Prognostic Value of Hypointense Cores within Chronic Myocardial Infarctions on Balanced Steady-State Free Precession MRI for the Prediction of Malignant Ventricular Arrhythmias

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TARGET AUDIENCE: Scientists and clinicians who are interested in post-myocardial infarction ventricular arrhythmias.

PURPOSE: Post-mortem MRI studies of the hearts of sudden cardiac death (SCD) victims with chronic myocardial infarctions (CMI) have consistently demonstrated regions of T2-weighted signal loss within the CMI territories; however, the histological substrate underlying this MRI observation remains unexplored. Recent experimental studies in canines have shown that iron depositions within scars of CMI can influence the electrical behavior of the heart. To date however, the association between post-infarction iron depositions and malignant ventricular arrhythmias (mVA) in humans has not been studied. The aim of this study was to examine the incremental prognostic value of hypointense cores (HIC) identified within CMI in balanced SSFP MRI, which is known to be sensitive to susceptibility shifting media, for the prediction of mVA.

METHODS: *Patient studies:* CMI patients (n=94) who underwent routine cardiac MRI protocol at 3.0T (MAGNETOM Trio, Siemens) prior to implantable cardioverter-defibrillator (ICD) implantation for primary and secondary prevention were retrospectively studied. Cine SSFP images (slice thickness=6mm, slice gap=4mm, TR/TE=2.6/1.3ms, flip angle=10°, in-plane resolution=2x2mm^2, 20-25 cardiac phases, BW=930Hz/pixel) and LGE images (segmented IR-FLASH, 10-15 minutes after IV administration of 0.15–0.2 mmol/kg Gadovist, optimal TI to null remote myocardium, slice thickness=10mm, no slice gap, TR=800ms, TE=3.9ms, flip angle=20°, in-plane resolution=1.5x1.5mm^2, BW=1500Hz/pixel) were acquired in sequential short-axis views covering the entire left ventricle (LV). The predictive values of HIC in SSFP images, conventional indices derived from cine and LGE images (LVEF, scar size, and border zone) and surface ECG parameters known to be implicated in mVA for combined primary outcome (appropriate ICD therapy, survived cardiac arrest, SCD) were compared. *Animal Studies:* The use of HIC within CMI on SSFP as a potential marker of iron deposition was histologically validated in canines (n=19) with CMI. All canine MRI studies were performed on a clinical 3.0T MRI system (MAGNETOM Verio, Siemens). Contiguous short-axis sections covering the entire LV were acquired using cine-SSFP (TR/TE=3.5/1.75ms, flip angle=70°, 20-25 cardiac phases, BW=930 Hz/pixel), T2*-weighted (mGRE sequence, TR=12ms, 6 TEs =2.0ms–9.5ms with ΔTE=1.5ms, flip angle=10° and BW=930Hz/pixel), and LGE imaging (IR-FLASH acquired 10-15 minutes following IV Magnevist infusion, optimal TI to null remote myocardium, TR/TE=3.0/1.5 ms, flip angle=25° and BW=586 Hz/pixel). Commonly used imaging parameters were in-plane resolution=1.4x1.4mm^2, slice thickness =6 mm, no slice gap, and number of averages =1.Animals were euthanized immediately after the MRI studies and their hearts were excised. Each heart was manually sliced into 5 mm thick slices along the LV short-axis, and ex-vivo triphenyl tetrazolium chloride staining was performed. The ex-vivo slices were carefully matched to the in-vivo MRI images based on the location of the papillary muscles and infarct morphology, and categorized as HIC+ and HIC-. Three ex-vivo slices each from the HIC+ and HIC- categories were embedded in a paraffin block, sliced into 5μm contiguous sections and stained with Elastin-modified Masson's Trichrome (for collagen deposition) and Perl's stains (for iron depositions) using standard techniques. *Image Analysis*: All quantitative image analyses were performed using the cvi[42] (Circle Cardiovascular Imaging Inc.).

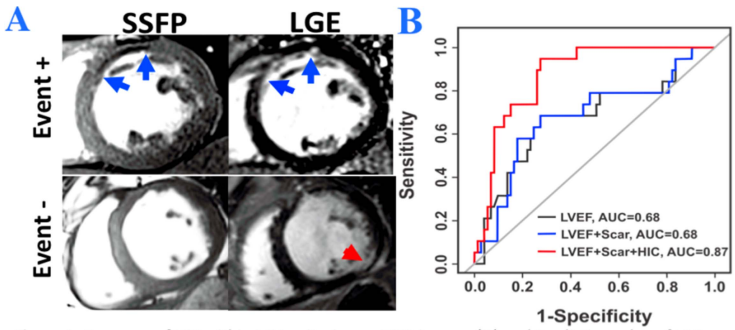

Figure 1. *Presence of HIC within MI territories on SSFP images (**A**) and Predictive value of HIC on SSFP images for primary endpoint (**B**). **A:*** Representative SSFP and LGE images from two patients receiving ICD therapy; one who met the primary endpoint (Event+) and one who did not meet the primary endpoint (Event-). For the Event+ patient, blue arrows denote the MI region on Late Gadolinium Enhancement (LGE) imaging and the Hypo-Intense Core (HIC) region on SSFP imaging. In the Event- patient, no HIC were observed by SSFP within the MI region, indicated by the red arrow on LGE imaging. **B**: Corresponding ROC curves for LVEF, LVEF + Scar Volume, and LVEF + Scar Volume + HIC for the prediction of the primary endpoint. While the addition of Total Scar Volume alone did not improve the predictive accuracy over LVEF, the addition of HIC improved the AUC from 0.68 to 0.87, suggesting additional prognostic value of HIC.

RESULTS: Nineteen patients met the primary outcome with events occurring 343±269 days after ICD placement. Of these 19 patients, 18 were classified as HIC+ while only one subject was classified as HIC-. Among the patients in whom the primary endpoint was not met, there were 28 HIC+ and 47 HIC- patients. ROC analysis demonstrated an additive prognostic value of HIC for mVAs by increasing the area under the cure (AUC) to 0.87 when added to LVEF (LVEF alone 0.68), while adding scar size to LVEF failed to change AUC. Both MRI and histological validation studies performed in canines demonstrated that HIC+ regions in SSFP images within CMI resulted from iron depositions.

CONCLUSIONS: Presence of hypointense cores within scars of CMI on SSFP MRI at 3.0T can be used as a marker of iron deposition and appears to yield incremental prognostic information toward the prediction of mVA.