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LETTER TO THE EDITOR

**Ferumoxytol-Enhanced CMR for
 Vasodilator Stress Testing:
 A Feasibility Study**

Researchers recently proposed using native myocardial T_1 mapping with vasodilator stress testing for evaluation of ischemic heart disease (IHD) (1). A change of 1.5% in native T_1 between rest and peak stress was able to detect significant epicardial coronary stenosis (1). Although this approach is promising, the modest amplitude and narrow dynamic range for native T_1 reactivity (percentage of change in T_1 at peak vasodilation relative to baseline) may pose challenges in daily clinical practice. We propose to increase the amplitude and dynamic range of T_1 reactivity through the off-label use of ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, Massachusetts). Ferumoxytol is used for intravenous treatment of iron deficiency anemia, but it has superparamagnetic properties with high r_1 relaxivity and a long intravascular half-life. We posited that ferumoxytol would sensitize the myocardial T_1 to the vasodilator-induced dynamic differences between rest and peak stress and significantly boost the T_1 reactivity. Because ferumoxytol shortens the T_1 , we expected the myocardial T_1 to decrease during vasodilator stress because of the increased distribution space of ferumoxytol.

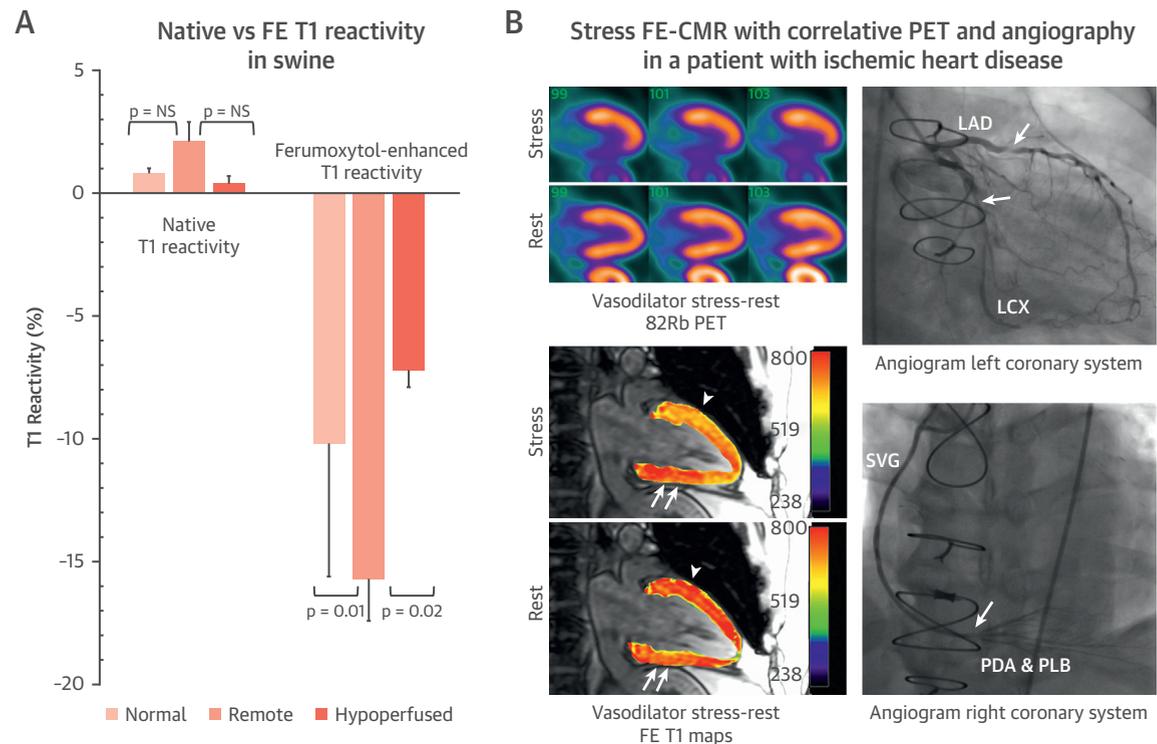
We studied Yorkshire swine (33 to 52 kg; $n = 4$ normal, $n = 3$ coronary stenosis [80% to 90%]) and patients with IHD ($n = 5$; age 38 to 71 years). For animal studies, we created partial stenosis of the mid-left anterior descending artery using a transcatheter balloon angioplasty technique (2). The animal stress cardiac magnetic resonance (CMR) protocol included the following: 1) pre-ferumoxytol cine and T_1 mapping at rest and peak stress (4-min adenosine infusion [200 to 400 $\mu\text{g}/\text{kg}/\text{min}$]); 2) ferumoxytol (4 mg/kg) infusion; and 3) rest and stress ferumoxytol-enhanced (FE) T_1 mapping. Five patients with positive ($n = 3$) or equivocal ($n = 2$) rubidium-82 positron emission tomography stress test results underwent regadenoson FE CMR. The FE CMR protocol included the following: 1) ferumoxytol (4 mg/kg infusion); and 2) multislice FE T_1 mapping at rest and stress (regadenoson 0.4 mg intravenously). We acquired T_1 maps in animal and human

subjects using 5(3)3 balanced steady-state free precession (bSSFP) Modified Look-Locker Imaging (MOLLI) and used an in-house T_1 fitting algorithm to account for heart rate variation. Groups were compared using paired Student's t -tests. Values are reported as mean \pm SD.

There were no ferumoxytol-related or vasodilator-related adverse events. Mean post-ferumoxytol blood pool T_1 values at baseline and at peak vasodilation were similar ($p = 0.5$). Compared with native T_1 reactivity (Figure 1A), ferumoxytol amplified the T_1 reactivity by 12.8-fold in normal myocardium (native T_1 reactivity: $0.8 \pm 0.2\%$; FE T_1 reactivity: $-10.2 \pm 5.4\%$; $p < 0.01$), 7.5-fold in remote myocardium ($2.1 \pm 0.8\%$ vs. $-15.7 \pm 1.7\%$; $p < 0.01$), and 18-fold in vasodilator-induced hypoperfused myocardium ($0.4 \pm 0.3\%$ vs. $-7.2 \pm 0.7\%$; $p < 0.01$). The effect size for FE T_1 reactivity was larger than native T_1 reactivity (6.5 [SD_{pooled} = 1.3] vs. 2.8 [SD_{pooled} = 0.6]). Compared with remote myocardium of patients with IHD, the FE T_1 reactivity values in hypoperfused segments were significantly blunted ($-8.8 \pm 1.9\%$ vs. $-3.2 \pm 15.9\%$; $p < 0.01$). Figure 1B illustrates the qualitative and quantitative potential of FE T_1 maps to depict hypoperfusion at rest and coronary steal physiology at peak vasodilation.

Our findings are hypothesis generating and support the early feasibility of FE CMR T_1 vasodilator testing for detection of IHD. The higher amplitude and dynamic range achieved with ferumoxytol increased the effect size of FE T_1 reactivity and improved its ability to differentiate between remote and hypoperfused myocardium. There are limitations, including the possibility of a blunted T_1 response from capillary leakage in the setting of ischemia. The use of ferumoxytol is also not without risks and needs to be weighed against the benefits. To date, however, ferumoxytol has demonstrated a positive safety profile for off-label diagnostic use under close monitoring (3). FE CMR T_1 reactivity testing has the potential to transform intramyocardial blood volume reserve quantification. Additional work is needed to systematically define its application for perfusion imaging.

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FIGURE 1 Native and (FE) T₁ Vasodilator Stress Testing

(A) Native and ferumoxylot-enhanced (FE) T₁ reactivity in normal, remote, and hypoperfused myocardium of swine models is shown. **(B)** Regadenoson stress rubidium-82 (⁸²Rb) positron emission tomography (PET) images from a patient with progressive angina show a large, reversible inferior wall perfusion defect. Ferumoxylot-enhanced cardiac magnetic resonance (CMR) T₁ map shows rest hypoperfusion in the inferior wall (arrows), which is visually absent on the rest perfusion positron emission tomography images. At peak stress, ferumoxylot-enhanced T₁ reactivity is 6% in the hypoperfused inferior wall (arrows) and -14% in the proximal anterior wall (arrowhead, net difference of 20%). The longer ferumoxylot-enhanced T₁ value in the inferior wall compared with the anterior wall (14.5% difference; 764 ms vs. 653 ms) at stress reflects coronary steal physiology. At rest, the ferumoxylot-enhanced T₁ difference between the affected inferior wall and the remote anterior wall is smaller (4.6%). Coronary angiograms show significant 3-vessel native coronary and graft disease. LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; NS = nonsignificant; PDA = posterior descending artery; PLB = posterior left branch; SVG = saphenous vein graft.

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