Electrical Characteristics of Chronic Iron-laden Myocardial Infarcts: Initial Study in Canine Hearts

Ivan Cokic[1], Avinash Kali[2], Xunzhang Wang[2], Hsin-Jung Yang[2], Richard L. Q. Tang[2], Anees Thajudeen[2], Michael Shehata[2], Allen M. Amorn[2], Enzhao Liu[2], Brian Stewart[3], Nathan Bennett[3], Doron Harley[3], Sotirios A. Tsaftaris[4], Warren M. Jackman[5], Sumeet S. Chugh[2], and Rohan Dharmakumar[2]

[1]Cedars-Sinai Medical Center, Los Angeles, CA, United States, [2]Cedars-Sinai Medical Center, CA, United States, [3]Rhythmia Medical-Boston Scientific, Inc., MA, United States, [4]Institute for Advanced Studies, Lucca, Italy, [5]Heart Rhythm Institute, OK, United States

Introduction: Myocardial infarction (MI) can lead to chronic iron deposition that can be accurately detected with T2* MRI imaging. However, its long-term fate and influence on myocardial electrical properties remain largely unexplored. In this study we used T2* MRI to characterize iron deposition in canines with chronic myocardial infarction in combination with impedance spectroscopy, surface ECG indices and electroanatomical maps (EAMs).

Methods: MI was created by permanently ligating the left anterior descending (LAD) artery distal to the first diagonal in 22 dogs (20–25 kg) and animals allowed to recover into the chronic phase of the infarction. Both ex-vivo (n=12) and in-vivo (n=10) groups were studied at 16 weeks post MI. All MRI studies were performed on a clinical 3T system (MAGNETOM Verio, Siemens Medical Solutions, Erlangen, Germany) and images were analyzed using cmr^{42} (v4.0, Circle Cardiovascular Imaging Inc., Canada). Hearts from the ex-vivo group were explanted and imaged with a multi-gradient echo sequence (TR = 12 ms, 6 TEs = 2.0 ms – 9.5 ms with ΔTE = 1.5 ms, flip angle = 10° and BW = 930 Hz/pixel) prior to sectioning into infarcted and non-infarcted segments. Impedance Spectroscopy: Subsequently, AC impedance spectroscopy was performed on infarcted myocardium with (IRON+) and without (IRON-) iron and non-infarcted (Remote) myocardium to derive electrical permittivity (ε) and conductivity (σ). The amount of iron ([Fe]) within the same samples was determined by mass spectrometry. Dogs from in-vivo group underwent late-gadolinium enhancement (LGE) imaging (inversion recovery prepared FLASH, TR / TE = 3.0/1.5 ms, flip angle = 25° and BW = 586 Hz/pixel) and T2*-weighted imaging (same as ex-vivo hearts). Surface ECG: 24-hour ECG recordings were obtained and used to examine Heart Rate (HR), QT interval (QT), QT corrected for HR (QTc) and QTc dispersion (QTcd). EAMs: EAMs were obtained and registered with cardiac MRI (late enhancement (for depiction of infarction) and T2* (for depiction of iron)). We used the presence of isolated late potentials (ILPs) within the infarcted territory to index the extent of electrical abnormality. From the T2* images registered with EAM, the number of ILPs occurring in and around the infarcted regions with and without iron were manually counted. To examine the relationship between the number of ILPs and substrate type (scar with and without iron) and extent, values normalized by the volume fraction of substrate type in each canine heart were computed and averaged across all animals.

Results: Impedance Spectroscopy: Compared to controls (IRON- and Remote), ex-vivo IRON+ hearts had significant T2* losses (p<0.001) and showed significantly higher ε with no difference in σ (p<0.001). There was significant relationships between ε and [Fe] and log(T2*) (p<0.001), while no such relationship was observed with σ (p=0.34). Surface ECGs: Among two in-vivo subgroups (Iron (<1.5%) and Iron (>1.5%)) with similar scar volumes (7.28%±1.02% (Iron (<1.5%)) vs 8.35%±2.98% (Iron (>1.5%)), p = 0.51) but markedly different iron volumes (1.12%±0.64% (Iron (<1.5%)) vs 2.47%±0.64% (Iron (>1.5%)), p = 0.02), QT and QTc were elevated and QTcd was decreased in the group with the higher iron volume during the day, night and 24-hour period (p<0.05). EAMs: A representative set of EAMs co-registered with MRI (LGE and T2*) is shown in Fig. 1. The relative fraction of ILPs (i.e. number of ILPs normalized to the appropriate substrate volume of interest) from regions with iron was markedly larger than the infarcted regions not containing iron.

Fig.1. *Representative co-registered MRI and EAMs* showing the association between ILPs and iron deposition in non-reperfused MI. Co-registered LGE MRI projected onto the blood pool surface (**A**) with MI territory (red color, 5SD above remove signal intensity), border zone (yellow and blue shades) and remote territories (purple)) with the corresponding bipolar map (**B**, color-coded to indicate low voltage areas, <1mv) are shown. Note the close correspondence between scar regions identified by MRI and bipolar voltage threshold in **B**. For reference, an ILP deep within the scar tissue (white arrow) is shown. Note the presence of an isolated low-voltage sharp ILP in the bipolar and unipolar traces following the local ventricular activation (yellow arrow) in (**C**). The activation map (**D**), a map of the ILPs (**E**), and iron containing regions (in red, **F**) are also shown for reference. Note that iron-rich regions have a greater incidence of ILPs and slow activation regions.
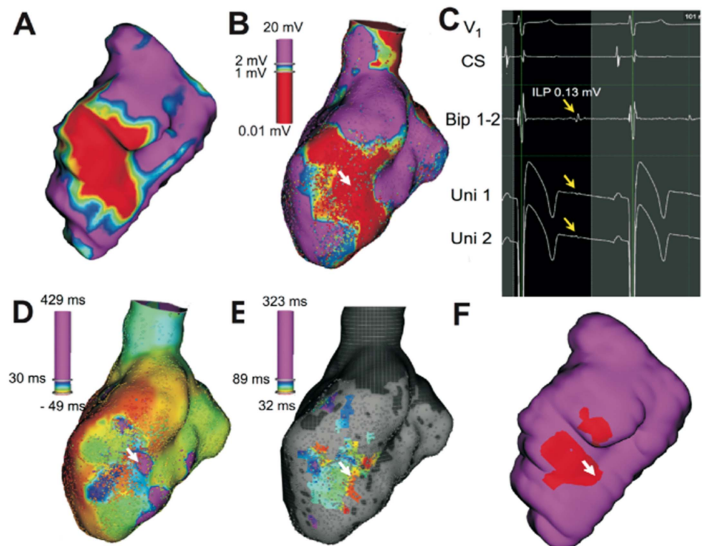
Conclusion: The electrical behavior of infarcted hearts with iron appears to be different from those without iron. Iron within infarcted zones may evolve as an arrhythmogenic substrate in the post MI period.