Apolipoprotein A1 Attenuates Myocardial Ischemia-reperfusion Injury by Blocking the Release of Cell-free DNA and HMGB1 from Ischemically-injured Myocardium

Aimee Zhang, MD, Lina Lai MD, Eric J. Charles MD PhD, Irving L. Kron MD,
Zequan Yang MD
University of Virginia

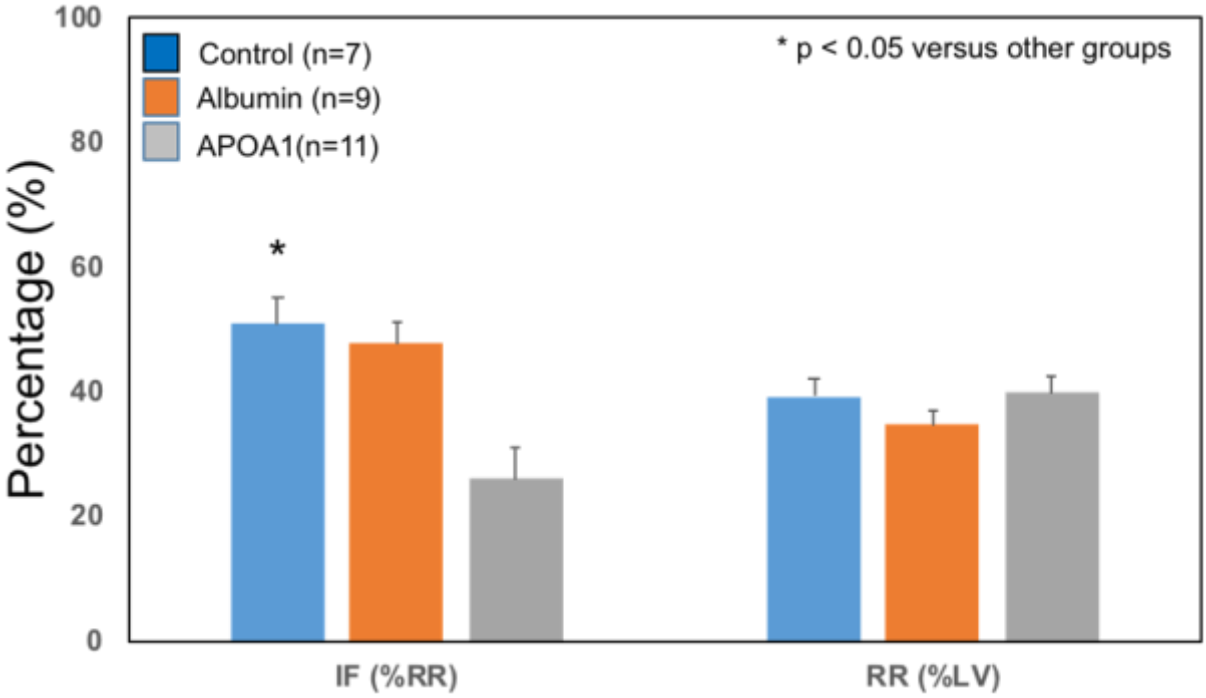
Objectives: Cell-free DNA (cfDNA) and HMGB1 are released into circulation by ischemic myocardium and mediate post-ischemic reperfusion injury. We hypothesized that high-density lipoprotein component apolipoprotein A1 (APOA1) attenuates myocardial ischemia-reperfusion injury by blocking the release of these damage-associated molecular patterns.

Materials and Methods: WT mice underwent 40 minutes of left coronary artery (LCA) occlusion followed by 60 minutes of reperfusion. Phosphate buffered saline (PBS) at a dose of 2 µl/g, albumin (0.5 µg/g), or APOA1 (0.5 µg/g) was administered as an IV bolus at 5 minutes before reperfusion. Infarct size (IF), denoted as a percentage of risk region (RR, % of LV), was measured with TTC-Phthalo blue staining at the end of 60 minutes of reperfusion. In parallel experiments, at the end of 40 minutes of LCA occlusion, hearts were harvested and perfused with PBS, albumin or APOA1 in a volume of 500 µl for five cycles. The cardiac perfusate was then collected, and cfDNA measured by Sytox green fluorescence.

Results: RR was comparable among all groups. IF in the control and albumin-treated groups were similar. In comparison, APOA1 significantly reduced IF by 49% (Figure). Plasma cfDNA and HMGB1, and cardiac perfusate cfDNA were also all significantly reduced in the APOA1-treated group compared to the control or albumin-treated groups ($p<0.05$).

Conclusions: APOA1 attenuates myocardial ischemia-reperfusion injury by reducing the systemic levels of cfDNA and HMGB1 released from ischemically-injured cardiomyocytes. A possible mechanism underlying this effect is the binding of APOA1 to necrotized cardiomyocytes blocking the release of cfDNA and HMGB1.

Fig.


100
80
60
40
20
0
Percentage (%)
Control (n=7)
Albumin (n=9)
APOA1(n=11)
* p < 0.05 versus other groups
*
IF (%RR)
RR (%LV)