounded by viable myocardium, (C) confluent areas of fibrosis containing only strands of viable cardiomyocytes, (D) confluent areas of fibrosis containing solitary viable cardiomyocytes and (E) transmural confluent fibrosis. The first two patterns were only found in 3 patients after reperfusion and matched with a patchy pattern of EA scar in the core infarct region. In

<table>
<thead>
<tr>
<th></th>
<th>All n=36</th>
<th>Reperfused n=14</th>
<th>Non-Reperfused n=22</th>
<th>p=</th>
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<tbody>
<tr>
<td>RFCA</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Complete</td>
<td>14(52)</td>
<td>5(45)</td>
<td>9(56)</td>
<td>0.3</td>
</tr>
<tr>
<td>Partial</td>
<td>9(33)</td>
<td>3(27)</td>
<td>6(38)</td>
<td>0.3</td>
</tr>
<tr>
<td>Failure</td>
<td>4(15)</td>
<td>3(27)</td>
<td>1(5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Intraoperative EC</td>
<td></td>
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<td></td>
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<tr>
<td>Complete</td>
<td>4(44)</td>
<td>1(33)</td>
<td>3(50)</td>
<td>0.5</td>
</tr>
<tr>
<td>Partial</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Failure</td>
<td>3(33)</td>
<td>2(67)</td>
<td>1(17)</td>
<td>0.5</td>
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<tr>
<td><strong>Overall Result</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Complete</td>
<td>18(50)</td>
<td>6(43)</td>
<td>12(55)</td>
<td>0.2</td>
</tr>
<tr>
<td>Partial</td>
<td>9(25)</td>
<td>3(21)</td>
<td>6(27)</td>
<td>0.2</td>
</tr>
<tr>
<td>No</td>
<td>7(20)</td>
<td>5(36)</td>
<td>2(10)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Two patients who underwent intraoperative EC did not undergo post-operative EPS, RFCA indicates radiofrequency ablation; EC, encircling cryoablation. Data are expressed as frequency(%).
2 patients with a patchy EA pattern of scar (one reperfused, one non-reperfused) transmural fibrosis with solitary viable cardiomyocytes was found at histological assessment. However, in these two patients the core infarct region which was resected consisted of dense scar at mapping (patient 5 in figure 4). In the 5 non-reperfused patients with a homogeneous scar on mapping no contiguous areas of viable myocardium were found. Three representative examples of EA maps (patient 1, 5 and 6) were incorporated in the figure. The assumed area that was resected by the surgeon is indicated on the maps.

Discussion

The current study evaluates the effect of early reperfusion of the infarct related artery on VT characteristics and the VT substrate by EPS, 3-D electroanatomical voltage mapping and histology in patients, who present with VT late after AMI.
The main finding of the study is that characteristics of low voltage scars after AMI are different in patients with and without reperfusion therapy. Early reperfusion is associated with less dense and less confluent electroanatomical scars that appear to give rise to faster spontaneous and inducible VTs. The electrophysiological findings match with the histological assessment demonstrating that the LV core infarct area consists of at least 50% viable myocardium in reperfused patients.

To the best of our knowledge this is the first study to report on differences in EA ventricular voltage maps between post-AMI patients with and without successfully reperfused IRA and their potential impact on clinical arrhythmias.

**Figure 4** The relation between viable myocytes and fibrosis was characterized. Five patterns of local histological scar were identified (A-E). The presence of any of these types in the assessed core infarct region was scored and compared to the presence of reperfusion and the pattern of electroanatomical scar in the 10 patients in whom histological assessment was performed. Three representative examples of EA maps (patient 1, 5 and 6) are shown, the assumed area that was resected by the surgeon is indicated. *(for figure in color see page: 257)*
**Reperfusion and myocardial scar**

Early reperfusion during AMI results in myocardial salvage and reduced mortality during follow-up. Animal studies showed that the duration of coronary artery occlusion is related to infarct size and extend of transmural necrosis. Early reperfusion resulted in necrosis of the inner third of the wall extending towards the midmyocardium, whereas late reperfusion or permanent occlusion resulted in an uniform transmural necrosis. Similar findings were made in human autopsied hearts with acute myocardial infarction after treatment with thrombolysis. These findings from the acute phase of AMI are supported and extended by our data as biopsies were taken in the chronic healing phase 13±9 years after the index MI in 10(28%) of the studied patients. Likely as a result of transmural necrosis the core infarct consisted of transmural fibrosis in non-reperfused patients whereas the majority of early reperfused patients showed no transmural fibrosis at all with thick layers of viable myocardium even in the core infarct region.

The current gold-standard in electrophysiology to define scars after MI is based on electroanatomical voltage criteria. Mapping studies in a porcine model of healed myocardial infarction after chronic occlusion of the IRA revealed large, homogeneous areas of very low voltages surrounded by only a small scar borderzone. These very low voltage areas, arbitrarily defined as <0.5mV, are likely to reflect dense, transmural scar typical for chronic occlusion of the IRA without collateral circulation, whereas the surrounding borderzone may reflect non-transmural scar areas which are partly supplied by non IRAs. A similar pattern of a central homogeneous dense scar area surrounded by the EA borderzone was found in the majority of non-reperfused patients in this study.

Total infarct size defined as areas of electrograms <1.5mV was similar in reperfused and non-reperfused patients. However, acute reperfusion with a median symptom onset to balloon/needle time of 3h30min does not completely abort myocardial infarction but resulted in non-transmural scars as confirmed by histology in a subgroup of patients and contributed to total infarct size using an EA cut-off value of <1.5mV.

Of importance, the total area of electrograms <0.5mV was significantly smaller and the scar borderzone defined by electrograms between 0.5 and 1.5mV significantly larger in reperfused patients which is in line with the histological findings demonstrating only non-transmural scar in the majority of reperfused patients.

In addition, reperfused patients had less confluent EA scar in which areas of lower voltage were frequently interspersed by areas that show relatively preserved or normal bipolar electrograms. These electrograms do not exclude intramural fibrosis as demonstrated by histology. The EA findings likely reflect an inhomogeneous distribution of viable myocardium and fibrosis. Preserved voltage areas are more likely to contain predominantly viable myocardium interspersed by fibrous tissue whereas dense EA scar likely reflects confluent areas of fibrosis containing only strands of viable cardiomyocytes (figure 3).
**Arrhythmia and EA scar**

Precondition for scar related VT is slow conduction through narrow bundles of surviving myocytes bounded by fibrous tissue.\(^{14}\)

VTCL is determined by circuit path length and conduction velocity. Increasing isthmus length contributes to circuit path length with consecutive longer VTCL.\(^{15}\) In a canine infarct model zones of slow conduction and lines of block, bordering the protected isthmus coincided with areas where the borderzone of viable myocardium was thinnest and where the local gradient in borderzone thickness was maximal. In contrast, regions of fast conduction coincided with areas of thicker borderzones with minimal gradients.\(^{1,16}\)

Tachycardia related slow conducting channels have been identified within dense EA scar areas in the majority of patients with monomorphic VT after AMI. The mean length of these channels was 23±11mm and the mean CL of the channel related VT was 365±77ms, similar to VLCL found in non-reperfused patients in our study.\(^{17}\)

The larger and confluent dense scar areas found in patients without reperfusion are more likely to contain longer protected slow conducting channels which may explain the observed longer arrhythmia CL.\(^{15}\) In contrast, in reperfused patients small areas of dense scars are interspersed with areas of preserved voltages and likely preserved conduction velocity referred to as patchy pattern. Small areas of dense scar and thicker infarct borderzones may result in shorter isthmus length, faster conduction and therefore shorter VTCL. (example provided as online supplement)

**Clinical implications**

The current study has demonstrated significant differences in the electroanatomical and histological substrate between early reperfused patients and patients with a chronically occluded infarct related artery. In addition, among post-AMI patients who underwent early reperfusion a shift seems to occur towards faster arrhythmias likely because of the reperfusion induced change of the substrate. Previous studies providing insights into the underlying substrate of reentry circuits of VT and the importance of the scar borderzone were performed in patients with a chronically occluded IRA.

Currently RFCA of fast and unstable VT requires a substrate based approach that targets the borderzone of scar relying on voltage mapping and pace-mapping. This substrate based approach was validated in an animal model of chronic occluded IRA with large homogeneous electroanatomical scars surrounded by a small borderzone. The larger border zone in reperfused patients with only small areas of dense scar on mapping and histology, however may require a different mapping approach. Pace-mapping to define VT exit sites, might be less reliable or not applicable if pacing is performed within short protected isthmuses. Whether a ‘patchy pattern’ of EA scar after reperfusion will pose a challenge in substrate based mapping and ablation needs further evaluation. Studies in animal models that reflect the anatomical substrate in the reperfusion era are warranted to reevaluate the relationship
of the VT circuit and the architecture of the scar which might influence the concept of substrate based ablation.

Limitations

Reperfused patients accounted for one third of the studied population. These patients presented on average 7.7 years earlier than non-reperfused patients. There might be an ascertainment bias such as that the non-reperfused patients represent a subgroup of long term survivors. In addition, alterations in the anatomy of the VT substrate over time that may occur due to increased wall stress, ischemia, hypertension or medication, or due to gradual changes after infarct healing can not be excluded as potential confounders to the presented results. However, the difference in presentation time might reflect advances in recognition and reperfusion strategies of ST-segment elevation AMI in our patient population. The observational nature and relatively small sample size of the study limits the further identification of possible confounders. Since all patients in the current study were referred for ablation of VT, larger studies in a general population of patients after MI are warranted to further elucidate the effect of early reperfusion on arrhythmogenesis and characteristics of VTs.

All biopsies were taken from the central part of the infarcted area as identified by the surgeon. The scar areas were not resected completely, therefore small areas of transmural fibrosis in the core infarcted area in reperfused patients might be missed. In addition, transmural biopsies were only available from the small subgroup of patients who underwent surgery.

Conclusions

There are marked differences in EA scar size and pattern between patients with and without successful reperfusion at the time of myocardial infarction. Less confluent EA scars match with layer of surviving myocyte bundles on biopsy. Early reperfusion and less confluent EA scar are associated with faster ventricular tachycardias which might influence substrate based ablation strategies.
Reference List


