FDA-approved Intralipid Can Protect Hearts Against Ischemic Reperfusion Injury: An Integrated Cellular and Functional Cardiac MRI Study

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in the United States. Timely restoration of coronary blood flow has greatly limited the loss of myocardium, decreased 30-day in-hospital death, and increased survival rate during the acute phase of myocardium infarction (MI). However, even with successful blood-flow restoration, ischemia reperfusion injury (IRI) often results; which triggers inflammation, resulting in greater tissue damage and adverse remodeling. The rate of developing post-MI heart failure increases as the acute mortality decreases . It would be very beneficial if there were therapeutic agents that could protect the heart against IRI, to reduce the extent of myocardial inflammation, stop the expansion of the infarct zone, and prevent or reverse the adverse myocardial remodeling. "Intralipid" is a FDA-approved safe fat emulsion as intravenous nutritious supplement. The goal of this study is to investigate the potential protective effects of Intralipid of the heart against IRI, in a pre-clinical rodent model, with integrated multi-parameter cellular and functional cardiac MRI.

METHODS

Animal model: We employed a rodent IRI model with 45-min transient left anterior descending (LAD) coronary artery occlusion, followed by reperfusion. 40 male BN rats were subjected to ischemia procedure, in which 18 of them were given Intralipid intravenously 1 hour prior and at the onset of the ischemia, whereas 22 without treatments. Additionally, 6 sham animals were subjected to the same open chest surgical procedure.

***In situ* inflammation:** The inflammation status of the myocardium is assessed by cellular MRI. Macrophages/monocytes were labeled in circulation by intravenous administration of micrometer-sized iron oxide (MPIO) particles, and the infiltration MPIO-labeled macrophages into the heart is by *in vivo* T_2^*-weighted MRI with Bruker 7-Tesla Avance III, with 156 μm in-plane resolution. After the end point, the heart was harvest for *ex vivo* T_2^*-weighted *vivo* MR microscopy (MRM) at 11.7-Tesla with 40–μm isotropic resolution.

Integrated multi-parameter cardiac function: Global systolic cardiac functions, anatomical changes, and wall thinning were evaluated with cine MRI over time. Regional wall motion and strains were assessed by tagging MRI followed by strain analysis. Myocardial perfusion and infarction is measured by 1st-pass dynamic with a single bolus Gd (Omniscan, 0.5mmol/kg) administration as well as late gadolinium enhancement (LGE).

RESULTS

After transient ischemia, although blood flow was fully restored, inflammation has already set in. Hypointensity can be detected in the IRI site of myocardium (Fig. 1 A-C) with *in vivo* T_2^*-weighted MRI, indicating the accumulation of MPIO-labeled macrophages. High-resolution *ex vivo* MR microscopy (MRM) and histological staining confirmed that the hypointensity is due to labeled macrophages (Fig. 2 A-D). Animals with Intralipid treatment, however, showed much reduced macrophage infiltration (Fig. 1 D-H & Fig. 2 E-H), indicating reduced *in situ* inflammation with Inatralipid treatment. In addition, Intralipid-treated animals did not exhibit similar myocardial atrophy over time (Fig. 2 G,H) as untreated animals (Fig. 2 C,D). Untreated animal exhibited much reduced wall thickness in the infarct site, the infero-lateral and antero-lateral LV wall regions; whereas the heart of the Intralipid-treated animal preserved mostly normal myocardium thickness across LV.

Intralipid-treated animals preserved much of the cardiac function after ischemic insults (Fig. 3-4). Intralipid treated hearts showed to preserve SV and EF with cine imaging (Fig.3), regional wall motion (Fig. 4 A,B) and myocardial perfusion (Fig. 4 C,D). Although Intralipid treatment greatly decreased the local myocardial inflammation in the IRI hearts, Intralipid did not change the immune cell composition in peripheral blood.

CONCLUSION

Our results indicate that Intralipid treatment can protect hearts against IRI. It can specifically reduce *in situ* myocardial inflammation, and preserve cardiac function, reduce myocardial remodeling, without altering systemic immune response.

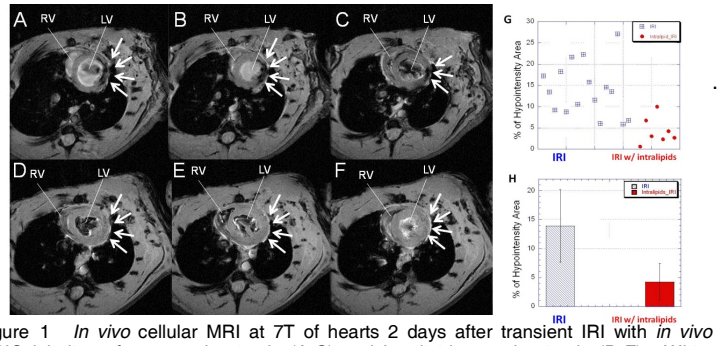

Figure 1 *In vivo* cellular MRI at 7T of hearts 2 days after transient IRI with *in vivo* MPIO labeling of untreated animals (A-C) and Intralipid-treated animals (D-F). White arrowheads point to the areas with hypointensity caused by infiltration of MPIO-labeled macrophages, or areas should have IRI. (G-H) Percentage of areas with hypointensity in myocardium for untreated IRI animals (blue) or Intralipid-treated IRI animals (red).

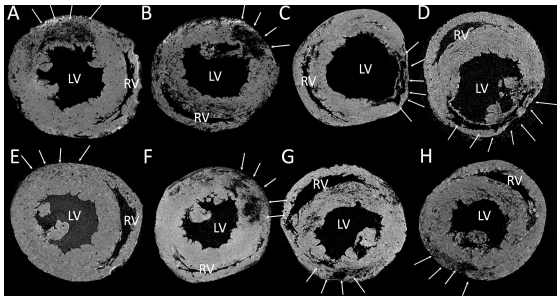

Figure 2 *Ex vivo* MR microscopy (MRM) at 11.7T, of hearts harvested 2 days (A, B, E, F); 1 week (C, G) and 2 weeks (D, H) after transient ischemic injury of untreated animals (A to D) or Intralipid-treated animals (E to H). White arrows point to spots with hypointensity, which are macrophages

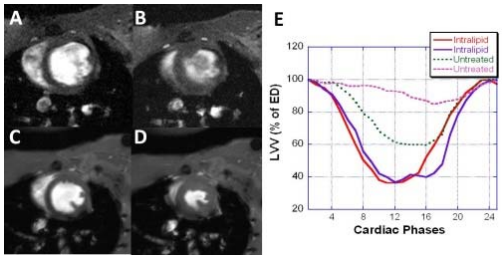

Figure 3 *In vivo* cine MRI by of (A, B) untreated and (C, D) Intralipd-treated ischemic hearts at (A, C) end-diastole and (B, D) end-systole. (E) Temporal changes of LV volume of 2 untreated animals (dotted lines) and 2 treated animals across different cardiac phases through a cardiac cycle.

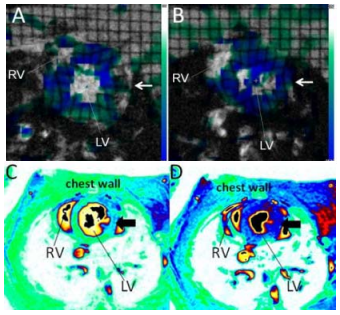

Figure 4 (A&B) Circumferential strain (Ecc) map, derived from tagging MRI; and (C&D) 1st-pass perfusion with bolus Gd administration, of (A, C) a untreated and (B, D) an Intralipd-treated IRI heart.