

# Structurally Abnormal Myocardium Underlies Ventricular Fibrillation Storms in a Patient Diagnosed With the Early Repolarization Pattern

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Structurally abnormal myocardium underlies ventricular fibrillation storms in a patient diagnosed with the early repolarization pattern.

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# Abstract

Introduction: The early repolarization pattern refers to abnormal ending of the QRS complex in subjects with structurally normal hearts and has been associated with ventricular fibrillation (VF). The aim of this study was to investigate the mechanism underlying QRS slurring in a patient with the early repolarization pattern in the electrocardiogram (ECG) and VF storms. Methods and Results: We studied a patient with slurring of the QRS complex in leads II, III and aVF of the ECG and recurrent episodes of VF. Echocardiographic and imaging studies did not reveal any abnormalities. Endocardial mapping was normal but subxyphoidal epicardial access was not possible. Open chest epicardial mapping showed that the inferior right ventricular free wall activated the latest with local J-waves in unipolar electrograms. The last moment of epicardial activation concurred with QRS-slurring in the ECG whereas the Jwaves in the local unipolar electrograms occurred in the ST segment of the ECG. Myocardial biopsies obtained from the late activated tissue showed severe fibrofatty alterations in the inferior right ventricular wall where fractionation and local J-waves were present. After ablation, the early repolarization pattern in the ECG disappeared and arrhythmias have been absent since (follow-up 18 months). Conclusion: In this patient, the electrocardiographic early repolarization pattern was caused by late activation due to structurally abnormal myocardium. The late activated areas were marked by J-waves in local electrograms. Ablation of these regions prevented arrhythmia recurrence and normalized the ECG.

# Condensed Abstract

The early repolarization pattern refers to abnormal ending of the QRS complex and has been associated with ventricular fibrillation in subjects with structurally normal hearts. We studied a patient with the early repolarization pattern and ventricular fibrillation storms, who underwent epicardial mapping during open chest surgery. Biopsies at the sites of electrical abnormality demonstrated extensive fibrosis in the right ventricular inferior wall. Epicardial ablation of these sites resulted in long-term normalization of the cardiac rhythm and of the QRS-complex.

Abbreviations

ECG = Electrocardiogram

VF = ventricular fibrillation

ICD = implantable cardioverter defibrillator

RVFW = right ventricular free wall

RVOT = ventricular outflow tract

ECGI = electrocardiographic imaging

Key words: Conduction, Early Repolarization, Ablation, Ventricular Fibrillation

#### Introduction

The early repolarization pattern refers to slurring or notching at the end of the QRS complex and is associated with sudden cardiac arrest due to ventricular fibrillation (VF) in patients with structurally normal hearts.(1,2) In patients with documented cardiac arrest and the early repolarization pattern, implantation of an automated implantable cardioverter defibrillator (ICD) is the recommended therapy. Identification of patients with the early repolarization pattern at risk for arrhythmias is challenging because it is common in the healthy general population. Previous syncope or a family history of sudden cardiac death have been identified as risk factors but their predictive power is low.(1) Recent reports indicate that ablation of myocardium with fractionated potentials can prevent VF in a subset of patients with the early repolarization pattern.(3,4) This implies that a localized and potentially arrhythmogenic substrate underlies life-threatening arrhythmias in patients with the early repolarization pattern.

We present the first open-chest epicardial electrophysiological mapping of a patient with the early repolarization pattern and VF storms in whom myocardial biopsies were obtained from tissue with fractionated potentials. Our data provide electrophysiological and histological evidence that localized myocardial structural abnormalities can be the underlying arrhythmogenic pathological substrate for life-threatening ventricular arrhythmias and early repolarization in the electrocardiogram (ECG). Epicardial ablation of the structurally abnormal myocardium prevented recurrence of VF and normalized the ECG. We propose that in similar patients with the early repolarization pattern in whom a structural substrate is present, ablation may be the therapy of choice.

#### Methods

This study was performed after written informed consent of the patient, and was executed in accordance with the declaration of Helsinki. The patient underwent standard medical diagnostics and care, and standard resuscitation procedures were followed.

Electrophysiological study

First the patient underwent an electrophysiologic study involving endocardial mapping using CARTO-mapping system (Biosense Webster Inc). Subsequently, electrocardiographic imaging (ECGI) mapping was executed with the CardioInsight system (Medtronic, St. Paul, MN). The ECGI methodology has been described before.(4,5) Body surface ECG recordings were acquired with a 252 electrode-vest wrapped around the torso. Low-dose computed tomography was used to localize the vest electrode positions relative to the heart and the torso. The vest remained in the same position during the electrophysiologic study and programmed stimulation. Body surface ECG recordings from the vest electrodes were acquired before and during the invasive mapping procedure. A 3D model of the heart was created using dedicated software (CardioInsight, Medtronic, St. Paul, MN). As a result of pericardial adhesions it was not possible to gain access to the pericardial space for detailed invasive mapping of the epicardium.

The CardioInsight system automatically displays epicardial wavefront patterns on the 3D reconstruction of the patient's heart based on the solution of the inverse problem.(5) In this manner, activation mapping was performed during spontaneous or induced VF. After adequate filtering and phase mapping, dynamic wavefront propagation maps were generated. Cardioversion was performed if VF lasted > 10 seconds.

The wavefront maps display the electrical wavefront at the pi/2 phase value of each ECGIcalculated unipolar electrogram morphology, serving as a surrogate for local activation. We analyzed the VF maps during an initial organized period of VF (the initial 5 seconds), as

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previously described.(6) VF drivers were defined as either focal breakthrough or full reentrant activity with a high activation frequency. Focal breakthroughs are detected when centrifugal activation originated from a given site. Rotations are detected when the rotational core, or singularity point, of a rotating wavefront is within a 2.5-cm area for  $\geq$ 1.5 rotations. We then created spatiotemporal density maps displaying the number, location, and spatial extent (of reentry trajectories) of VF drivers. We marked (colored hexagons) the number and location of epicardial focal breakthrough.

# Open chest multi electrode mapping

A midsternal sternotomy was performed. After opening of the pericardium and careful dissection of the pericardial adhesions, sequential unipolar epicardial mapping was executed using a rectangular 8x8 multi-electrode grid (64 electrodes, 5 mm interelectrode distance). The electrode grid was sequentially placed on 9 locations of the epicardium to cover the entire surface of the heart. The reference electrode was placed in the thoracic wound. A three lead ECG was recorded simultaneously. During the entire mapping procedure, a train of 8 S1 stimuli were delivered from the right atrium (cycle length 800 msec), followed by a single S2 from the left ventricular apex (coupling interval 580). Primary data analysis was performed in the operating theatre to guide ablation. Local moments of repolarizations were defined as maximum positive dV/dt of the local T-wave (7).

# Radiofrequency ablation

Ventricular epicardial ablation was performed by radiofrequency energy (20-45 Watt, duration ranging 10-60 seconds) delivered by a ThermoCool catheter (Biosense Webster, California USA).

#### Histology and 3D reconstruction

Biopsies were obtained from selected sites in the right ventricular inferior wall and basal free wall and directly snap frozen in liquid nitrogen. The biopsies were cryo-sectioned (8  $\mu$ m) and stained with picro-sirius red. The 3D model was generated in Amira (version 6.5, Thermo Fischer Scientific, USA). We imported the images (2560x1920 pixels at 600 dpi, resolution of 1.95 $\mu$ m/pixel) of 49 histological sections (collagen is red, myocardium yellow) and a 3D reconstruction was generated as published previously.(8) The images were imported and converted to grayscale images which rendered collagen dark grey and myocardium light grey, with a high contrast between the two. We then automatically aligned the images. Alignment errors were corrected manually. Next, we surveyed the image stack for clusters of myocardium, the core of which could be reliably traced on at least 10 consecutive sections (on every section this core of myocardium also had peripheral parts which could not always be traced on the neighbouring sections). Myocardial clusters were labelled green.

#### Results

### Diagnosis of the early repolarization pattern

The patient, a 36-year-old man, suffered aborted sudden cardiac arrest at age 30 and was transferred to the nearest hospital after cardiopulmonary resuscitation in 2012. During the hospital admission, the patient had documented VF and was defibrillated by a DC shock. An ICD was then implanted. VF episodes recurred one year later, increasing in frequency from 1 to 4 episodes per month. The patient then received oral propranolol (10 mg q8h). In May 2018, the patient experienced palpitations and dizziness while sitting at home, 10 seconds before the ICD delivered a shock. Four more appropriate shocks were delivered at the same day and the patient was referred to our hospital.

We observed an apparently healthy young man with a midline sternotomy scar resulting from prior chest surgery performed because of a chest trauma when he was 6 years old. The ECG showed slurring of the QRS complex ( $\geq 1$  mV) in leads II, III and aVF, typical of the early repolarization pattern (Figure 1A). An ECG recorded during childhood was not available. Intravenous bolus administration of Ajmaline (1 mg/kg; total 60 mg) did not provoke right precordial ST-segment elevation, a characteristic of the Brugada ECG pattern. Echocardiographic and imaging studies did not reveal any abnormalities. Family screening revealed that an uncle had (unspecified) heart disease. The patient's parents, his 3 brothers, his 2 children did not have a history of arrhythmias. The patient's symptoms and unexplained cardiac arrest meet the standards for diagnosis of a malignant early repolarization pattern according to the Shanghai Score System (9).

An electrophysiological percutaneous catheter study did not reveal endocardial electrical abnormalities (low voltage or fractionated potentials, Supplemental Figure 1). During the electrophysiological study, spontaneous short-coupled premature ventricular

contractions and polymorphic ventricular tachycardias occurred frequently (Figure 2A). Subxyphoïdal access was impossible due to pericardial adhesions. Non-invasive ECGI during sinus rhythm and of ventricular fibrillation suggested an arrhythmogenic substrate at the right ventricular free wall epicardium (Figure 2B/C).

The patient then underwent open chest surgery to identify a possible epicardial arrhythmogenic substrate and to perform epicardial ablation, if necessary.

### Late activation of the right ventricular inferior wall

The electrode grid was placed over 7 anterior locations (Figure 3A) as well as 2 posterior locations of the heart. Figure 3B shows the activation patterns of three subsequent beats recorded from the right ventricular outflow tract (RVOT) and RV inferior wall (red in panel A). Figure 3C shows unipolar electrograms (a-g indicate electrode positions in 3B) and lead II of the ECG. The earliest onset of the body surface ECG was taken as the reference time. During S1 pacing, the inferior right ventricular free wall (RVFW) activated last, also relative to all other grid positions (Figure 4A) and later than the right ventricular outflow tract (Figure 3A/B). Activation of the inferior RVFW concurred with the QRS-slurring in lead II of the ECG, both during the basic (S1, dotted line) and the premature (S2) activation (Figure 3C). Following S2 (coupling interval 580 ms) activation delay occurred and a drastic reduction in the voltage of sites b, d, f and g, and fractionated local potentials in the same tissue became evident. Note that following S2, a notch has appeared in lead II, coinciding with last activation in the right ventricular inferior wall, and that the RV inferior wall remained activated late despite the difference in activation patterns between the atrial and ventricular beats (see QRS-morphology in lead II).

### Early repolarization did not coincide with the early repolarization pattern in the ECG

Based on local multi-electrode recordings from 9 different locations we reconstructed the activation and repolarization patterns of the entire epicardial surface of the heart during atrial

pacing (Figure 4A, only anterior view shown). The anterior wall of the right ventricle activated the earliest whereas the right inferior wall activated last, slightly later than the RVOT (85 vs 83 msec, respectively). Repolarization was the earliest in the anterior wall of the right ventricle. The RVOT and apex of the left ventricle repolarized last. Repolarization in the right ventricular inferior wall was heterogeneous; parts repolarized relatively early (location a) and other parts relatively late (location b). However, the earliest repolarization times occurred much later than the slurring of the ECG (figure 4B).

The last activated myocardium in the inferior RVFW showed local J-waves in the unipolar electrograms which occurred during the ST-segment of lead aVF, but after the moment of slurring or of the notch in the QRS complex (Figure 4B). Figure 4C (left panel) shows that the largest J-waves in the local electrograms occurred in the last activated tissue. Indeed, the amplitude and timing of the peak of the J-wave in the local electrograms correlated with the moment of local activation (Figure 4C mid and right panel).

# Epicardial ablation of structural abnormal right ventricular inferior wall

Two transmural right ventricular biopsies were obtained before epicardial ablation was performed. Fractionation at these sites was confirmed by unipolar and bipolar electrogram recordings obtained with the ablation electrode (Figure 5A). One biopsy was taken from the last activated tissue of the inferior RVFW, showing local J-waves or fractionation (Figure 5A), and one from the basal right ventricular wall. The biopsy of the right ventricular inferior wall showed extensive fibrosis (Picrosirius Red staining, collagen is red) with fragments of surviving myocardium. In contrast, the basal right ventricle only showed increased diffuse fibrosis without loss of myocardium (Figure 5B). Three-dimensional reconstruction of the fibrotic tissue showed a fine network of interconnecting individual bundles of myocardium (Figure 5C, green).

Immediately after radiofrequency ablation of the epicardial myocardium that showed fractionated potentials and/or J-waves, the QRS notching in the ECG leads was absent (not shown). The early repolarization pattern has remained absent during the follow-up period (publication date) and the patient has been free of VF since the procedure (Figure 1B).

#### Discussion

In this case study, we combined high resolution epicardial electrophysiological mapping and histological analysis in a patient with the documented early repolarization pattern. Although endocardial abnormalities were not detected, we show that localized structural abnormalities in the subepicardium were the cause for the electrocardiographic pattern and for VF-storms. Ablation of these regions with structural abnormalities normalized the electrocardiogram and prevented arrhythmia recurrence.

We describe severe but localized interstitial fibrosis in RV myocardium and recorded fractionated unipolar electrograms from the same locations. This resembles post-infarcted myocardium, where surviving myocardial strands within the fibrotic infarcted tissue constitute a substrate for life threatening arrhythmias.(10) The loose myocardial network within a fibrotic area may well form the basis for delayed conduction or failure of conduction by current-to-load mismatch (11,12). If local fibrosis is present in already late activated myocardium- as is the case for the subepicardium of the right and left ventricular wall of the described patient- local activation may be delayed beyond the end of the QRS complex and become visible as slurring or notching. In this patient, the structural abnormalities provided the substrate for arrhythmias as confirmed by ablation of these sites that resulted in an arrhythmia-free follow up.

Our data also indicate that a loose myocardial network within a fibrotic area is associated with local J-waves. J-waves in unipolar electrograms are caused phase-1 repolarization at the action potential level, particularly at the subepicardium. The common mechanistic explanation of the early repolarization pattern is that enhanced phase-1 repolarization causes J-waves in local electrograms which are visible in the ECG as notching or slurring of the QRS complex (9). However, in our patient local J-waves recorded in late activated myocardium did not coincide with the QRS slurring and were not visible in the ECG. This observation challenges the common view that all cases of early repolarization pattern are caused by enhanced phase-1 repolarization.

Recent reports have shown that idiopathic VF is associated with fractionated local unipolar electrograms or with electrograms with a J-wave.(3,13) Our patient had both local fractionated potentials and local J-waves, indicating that these conditions can co-exist. We have previously argued that local J-waves can be recorded at epicardial sites that are activated late.(14) The plots in Figure 3C confirm that both the time and the amplitude of local J-waves correlated with activation time. Our data show that the choice of potential ablation sites can be guided by local fractionation activity and local- J waves, as expression of late activation.(14)

We show that the inferior wall activated late and repolarized relatively early compared to the surrounding myocardium (Figure 3A). Consequently, the activation-recovery-interval (ARI) – surrogate for action potential duration – was short in this region. Short ARIs in the right inferior wall have been described before in patients with a similar early repolarization pattern in the ECG as the case we describe here.(15) However, it is unlikely that the brief action potentials alone explain the early repolarization pattern in the ECG as they are only present in regions that are activated late. Also, in our patient the earliest moment of repolarization occurs much later than the moment of QRS-slurring in the ECG. The mechanism of the relatively early repolarization in this late activation myocardium is unclear. We speculate that adjacent unexcited (or not yet) myocardium electrotonically shortens local repolarization. Our observations do not allow speculation about the transmural repolarization gradient.

#### Considerations

We cannot exclude the possibility that the chest surgery that the patient has undergone in his youth has contributed to the localized structural changes. Neither can be ruled out the possibility that the antiarrhythmic effects were mediated by a suppression of the triggering mechanism associated with the scar tissue. A common view is that a J-wave syndrome is only truly a J-wave syndrome by exclusion of a scar or other structural abnormalities. Our observations, however, show that small structural abnormalities can be present in patients diagnosed with the early repolarization syndrome. In our patient the diagnosis of early repolarization syndrome (or early repolarization pattern) was made based on aborted sudden cardiac death, documented VF or polymorphic tachycardia in combination with the early repolarization pattern in the ECG (Shanghai score system) (9). The patient does not meet the criteria for any pathology listed as other causes for ERP. This means that current (clinical) detection methods may not be sufficient to exclude small regional structural abnormalities that can underlie VF in patients with the early repolarization syndrome. This makes the mechanistic insight into the early repolarization syndrome provided by this study relevant for patient management.

#### Conclusion

We show that the early repolarization pattern can result from localized structural abnormalities. These abnormalities were diffuse and not detected with standard clinical tools. We do not imply that structural abnormalities are present in all patients with the early repolarization pattern. However, our observation does challenge the definition of a structurally normal heart and the notion that a single functional pathophysiological mechanism can be established for all patients with the early repolarization pattern.

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# Perspectives

# Competency in Medical Knowledge

The current view is that patients diagnosed with the early repolarization syndrome have structurally normal hearts. We demonstrate that clinically concealed right ventricular subepicardial structural abnormalities cause ventricular fibrillation in a patient with the early repolarization syndrome.

# Translational Outlook

Localized structural abnormalities (fibrosis) can cause the early repolarization pattern and can form an arrhythmogenic substrate. Detailed electrophysiological and anatomic imaging should be performed to identify a substrate that can be ablated in patients with the early repolarization syndrome. Figure 1. A) Twelve-lead electrocardiogram of the patient at rest. B) Twelve-led electrocardiogram 10 days after ablation. ECG, electrocardiogram.

Figure 2. Electrocardiographic imaging predicts arrhythmogenic focus at the inferior right ventricular free wall. A) Lead II showing a spontaneous polymorphic ventricular tachycardia. B) Reconstructed activation patterns during sinus rhythm and apical stimulation based on ECGi. Sinus rhythm: Note late activation in the RV inferior wall and local crowding of isochrones. Pacing: crowding of isochrones in RV inferior wall. C) Three dimensional ECGI (anterior-posterior view on the left, caudal view of the inferior aspect in the middle, and left posterior oblique view on the right, see mannequins in corner) during the first 5 second of VF. The numbers on the ECGI map represent the number of rotations at each point on the heart. The colored hexagons represent the number and location of epicardial focal breakthroughs. Note that the majority of rotational and focal activities are located in the inferiolateral and the bottom of the right ventricle. ECGI, electrocardiographic imaging.

Figure 3. QRS slurring coincides with late activation of the right ventricular inferior wall. A) Schematic representation of the anterior side of the heart showing the 7 locations of the multielectrode (8x8) (2 locations at the posterior side are not shown). B) Activation maps of the RVOT (upper) and right ventricular inferior wall (lower) during right atrial stimulation (left and middle) and premature ventricular stimulation (right). C) Local electrograms (upper 7) from selected locations indicated in panel B. The lower trace shows lead II. The early repolarization pattern in the ECG coincided with the last moment of activation in the right ventricular inferior wall. Note that during left ventricular premature stimulation the right ventricular inferior wall remained late activated despite inversion of the QRS complex. RVOT, right ventricular outflow tract.

Figure 4. Early local repolarization does not coincide with the early repolarization pattern in the ECG. A) The activation (upper) and repolarization (lower) patterns based on local electrograms recorded with the multielectrode (8x8) from 9 different locations. The signals are aligned to the onset the QRS complex in lead aVF. B) Lead aVF and 4 local electrograms recorded from locations depicted in panel A. The moment of repolarization in the local electrograms are marked with a red star. QRS-slurring in the ECG coincided with the last activation in the right inferior wall but not with the time of peak of the local J-wave or local repolarization. C) The right ventricular inferior wall was activated last (Figure 2B) and showed local J-waves with the highest amplitude (Voltage map of J-wave amplitude at the right). Activation times correlated with both the moment (R=0.5) and the amplitude (R=0.7) of the J-wave peak. ERP, early repolarization pattern; AO, aorta; RA, right atrium; RV, right ventricle; PT, pulmonary trunk; LA, left atrium.

Figure 5. Activation delay of the right ventricular inferior wall is due to structural abnormalities. A) The traces (from the ablation catheter) show unipolar and bipolar recordings from the right inferior wall before ablation. B) Schematic drawing shows where biopsies were taken and the epicardial region that was ablated (pink). The sections of the biopsies were stained using picro-sirius Red. C) The 3D model of the biopsy is based on 17 serial sections. The clustered myocardium is labelled green and connected resulting in a 3D network of myocardial fibers.

Supplemental Figure 1. CARTO-merge map of biventricular endocardium. The cardiac computed tomography of the patient's heart is merged with the electroanatomic maps of the RV and LV endocardium recorded during electrophysiologic studies. Areas in the CARTO-merge are color-coded according to the local EGM voltage, ranging from red (lowest local

signals with  $\leq 0.5$  mV amplitude) to magenta (highest voltage, i.e.,  $\geq 1.5$  mV). The insets display samples of the eletrograms (EGMs) recorded from the Decapolar Navistar (DecaN) catheter at various sites of RV and LV epicardium. The voltage map and the representative bipolar and unipolar tracings are shown. Note that the endocardial EGMs of the RV are normal without signs of late activation. The right panel-inset displays recording from the LV septum and shows the His -bundle recording on DecaN<sub>9-10</sub>. DecaN<sub>5-6</sub> and DecaN<sub>7-8</sub>, exhibited low voltage signals but they were recorded just below the aortic valve with poor contact and EGMs duration < 70 ms. Because also the unipolars 5 and 7 were normal we interpreted these normal EGMs with poor contact artefacts on electrodes 6 and 8. Another explanation could be that the activation front was perpendicular to the normal between the electrodes. We cannot exclude that a scar was present in this region. However, this region was not ablated and yet the ERP was resolved and the arrhythmias prevented, showing that this region is not causal. RVA<sub>p</sub> = Right ventricular apex;

Central figure. The early repolarization pattern can result from localized structural abnormalities. At the right, a 3D model of a biopsy from the right inferior wall of a patient diagnosed with the early repolarization syndrome. The biopsy shows separated myocardial bundles because of interstitial fibrosis. Activation of the right inferior wall was delayed and coincided with the early repolarization pattern in the electrocardiogram. J-waves present in local electrograms recorded from the late activated right inferior wall occurred after the early repolarization pattern in the electrocardiogram.

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#### A 12-Lead ECG of the Patient









В

Sinus rhythm

Pacing on apex



C Non-invase epicardial mapping during first 5 second of ventricular fibrillation





Figure 4







### Figure 5



С

#### 3D-reconstruction of structurally abnormal myocardium

