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Persistent Iron Within the Infarct Core After ST-Segment Elevation Myocardial Infarction

Implications for Left Ventricular Remodeling and Health Outcomes

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ABSTRACT

OBJECTIVES This study sought to determine the incidence and prognostic significance of persistent iron in patients post–ST-segment elevation myocardial infarction (STEMI).

BACKGROUND The clinical significance of persistent iron within the infarct core after STEMI complicated by acute myocardial hemorrhage is poorly understood.

METHODS Patients who sustained an acute STEMI were enrolled in a cohort study (BHF MR-MI [Detection and Significance of Heart Injury in ST Elevation Myocardial Infarction]). Cardiac magnetic resonance imaging including T_2* (observed time constant for the decay of transverse magnetization seen with gradient-echo sequences) mapping was performed at 2 days and 6 months post-STEMI. Myocardial hemorrhage or iron was defined as a hypointense infarct core with T_2* signal <20 ms.

RESULTS A total of 203 patients (age 57 ± 11 years, n = 158 [78%] male) had evaluable T_2* maps at 2 days and 6 months post-STEMI; 74 (36%) patients had myocardial hemorrhage at baseline, and 44 (59%) of these patients had persistent iron at 6 months. Clinical associates of persistent iron included heart rate ($p = 0.009$), the absence of a history of hypertension ($p = 0.017$), and infarct size ($p = 0.028$). The presence of persistent iron was associated with worsening left ventricular (LV) end-diastolic volume (regression coefficient: 21.10; 95% confidence interval [CI]: 10.92 to 31.27; $p < 0.001$) and worsening LV ejection fraction (regression coefficient: −6.47; 95% CI: −9.22 to −3.72; $p < 0.001$). Persistent iron was associated with the subsequent occurrence of all-cause death or heart failure (hazard ratio: 3.91; 95% CI: 1.37 to 11.14; $p = 0.011$) and major adverse cardiac events (hazard ratio: 3.24; 95% CI: 1.09 to 9.64; $p = 0.035$) (median follow-up duration 1,457 days [range 233 to 1,734 days]).

CONCLUSIONS Persistent iron at 6 months post-STEMI is associated with worse LV and longer-term health outcomes. (Detection and Significance of Heart Injury in ST Elevation Myocardial Infarction [BHF MR-MI]; NCT02072850) (J Am Coll Cardiol Img 2017;■:■–■) © 2017 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

LV = left ventricular

MACE = major adverse cardiac events

STEMI = ST-segment elevation myocardial infarction

Myocardial hemorrhage (1) and microvascular obstruction (2) are common and prognostically important complications of reperfused ST-segment elevation myocardial infarction (STEMI), and they are independently associated with adverse remodeling and heart failure in the longer term (2). The improvements in survival after acute STEMI in recent decades translate to more surviving patients with injured hearts who are at risk of developing longer-term complications (3,4). Because there are no evidence-based treatments for microvascular obstruction and myocardial hemorrhage, more research is needed to understand the pathophysiology of these disorders more fully.

Myocardial hemorrhage is a result of severe microvascular injury, with extravasation of erythrocytes secondary to loss of endothelial integrity (1,5-8). Hemoglobin degradation products are toxic (9-11), and their persistence is evidenced by immunohistochemical staining of iron within macrophages reflecting sustained inflammation within the infarct zone (10). Information relating to the clinical significance of persistent iron within the infarct core in patients with acute STEMI complicated by myocardial hemorrhage has been limited (e.g., sample size of $n \leq 40$ [11-13]), and prognostic data on health outcomes are lacking.

We aimed to determine the incidence of persistent iron in a large cohort of STEMI survivors using contemporary T_2* (observed time constant for the decay of transverse magnetization seen with gradient-echo sequences) mapping (14,15). Additionally, we aimed to identify which clinical characteristics would be associated with persistent iron and whether persistent iron may be associated with adverse clinical outcomes.

We hypothesized that persisting iron would: 1) be associated with markers of the initial severity of STEMI; 2) present with distinct clinical characteristics when compared with resolved iron; 3) be associated with adverse myocardial remodeling; and 4) be associated with a worse prognosis in the longer term.

METHODS

The full methodology has been reported previously (16-19) and is detailed in the Online Methods.

CARDIAC MAGNETIC RESONANCE IMAGE ANALYSIS. Cardiac magnetic resonance (CMR) imaging analysis was performed on a Siemens workstation (Siemen Healthcare, Erlangen, Germany). Left ventricular (LV) volumes and ejection fraction were assessed using computer-assisted planimetry (syngo.MR, Siemens Healthcare).

T_2* measurement and myocardial hemorrhage. LV contours were delineated with computer-assisted planimetry on the raw T_2* image and then copied onto color-coded spatially co-registered maps (Online Methods). Regions of interest were drawn in the infarct area surrounding core, core, and remote zones. Myocardial hemorrhage at 2 days and iron at 6 months were defined as regions of signal intensity <20 ms within the infarcted area and were measured as a percentage of LV mass and as a percentage of infarct size (20-22). Each T_2* map was assessed by 2 independent CMR analysts for the presence of myocardial hemorrhage or iron.

T_2 measurement and myocardial edema. LV contours on the last corresponding T_2 (the transverse relaxation time)-weighted raw image with an echo time of 55 ms were planimetered and then copied to the map (23). Regions of interest were drawn in the surrounding infarct and remote zones. The extent of myocardial edema was defined as LV myocardium with pixel values (T_2) >2 SD from remote myocardium (23,24).

Infarct definition and size. The territory of infarction was quantified using computer-assisted planimetry and was expressed as a percentage of LV mass (25).

Myocardial salvage. Myocardial salvage was calculated by subtraction of percentage of infarct size from percentage of myocardial edema (7,26,27). The myocardial salvage index was calculated by dividing the myocardial salvage area by the initial percentage of myocardial edema.

Adverse remodeling. Adverse remodeling was defined as an increase in LV end-diastolic volume at 6 months from baseline by 20% or more (17).

HEALTH OUTCOMES. We pre-specified adverse health outcomes that are implicated in the pathophysiology and natural history of STEMI. The primary composite outcome was all-cause death or first heart failure event (hospitalization for heart failure or defibrillator implantation) following the 6-month CMR scan. The secondary composite outcome was major adverse cardiac events (MACE).

STATISTICAL ANALYSIS. The full statistical methods are reported in the Online Methods. All p values were 2-sided. A p value >0.050 indicated the absence of a statistically significant effect. Analyses were performed using SPSS version 22 for Windows (SPSS, Inc., Chicago, Illinois), or R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).