

Infarct-related Myocardial Regions with Functional Relevance During Pacing and Ventricular Tachycardia Show Similar Underlying Substrate

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Abstract

Ventricular remodeling after myocardial infarction is associated with a potential proarrhythmic substrate. However, the interplay between the structural and functional substrate for ventricular tachycardia (VT) maintenance is not completely understood. Here, we aimed to study the scar and fiber disorganization substrate associated with functional alterations during ventricular pacing and VT mapping. Fourteen pigs with infarct-related substrate underwent state-of-the-art cardiac imaging and invasive mapping procedures to identify the functional and structural properties associated with abnormal wave-front propagation and VT maintenance. The results show that deceleration zones during ventricular pacing and critical isthmus sites during VT mapping show similar underlying scar properties and myocardial fiber disorganization. However, deceleration zones derived from one pacing location were not sufficient to identify critical VT isthmus sites in all animals.

1. Introduction

Ventricular tachycardia (VT) is one of the main potentially lethal complications in patients with ischemic cardiomyopathy. This arrhythmia requires a substrate that affects normal impulse propagation and favors a re-entrant mechanism that self-perpetuates de tachycardia. More specifically, VT maintenance requires critical sites of surviving myocardial fibers within the infarcted regions that make the wave-front to propagate slowly and reach the exit site when the myocardial tissue is fully excitable.[1] Electrophysiological characterization of VT isthmus sites is challenging, especially in VT episodes with hemodynamic collapse. In this context, other mapping strategies have been proposed to identify VT isthmus sites

during sinus rhythm or ventricular pacing.[2] Such strategies are less specific to precisely detect protected isthmus sites, although the risk of hemodynamic instability is substantially diminished. In parallel, imaging-based strategies mainly based on late-gadolinium enhancement cardiac magnetic resonance (LGE-CMR) imaging have also been proposed to identify potentially proarrhythmic scar regions that may be related to critical isthmus sites.[3]

Prior studies have also addressed the relevance of myocardial fiber disposition within scar to generate abnormal impulse propagation. Interestingly, Diffusion Tensor Imaging (DTI) is able to reveal the organization of microstructures such as myocardial fibers, which has the potential to more specifically identify the underlying substrate associated with VT maintenance. Although *in vivo* DTI sequences are still limited in resolution for routine clinical applications, *ex vivo* DTI has proven to be a good technique to asses fiber orientation in infarcted hearts.[4] In fact, high-density maps during VT have shown that VT isthmus sites are regions with intermediate 3D fiber disorganization compared to healthy myocardium regions and dense scar areas.[5]

Regions with intermediate fiber disorganization may also decelerate wave-front propagation during ventricular pacing, which might represent a practical strategy to identify potential proarrhythmic sites in non-tolerated VT episodes. However, this may have limitations to identify actual VT isthmus sites, since the spatial interaction between the wave-front and the regions with disorganized fibers can be sensitive to the pacing site.

Here, we hypothesize that regions with wave-front deceleration during ventricular pacing from the right ventricle will identify a myocardial substrate with underlying fiber disorganization. However, such regions will not be specific for critical isthmus sites during VT.

2. Methods

2.1. Experimental Study

The experimental procedures were performed in a cohort of 14 pigs undergoing percutaneous catheterization and ischemia-reperfusion for 60 min in the territory of the left anterior descending coronary artery. Ten-to-twelve weeks after the infarction, all pigs underwent *in vivo* studies using LGE-CMR imaging. Afterwards, all pigs underwent an invasive mapping procedure to identify deceleration zones (DZ) during ventricular pacing and further VT induction and mapping to localize critical isthmus sites. Finally, *ex vivo* DTI sequences were obtained to correlate the scar and functional substrate with the underlying fiber disorganization. All the procedures were performed under general anesthesia. The animal protocols were approved by the Centro Nacional de Investigaciones Cardiovasculares (CNIC) Committee on Use and Care of Animals and by the Comunidad de Madrid (Ref#PROEX097/17). Animal experiments complied with Spanish (RD53/2013, ECC/566/2015), and European (2010/63/EU) regulations.

2.2. In Vivo LGE-CMR imaging

LGE-CMR sequences were acquired using a Philips Achieva 3T-Tx whole body scanner equipped with a 32-element and phased-array cardiac coil (Philips Healthcare, Best, The Netherlands). After contrast administration of 0.2 mmol/Kg gadoteric acid (Dotarem, Guerbet, France), the sequences were acquired at 1.5x1.5x1.5 mm resolution (reconstructed to: 0.57x0.57x0.75 mm). Cine sequences were also acquired to assess left ventricular ejection fraction (LVEF). LGE-CMR images were processed in Matlab for accurate segmentation of the epicardial and endocardial surfaces of the LV. The myocardial scar was segmented using the full-width-half-maximum approach. Scar regions were defined as those with signal intensity above 45% of maximum signal intensity, and dense scar regions as those with signal intensity above 67% of maximum signal intensity.[5]

2.3. Invasive electrophysiological study

Invasive mapping was performed using arterial and venous femoral access. All procedures were performed using 3D electroanatomical guidance with the Carto3 system (Biosense Webster, Diamond Bar, USA). After anatomical reconstruction of the cardiac chambers, continuous ventricular pacing at 500 ms cycle length (CL) was performed to identify deceleration zones (DZ). A screw-in catheter was positioned in the right ventricle to keep stable the pacing site. High density activation maps during pacing were obtained from the right and LV.

Afterwards, VT induction was attempted using up to five basic drive CLs (350, 300, 280, 260 and 250 ms) with up to four coupled extrastimuli until VT induction. If the induced VT was hemodynamically tolerated, high-density activation mapping and entrainment maneuvers were performed to identify the critical isthmus sites.

2.4. Functionally-relevant regions of interest

Data exported from the electroanatomical mapping system was processed using custom Matlab code. DZ during ventricular pacing (pacing regions of interest, ROI) were obtained from isochronal maps to identify areas with isochrone crowding. Such areas were defined as regions with a statistically significant increase in the standard deviation of isochrones within the entire map. This enabled us to identify areas with a sudden decrease in wave-front propagation and an increase in isochrone crowding. The line with the minimum distance from the first point on the isochrone crowding region to the latest activation point on the map was used as the reference for border delineation of the DZ. Thus, the final DZ region was contained within a range of distances from latest activation point to a maximum of +25% of the initial line with the minimum distance (Figure 1A).

In activation maps during VT, the VT ROI was defined as the area with activation times from the latest activation point to -35% of the tachycardia CL and from the earliest activation point to +10% of the tachycardia CL. The VT ROI also included the junction between the earliest and latest activation points (Figure 1B).

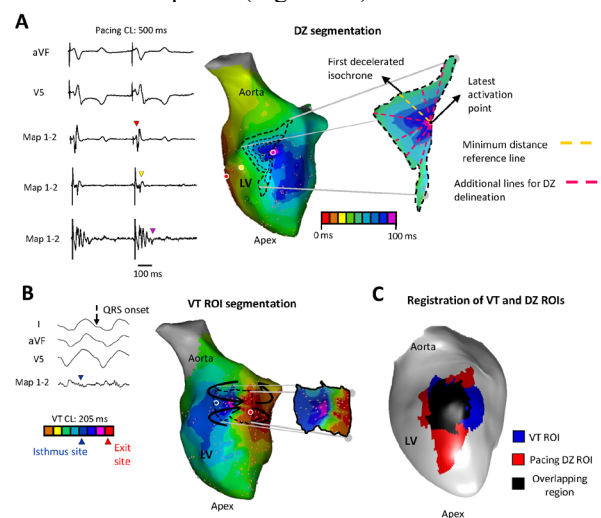


Figure 1. A, Sample deceleration zone (DZ) identification and segmentation during ventricular pacing at 500 ms CL. B, VT ROI segmentation with representative electrograms. C, Registration of the VT and DZ ROIs onto the LGE-CMR-derived 3D mesh.

The comparisons between functional and structural data

were performed after registration of the electrophysiological maps onto the 3D mesh from LE-CMR (Figure. 1C).

2.5. Ex Vivo Diffusion Tensor Imaging

After the *in vivo* mapping and euthanasia, the excised hearts were filled with a 2% warm agarose gel solution to maintain physiological volumes during the acquisition of DTI images. The hearts were placed in a watertight plastic CMR-compatible container also filled with agarose to fix the heart position during acquisition. DTI acquisition was performed with a single shot spin echo-planar imaging sequence applying 15 different diffusion directions. The images were acquired at 1.1x1.1x1.1 mm resolution.

2.6. Analysis of 3D fiber disorganization

DTI sequences were used for further analysis of the underlying fiber disorganization substrate of the LV. Cardiac tractographies were computed using DTIStudio (Johns Hopkins University, School of Medicine, USA). Then, fiber disorganization was calculated using the fiber disorganization index (FDI), which was defined as the cumulative 3D angle between the main direction of a given eigenvector and its neighbors (26 neighbors, radius 1), relative to a fixed maximum disorganization of 90° in each neighboring eigenvector, as reported elsewhere.[5] A schematic representation of FDI calculation is shown in Figure 2A. Transmural fiber disorganization data were projected on the endocardial surface using the median FDI values across the streamlines from the endocardial to the epicardial surface. The latter enabled us to obtain FDI maps with transmural information. Further analysis included the FDI values on functionally relevant regions (VT and pacing DZ ROIs) and different scar regions. A sample FDI map from a VT ROI is shown in Figure 2B.

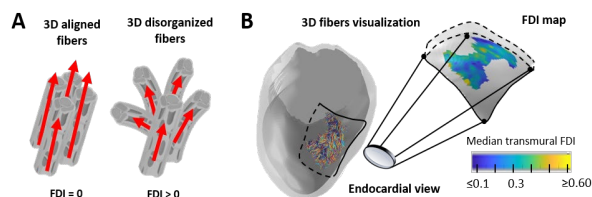


Figure 2. A, Fibers scheme showing two different FDI scenarios. B, Sample FDI map with transmural information associated with a segmented VT ROI.

2.7. Statistical analysis

Data are expressed as median and interquartile range for quantitative variables. Data normality was assessed with the Shapiro-Wilk test. Statistical significance was assessed by the T-test or the Mann-Whitney/Wilcoxon test, as appropriate. A $p < 0.05$ was considered statistically significant for differences in group comparisons.

3. Results

3.1. Comparison between VT and pacing DZ ROIs

The study in animals included 8 pigs (males 100%, age 5 months [5, 6 months], weight 60.2 Kg [54.4, 64 Kg], LVEF 33.9% [30.8, 37.5%]) with full electrophysiological characterization of at least one reentrant VT morphology during the invasive mapping procedure. In the remaining 6 pigs of the series, early hemodynamic collapse upon VT induction did not enable us electrophysiological characterization of at least one VT ROI. A total of 11 VT morphologies out of 19 inducible VTs were characterized using activation maps. Other pacing and VT data during the invasive procedures are shown in Table 1.

Table 1. VT and pacing data

Inducible VT morphologies, n	2.5 (1.0,3.5)
VT cycle length, ms	244 (207.3, 285)
Valid mapping points on activation maps during VT, n	648 (337, 755)
Valid activations points on pacing maps for the LV, n	224 (216, 289)

In 4 animals VT and pacing DZ ROIs showed overlapping regions between the two. Two sample cases with and without overlapping regions between VT and pacing DZ ROIs are shown in Figure 3A. Overall, only 3.5% [0, 35.5%] of the VT ROIs overlapped with DZ ROIs (Figure 3B), although this was highly variable among animals.

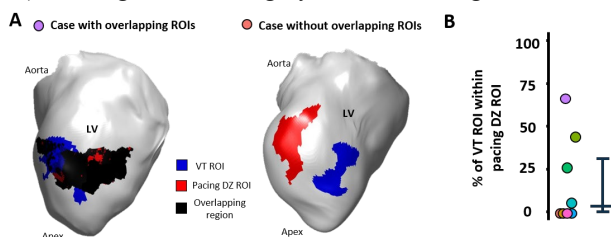


Figure 3. A, Left, sample case with large overlapping between VT and pacing DZ ROIs. Right, sample case without overlapping between VT and pacing DZ ROIs. B, Percentage of VT ROIs contained within pacing DZ ROIs (n=8).

3.2. Pacing DZ ROIs and VT ROIs show fiber disorganization values associated with heterogeneous scar areas

First, transmural fiber disorganization in pacing DZ ROIs was compared with that of VT ROIs. Two sample FDI maps on a VT ROI and a DZ ROI from the same case are shown in Figure 4A. Overall, pacing DZ ROIs showed similar FDI values to VT ROIs (0.23 [0.20, 0.27]) vs. 0.25 [0.21, 0.33], respectively, $p = 0.52$. Figure 4B).

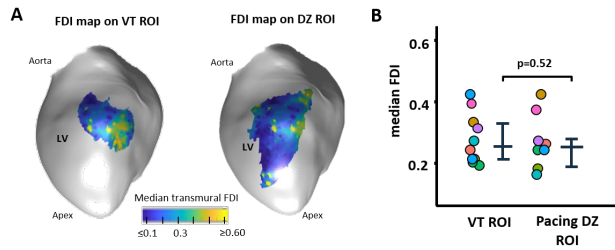


Figure 4. A, Sample FDI maps on the VT ROI and pacing DZ ROI from the same animal. B, Comparison of FDI values between VT ROIs and pacing DZ ROIs (n=8).

Second, further analysis using the information from DTI and LGE-CMR sequences showed significantly lower FDI values in healthy myocardium regions compared to dense scar and heterogeneous scar regions. Dense scar regions also showed significantly higher FDI values compared to heterogeneous scar areas. Sample FDI maps on healthy, heterogeneous and dense scar regions are shown in Figure 5A. Overall comparisons are shown in Figure 5B.

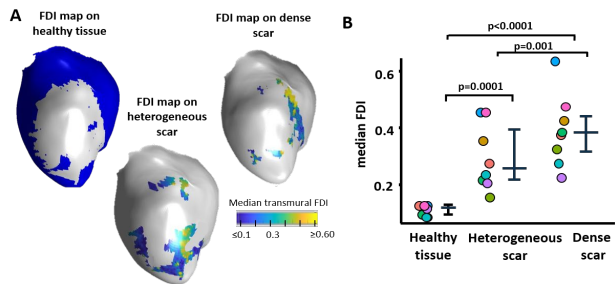


Figure 5. A, Sample FDI maps on the healthy tissue, dense scar and heterogeneous scar areas from the same animal. B, Comparison of FDI values between healthy tissue, heterogeneous scar and dense scar. (n=8)

Finally, the integration of functional and structural data showed that pacing DZ ROIs and VT ROIs showed similar transmural FDI values to heterogeneous scar regions from LGE-CMR sequences, without statistically significant differences among these 3 regions.

4. Discussion

The main results of this study show that left ventricular DZ ROIs during right ventricular pacing and VT ROIs during tachycardia are regions with intermediate values of 3D fiber disorganization. These functional regions also show similar fiber disorganization values to heterogeneous scar areas from LGE-CMR images. Therefore, functional alterations during ventricular pacing or VT mapping share similar underlying structural characteristics after myocardial infarction. However, VT ROIs not necessarily overlapped with pacing DZ ROIs. The latter highlights that VT ROIs may also involve additional underlying remodeling on ion channels or scar organization within the surviving fibers, which make a particular scar region

sensitive to VT initiation and maintenance.

Additional pacing locations may help to identify more pacing DZ ROIs within the LV, which may also increase the possibility of detecting all the functional substrate relevant for VT maintenance. The latter would be time-consuming in clinical practice. However, computational models may provide results from different pacing locations and aid physicians on procedure planning.[6]

5. Conclusions

Ventricular pacing from the right ventricle can be used to partially identify potential proarrhythmic regions associated with VT maintenance and underlying scar and fiber disorganization properties. However, pacing DZ ROIs from one pacing location will not be sufficient to identify all myocardial regions associated with VT maintenance.

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