

Cardioprotective and Pulmonary Effects of Intralipid on Myocardial Ischemia- Reperfusion Injury in Rat Heart and Lung Tissue

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Abstract

Objective(s):

Myocardial ischemia-reperfusion (I/R) injury is a major contributor to cardiac damage after coronary revascularization. Intralipid, a soybean oil-based lipid emulsion, exerts cardioprotective effects via activation of prosurvival signaling pathways and preservation of mitochondrial function, but its optimal timing and its effects on remote pulmonary injury remain unclear. This study evaluated the cardioprotective and pulmonary effects of Intralipid administered at different time points during myocardial I/R injury in rats.

Materials and Methods

Fifty male Wistar rats (300–350 g) were randomly assigned to five groups (n = 10/group). Myocardial I/R injury was induced by 30 min occlusion of the left anterior descending artery followed by 120 min of reperfusion. Intralipid was administered before or during reperfusion according to different protocols. Heart and lung tissues were evaluated histopathologically, and myocardial necrosis and inflammatory cell infiltration were quantified by histomorphometry.

Results

The control group showed extensive myocardial necrosis and inflammatory cell infiltration. All Intralipid-treated groups showed significantly less myocardial injury than controls ($P < 0.05$). The repeated-dose group showed the greatest protection, with the lowest necrosis ($7.0 \pm 0.3\%$) and inflammatory cell infiltration (4.3 ± 2.5 cells/HPF) versus $31.5 \pm 3.4\%$ and 29.3 ± 9.4 cells/HPF in controls. Remote pulmonary injury, marked by hemorrhage and inflammatory cell infiltration, was also observed; Intralipid reduced pulmonary damage, but less markedly than myocardial damage.

Conclusion

Repeated administration of Intralipid during early reperfusion confers significant cardioprotection and may represent an important pharmacological postconditioning strategy for limiting myocardial I/R injury.

1. Introduction

Cardiovascular disease remains the leading cause of death worldwide.(1) Ischemia-Reperfusion (I/R) injury paradoxically worsens tissue damage during blood flow restoration and is a key factor to myocardial injury after revascularization. (2, 3) The pathophysiology of I/R injuries is complex and involves different mechanisms including a burst of reactive oxygen species (oxidative stress), cellular injury, activation of inflammatory cells, extracellular matrix (ECM) remodeling, intracellular calcium

overload, fibrosis, cardiomyocyte hypertrophy, and mitochondrial dysfunction.(4–7) The latter event occurs by the opening of a channel in the mitochondrial membrane called the mitochondrial permeability transition pore (mPTP). When this pore opens, the mitochondria swell, burst, and release proteins that trigger cell death.(8) Therefore, preventing mPTP opening is the ultimate goal of most cardioprotective interventions.

Ischemic conditioning including preconditioning, postconditioning, and remote conditioning is an endogenous cardioprotective strategy against myocardial I/R injury.(9) These interventions activate pro-survival signaling pathways and preserve mitochondrial function which results in reduction of infarct size and improved cardiac recovery.(10, 11) Consequently, pharmacological conditioning reproduces the protective effects of ischemic conditioning using pharmacological agents administered before, during, or after ischemia. Various compounds, such as isoflurane, adenosine, and cyclosporine A1 have demonstrated cardioprotective potential by targeting key pathways involved in I/R injury.(12–14)

Among these drugs, Intralipid has played a major role in pharmacological conditioning strategy because of its favorable safety profile and ability to activate cardioprotective signaling pathways in porcine and rat models.(15, 16)

Intra-lipid is a soybean oil-based intravenous lipid emulsion approved for parenteral nutrition and local anesthetic toxicity reversal.(17, 18) Rahman et al.(19) first showed that Intra-lipid reduces infarct size in rodent I/R models. Beyond the heart, remote organs particularly the lung are vulnerable to I/R induced systemic inflammation. (20) The lung receives the entire cardiac output and contains large amounts of immune cells, making it particularly susceptible to remote injury.(21)

Although the beneficial effects of using intra-lipid as pharmacological postconditioning have been demonstrated in previous studies, its optimal timing remains inconclusive as different outcomes may occur depending on when the Intra-lipid is initiated during reperfusion.(15, 22) Furthermore, the effects of Intra-lipid on pulmonary injury following cardiac I/R remain unexplored. Therefore, this study evaluated both cardioprotective and pulmonary effects of Intra-lipid in Wistar rat model of myocardial I/R injury.

2. Materials and Methods

Animals and Ethical Approval

Fifty adult male rats weighing 300–350 grams were used in this experimental study. Animals were retained standard laboratory conditions with free access to food and water and maintained under a 12-h light/dark cycle. All experimental procedures were performed in accordance with the National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Ethics Committee of Shaheed Rajaie Cardiovascular Institute.

Experimental Design and Randomization

Animals were randomly divided into five experimental groups (n = 10 per group) using a simple randomization method. Sample size was determined based on previous studies investigating myocardial I/R injury and the cardioprotective effects of Intra-lipid.

Induction of Myocardial Ischemia/Reperfusion Injury

Rats were anesthetized with a ketamine (80 mg/kg) and xylazine (10 mg/kg) combination. After shaving the thoracic area, animals were placed in the supine position and a left thoracotomy was performed through the third and fourth intercostal spaces under sterile conditions. The heart was exposed using a 10-mm retractor.

The left anterior descending coronary artery (LAD) was identified on the anterior surface of the heart and tightened approximately 1–2 mm below the tip of the left atrial appendage by a polypropylene suture. Successful coronary occlusion was confirmed by immediate blanching of the anterior wall of the left ventricle and ST segment elevation in electrocardiography.

Myocardial ischemia was maintained for 30 min, followed by 120 min of reperfusion achieved by releasing the ligature. At the end of the reperfusion period, animals were monitored until completion of the experimental protocol. Animals that failed to survive the entire 150-min experimental period were excluded from the study.

Experimental Groups

The animals were assigned to the following groups:

Control Group

Rats received 1 mL normal saline intraperitoneally at the onset of ischemia immediately after LAD ligation.

Group 1 (Intralipid-Ischemia)

Rats received 1 mL of 10% Intra-lipid intraperitoneally at the onset of ischemia.

Group 2 (Intralipid-Reperfusion)

Rats received 1 mL of 10% Intra-lipid intraperitoneally immediately before reperfusion (30 min after LAD ligation).

Group 3 (Post-Reperfusion Intralipid)

Rats received 1 mL of 10% Intra-lipid intraperitoneally 30 min after reperfusion.

Group 4 (Repeated Intralipid Administration)

Rats received 1 mL of 10% Intralipid intraperitoneally at the onset of reperfusion and a second identical dose 30 min later.

Histopathological Assessment

Following completion of the experimental protocol, the hearts and lungs were removed and fixed in 10% buffered formalin for 48 h. Tissue samples were processed routinely, embedded in paraffin, and sectioned at a thickness of 5 µm. Histological sections were stained with hematoxylin and eosin (H&E) and Masson Trichrome (MT) for evaluation of myocardial injury and tissue remodeling with optical microscope (Olympus BX51, Tokyo, Japan). Histopathological assessments were performed by an experienced pathologist who was blinded to the treatment groups to minimize bias.

Statistical Analysis

For the ex vivo studies with four or five groups, mean profiles over time were compared across groups using repeated measure analysis of variance (ANOVA) methods. Under the ANOVA model, pairwise mean comparisons were judged significant using the Tukey studentized range criterion. SPSS, version 29.00, was used to carry out the computations. As all outcomes were continuous, results were summarized with Means $\pm$ Standard deviations (SD). Correlation was assessed by Pearson's test. $p < 0.05$ was significant.

3. Results

Histopathological Findings

Histopathological evaluation of heart and lung tissues was performed in all experimental groups following H&E staining. Representative micrographs of heart and lung tissues of control group are shown in Fig. 1. In the control group, myocardial sections demonstrated extensive cardiomyocyte necrosis accompanied by marked infiltration of acute inflammatory cells, predominantly neutrophils. The lungs showed pulmonary hemorrhage and inflammatory cell infiltration. Figures 2 and 3 shows the histopathological sections of lung and heart in different experimental groups. In Group 1, myocardial injury was significantly reduced compared with the control group, with a decrease in both necrotic areas and inflammatory cell infiltration. Histological examination revealed preservation of myocardial tissue with only mild inflammatory changes. In Groups 2 and 3, moderate myocardial necrosis and inflammatory cell infiltration were observed. Histological findings also demonstrated evidence of reperfusion injury, characterized by focal hemorrhage and sarcolemma disruption. Mild inflammatory changes were additionally detected in these groups. Among all experimental groups, Group 4 showed the most favorable histopathological outcomes. Cardiac sections demonstrated minimal cardiomyocyte necrosis with almost complete preservation of myocardial structure and absence of significant inflammatory cell infiltration. Similarly, lung tissues exhibited notably reduced hemorrhage and inflammatory changes compared with the other groups.

Quantitative histomorphometry analysis confirmed the histological observations (Table 1). The control group exhibited the highest percentage of myocardial necrosis ($31.5 \pm 3.4\%$) and the greatest number of inflammatory cells (29.3 ± 9.4 cells/HPF). Compared with the control group, all intervention groups demonstrated significantly lower necrotic areas and inflammatory cell counts ($P < 0.05$). The lowest necrosis percentage and inflammatory cell infiltration were observed in Group 4 ($7.0 \pm 0.3\%$ and 4.3 ± 2.5 cells/HPF, respectively). Group 1 also showed substantial protection, with necrosis reduced to $12.8 \pm 1.3\%$ and inflammatory cell counts reduced to 8.4 ± 3.1 cells/HPF. Intermediate values were observed in Groups 2 and 3, with necrosis areas of $24.3 \pm 1.5\%$ and $22.7 \pm 2.2\%$, respectively. Overall, Group 4 demonstrated the greatest cardioprotective effect, as evidenced by the lowest degree of myocardial necrosis and inflammatory cell infiltration among all experimental groups.

Table 1 Histopathological scoring of heart tissue		
Group	Necrosis area (%)	No. inflammatory cells / 3 HPF
Control	31.5 ± 3.4	29.3 ± 9.4
1	$12.8 \pm 1.3^*$	$8.4 \pm 3.1^*$
2	$24.3 \pm 1.5^*$	$11.8 \pm 2.5^*$
3	$22.7 \pm 2.2^*$	$14.0 \pm 2.6^*$
4	$7.0 \pm 0.3^{**}$	$4.3 \pm 2.5^{**}$

* $P < 0.05$ vs. Control group; ** $P < 0.05$ vs. Groups 1, 2, and 3. HPF, high-power field. Values are expressed as mean $\pm$ SD.

4. Discussion

The representative experimental study investigated the effectiveness of different timing of Intralipid administration on myocardial I/R injury and its associated remote pulmonary damage in rats. The histopathological findings illustrated that Intralipid significantly reduced myocardial infarct size, myocardial I/R injury induced substantial histopathological lung damage, and the protective effects of Intralipid on the lungs were considerably less remarkable than those observed in the myocardial tissue. Moreover, our findings indicated that the timing of intralipid administration play an important role in the level of myocardial protection. Group four has demonstrated the least myocardial injury and remote lung damage.

In consistent with our study, previous investigations demonstrated the cardioprotective impacts of Intralipid during reperfusion. Rahman et al. reported that administration of Intralipid at the onset of reperfusion reduced myocardial infarct size by approximately 70% and significantly improved cardiac recovery following ischemic injury. (19) Similarly, Liu et al.(23) showed that Intralipid administration after ischemia can improve mechanical function of the heart. In addition, Li et al.(13) compared the

cardioprotective effects of Intralipid and Cyclosporine-A in experimental models of myocardial I/R injury and they showed infarct size was significantly smaller in the Intralipid-treated group than in the Cyclosporine-A group. Similarly, in isolated hearts, Intralipid resulted in better post-ischemic cardiac function and a greater reduction in infarct size.

Several mechanisms may explain the observed myocardial protection. Previous studies revealed that Intralipid activates prosurvival signaling pathways, including PI3K/Akt and ERK1/2, leading to inhibition of glycogen synthase kinase-3 β (GSK-3 β). These signaling events increase the capacity of calcium retention of mitochondria and eventually prevent the opening of the mPTP. By preserving mitochondria, reducing oxidative stress, and maintaining ATP production, Intralipid limits cardiomyocyte death and reduces infarct development.(15, 24) In addition, studies have recently showed that hearts which have undergone remodeling post-infarction, and possess limited oxidative capabilities, increase fatty acid oxidation for ATP generation instead of glucose oxidation after undergoing conditioning against I/R injury.(25, 26) Therefore, the cardioprotective effects observed in the present study are likely attributable to similar molecular mechanisms.

An important finding of our study is the presence of remote pulmonary injury following myocardial I/R injury. Lung tissues from the control group demonstrated pulmonary hemorrhage and inflammatory cell infiltration, indicating that myocardial I/R injury extends beyond the heart and results in systemic inflammatory responses. Several studies indicated that myocardial reperfusion injury as a systemic inflammatory syndrome involving activation of leukocytes, producing of reactive oxygen species (ROS), and release of pro-inflammatory cytokines into the circulation.(27, 28) These circulating factors can subsequently damage distant organs, including the lungs

The mechanisms responsible for remote lung injury are complex and multifactorial. Following myocardial reperfusion, activated neutrophils, inflammatory cytokines, ROS, and damage-associated molecular patterns (DAMPs) enter the systemic circulation and lead to endothelial dysfunction and increase pulmonary vascular permeability. Recent studies have identified endothelial barrier dysfunction as a main mechanism in lung I/R injury, facilitating inflammatory cell migration into pulmonary tissue and promoting interstitial edema and hemorrhage. The pulmonary lesions observed in our study are therefore consistent with current concepts of systemic inflammatory injury secondary to myocardial reperfusion.(29)

Limitations

This study has several limitations. First, our study was conducted exclusively on healthy young male rats, while the typical cardiovascular disease patient is often older, typically diabetic or hypertensive, and may be using various concurrent medications. Second, the duration of the reperfusion period was comparatively brief (2 hours), and extending this to 24–72 hours may uncover different patterns of protection or the progression of injury. We only evaluated histopathology, incorporating biochemical markers (such as troponin and inflammatory cytokines) and functional assessments (like echocardiography) would offer additional insights. Future research should include aged subjects, both

genders, relevant comorbidities, concurrent medications, extended reperfusion durations, and molecular endpoints. Furthermore, the ideal dosage and timing for Intra lipid administration to achieve multi-organ protection remains unclear and needs thorough examination.

5. Conclusion

In conclusion, our findings indicate that Intralipid is a pharmacological post conditioning for reducing myocardial reperfusion injury, particularly when administered repeatedly during the early reperfusion phase. However, the incomplete protection against remote lung injury highlights the need for adjunctive therapies targeting systemic inflammation and endothelial dysfunction. Further experimental studies are required to define the molecular mechanisms underlying these effects and to determine the optimal therapeutic strategies for minimizing both cardiac and extra-cardiac consequences of I/R injury.

Abbreviations

H&E: Hematoxylin and Eosin

HPF: High-Power Field

I/R: Ischemia-Reperfusion

LAD: Left Anterior Descending

mPTP: Mitochondrial Permeability Transition Pore

MT: Masson Trichrome

NIH: National Institutes of Health

PI3K : Phosphoinositide 3-Kinase

ROS :Reactive Oxygen Species

SD: Standard Deviation

Declarations

Ethics approval:

All animal procedures were approved by the Institutional Animal Ethics Committee (RHC.AC.IR.REC.1396.5) and conformed to the Guide for the Care and Use of Laboratory Animals.

Conflict of Interest Statement

Authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Consent for publication

Not applicable

Data Availability Statement

The data supporting this study are available from the corresponding author upon reasonable request.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used large language model-based tools (ChatGPT, OpenAI) in order to assist with language editing and manuscript formatting also for enhancing the graphical abstract. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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Not applicable

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Figures

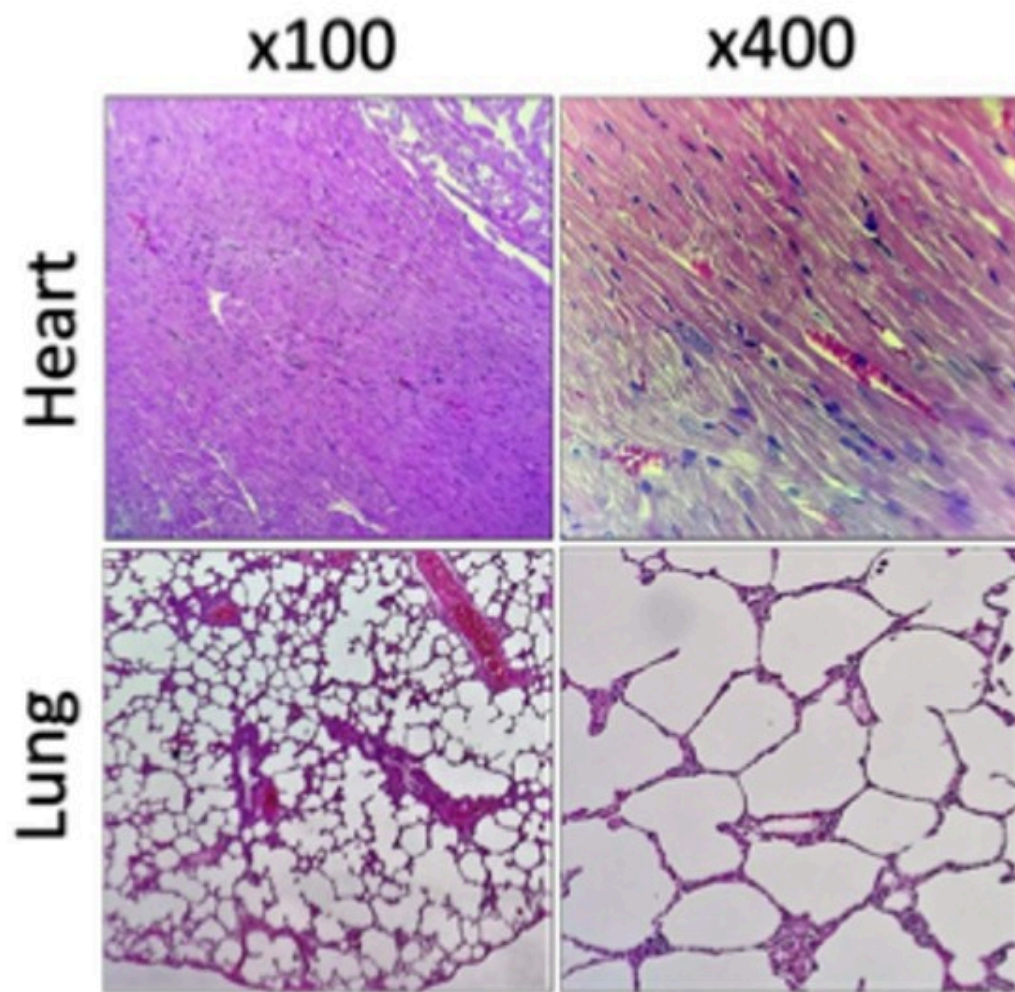


Figure.1 Histopathologic sections of heart and lung in control groups.

Figure 1

See image above for figure legend

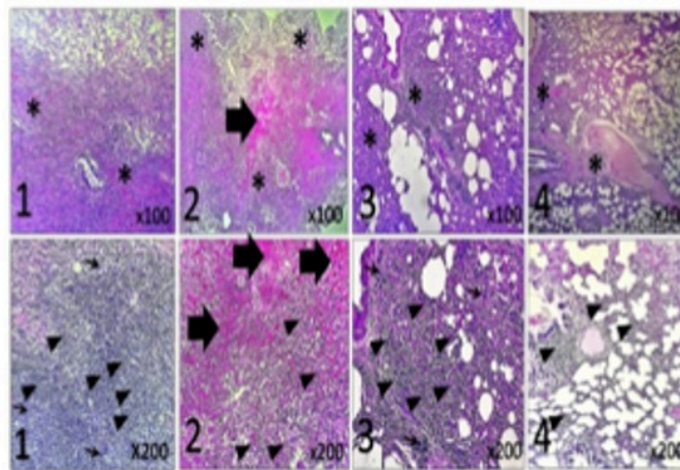


Figure.2 Histopathologic sections of lung in different experimental groups, Thick arrows: hemorrhage, Thin arrows: infiltration of macrophages, arrowheads: infiltration of lymphocytes, Asteroids: accumulation of inflammatory cells. H&E stain, X400

Figure 2

See image above for figure legend

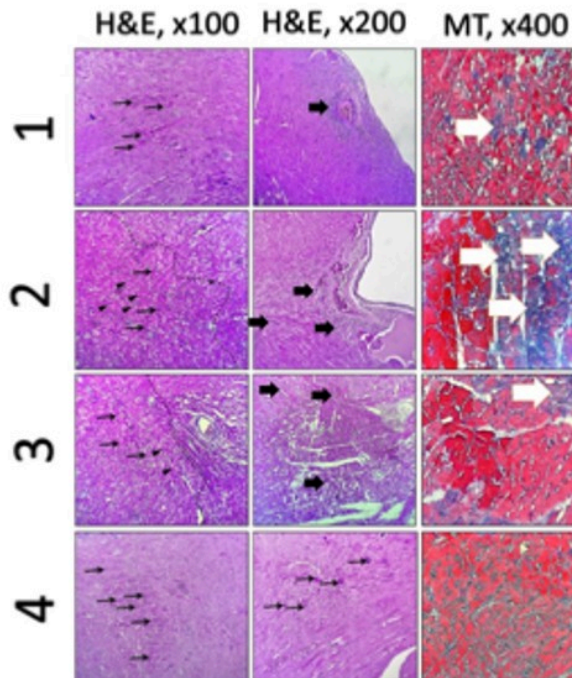


Figure.3 Histopathologic sections of heart in different experimental groups, Thick arrows: infiltration of inflammatory cells, Thin arrows: necrotic cardiomyocytes, arrowheads: contraction band necrosis, white arrows: necrotic cells. H&E stain, X40

Figure 3

See image above for figure legend