Effect of intralipid on myocardial injury during valve replacement surgery with concomitant radiofrequency ablation

A randomized controlled trial

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Abstract

Background: This study aimed to evaluate the effect of intralipid postconditioning (ILPC) on myocardial damage in patients undergoing valve replacement surgery with concomitant radiofrequency ablation (RFA) for atrial fibrillation (AF).

Methods: Randomized patient and assessor-blind controlled trial conducted in adult patients undergoing valve replacement surgery with concomitant RFA. Sixty-nine patients were randomly assigned to ILPC group (n = 34) or control group (n = 35): ILPC group received an intravenous infusion of 20% intralipid (2 mL/kg) just 10 minutes before aortic cross-unclamping, and control group received an equivalent volume of normal saline. Serum cardiac troponin-T (cTnT) and creatine kinase-MB (CK-MB) was measured before surgery and at 4, 12, 24, 48, and 72 hours after surgery. The primary endpoints were the 72-hour area under the curve (AUC) for cTnT and CK-MB.

Results: The total 72-hour AUC of cTnT ($P = .33$) and CK-MB ($P = .52$) were comparable between 2 groups. The left ventricle ejection fraction at discharge ($P = .011$) was higher in the ILPC group than that in the control group, while the AF recurrence did not differ significantly between 2 groups.

Conclusions: There was no observed beneficial effect of ILPC on myocardial injury documented by the cardiac biomarkers in patients undergoing valve replacement surgery with concomitant RFA, and the effect of intralipid against myocardial I/R injury is undetectable within the background of massive biomarker release following ablation owing to localized myocardial necrosis. Besides, there are no other published data about the cardioprotective role of intralipid in patients undergoing this procedure and benefits of this protection need further studies to validate.

Abbreviations: AF = atrial fibrillation, AUC = area under the curve, CK-MB = creatine kinase-MB, CPB = cardiopulmonary bypass, cTnT = cardiac troponin-T, ECG = electrocardiogram, ERAF = early recurrence of AF, I/R = ischemic/reperfusion, ICU = intensive care unit, ILPC = intralipid postconditioning, LA = left atrial, LV = left ventricular, LVEF = left ventricle ejection fraction, mPTP = mitochondrial permeability transitioning pore, PV = pulmonary vein, RFA = radiofrequency ablation, RHD = rheumatic heart disease.

Keywords: atrial fibrillation, cardiac surgery, cardiac troponin-T, creatine kinase-MB, intralipid, rheumatic heart disease

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1. Introduction

Among patients with rheumatic heart disease (RHD), up to 30% to 50% present with atrial fibrillation (AF),[1] which has been proved to be associated with increased rates of thromboembolism, heart failure, and mortality.[2–4] Valve replacement surgery combining with the surgical ablation has been taken in patients of RHD associated with AF.[5] However, radiofrequency ablation (RFA) produces myocardial damage induced by a thermal necrosis of the atrial myocardium,[6] which might result in the early recurrence of AF (ERAF) following the proinflammatory processes initiated during ablation therapy.[7–9]

Our recent study reported the cardioprotective effects of intralipid postconditioning (ILPC) against the ischemic/reperfusion (I/R) injury during cardiopulmonary bypass (CPB) in patients undergoing isolated valve replacement surgery without AF.[10] However, it remains unknown whether the nonischemic damage of myocardium induced by RFA for AF following the inflammatory processes during valve replacement surgery could benefit from ILPC. A recent animal study showed that intralipid

could mitigate limb I/R injury in rats through attenuation of local inflammatory mediators and the subsequent systemic inflammatory response.[11] Thus, we hypothesized that ILPC could attenuate the degree of myocardial injury in patients undergoing valve replacement surgery with RFA, possibly through attenuate the inflammatory response. We administered intralipid just before reperfusion but after RFA and focused on the myocardial injury documented by the release of cardiac troponin T (cTnT) and creatine kinase-MB (CK-MB) and associated clinical outcomes.

2. Methods

2.1. Study design

This study was a prospective, randomized, assessor-blinded, placebo-controlled trial with 2 parallel arms undertaken in West China Hospital of Sichuan University, China. The West China Hospital of Sichuan University Biomedical Research Ethics Committee approved the study protocol. All patients provided written informed consent before inclusion. Randomization was performed using a computer-generated randomization sequence and allocation concealment was maintained until the time of anesthesia induction by using opaque, numbered and sealed envelopes. The trial was prospectively registered at Chictr.org.cn (ID ChiCTR-IOR-14005318).

2.2. Inclusion and exclusion criteria

Patients were eligible for participation if they met the following criteria: elective valve replacement surgery with RFA, and age older than 18 years. Exclusion criteria were as follows: previous ablation for AF or intracardiac thrombus; combined valve and coronary surgery, redo cardiac surgery, significant coronary stenosis (>70%), ventricular fibrillation, left ventricular (LV) ejection fraction less than 30%, positive baseline serum cTnT or CK-MB, experienced cardiogenic shock or cardiac arrest, hyperlipidemia, significant hepatic (INR > 2.0), pulmonary (forced expiratory volume-1 < 40% predicted) or renal disease (serum creatinine level ≥ 150 μmol/L), uncontrolled hypertension, current infections, any disorder associated with immunological dysfunction (e.g., malignancy, positive serologic test for the human immunodeficiency virus) in the last 6 months, preoperative treatment with intralipid in the last 1 month, or preoperative treatment with nicorandil (an adenosine triphosphate-sensitive potassium channel opener), sulfonylurea (an adenosine triphosphate-sensitive potassium channel blocker). Patients who are participating in other interventional studies are also ineligible.

2.3. Experimental protocol

Patients who met the enrollment criteria were randomized 1:1 to either ILPC or control group. Less than 10 minutes before aortic cross-unclamping, patients in the ILPC group received an intravenous infusion of 2 mL/kg of 20% intralipid (medium and long chain fat emulsion injection C6–C24, SINO SWED Pharmaceutical Corp. Ltd, Jiangsu, China). Intralipid should be infused over 10 minutes in constant speed. Patients in the control group received an equivalent volume of normal saline. The dose of intralipid was chosen on the basis of the bolus dose when it is used in the treatment of severe cardiotoxicity from intravenous overdose of bupivacaine.[12,13]

2.4. Standard procedures

The anesthesia protocol and CPB technique have been previously described in detail.[10] All patients underwent a median sternotomy. Surgical ablation was started after CPB was established. Left atrial (LA) ablation comprised the following steps (Fig. 1S, http://links.lww.com/MD/C63)[14,15]: First, right and left pulmonary veins (PVs) isolation were performed before aortic cross-clamping by bipolar clamp; second, after cardioplegic arrest, 2 holes were punched near the right superior PV and right inferior PV, through which a "roof lesion" connecting the left and right superior PVs and a "floor lesion" connecting the bilateral inferior PVs were performed, respectively; third, mitral isthmus line from the right inferior PV through the coronary sinus to the mitral annulus was performed using a bipolar clamp; fourth, after removing the LA appendage, a bipolar clamp was used to create a lesion from this site to the left superior PV. Concomitant valve replacement surgery was performed after ablation. After the valve replacement procedure, the heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. CPB was discontinued and protamine used to reverse the effect of heparin. Temporary pericardial pacing wires were implanted before sternal closure. Patients were transferred to the intensive care unit (ICU) after surgery and were extubated at the earliest clinically appropriate time when their ventilator, hemodynamic, and neurologic states were deemed to be stable by the attending physician.

2.5. Outcomes

2.5.1. Primary endpoints. The primary endpoints were the total 72-hour area under the curve (AUC) for c-TnT and CK-MB release. Blood samples were taken before surgery and 4, 12, 24, 48, and 72 hours after surgery.

2.5.2. Secondary endpoints. These included the followings:

1. Cardiac function assessment: including inotrope requirement over 48 hours and left ventricle ejection fraction (LVEF) at discharge. Transthoracic echocardiography was performed in all patients before surgery and at hospital discharge. LVEF quantification with echocardiography was done with Simpsons and reevaluated after 1 week. The average values were calculated and analyzed to eliminate intraobserver variability.
2. AF recurrence: a clinical assessment and 12-lead electrocardiogram (ECG) were performed on all patients at discharge and at each of the 1, 3, and 6 months follow-up visits in a dedicated arrhythmia outpatient clinic. AF recurrence was defined as the presence of any AF or atrial flutter episode lasting more than 30 seconds on 12-lead ECG monitoring at each visit. An electrical conversion was given to terminate the AF.
3. The extubation time, length of stays in ICU and hospital were collected.
4. All complications occurring during hospitalization and 3 months after surgery: other arrhythmias, all-cause death, myocardial infarction, stroke, infection, respiratory failure, hepatic or renal failure and any complications related to operation.
5. The serum levels of blood lipids: triglyceride, total cholesterol, high density lipoprotein, and low density lipoprotein. The blood samples were taken before surgery, 4 hours after surgery and at hospital discharge.
6. The examination of hepatic and renal function before surgery, 24 hours after surgery and at hospital discharge, measured by

blood urea nitrogen, serum creatinine, total bilirubin, direct bilirubin, and indirect bilirubin.

2.6. Statistical analysis

We hypothesized that ILPC would cause a 25% reduction of cTnT-AUC release compared with that in the control group. At 90% power and significance at the 2-sided 5% level, this required a sample size of 60 subjects (30 per group), which we increased by 33% to accommodate withdrawal or missing data points. All analyses were performed by an independent expert unaware of the allocated treatment group.

Data are expressed as mean ± standard deviation. The 72 hours AUC for plasma cTnT and CK-MB concentrations were analyzed using integration by software originpro 8.0. Comparisons between both independent groups were performed using unequal-variance Student t test for continuous variables followed a normal distribution. Chi-square or Fisher exact tests were used as appropriate for categorical variable comparisons between groups. A 2-way ANOVA with repeated measures was used to analyze the comparison of the plasma cTnT and CK-MB concentrations, hepatic and renal function between groups. When appropriate, post hoc analysis was performed with the Tukey test to identify time and within and between treatment differences. Results were considered statistically significant at a P-value less than .05. Statistical analyses were done using statistical software SPSS 17.0.

3. Results

3.1. Characteristics of the study population

From October 2014 to April 2015, 318 patients underwent valve replacement surgery with concomitant RFA were recruited. Among them, 80 were included and randomly assigned to ILPC group (n=40) or control group (n=40). After randomization, 11 patients were excluded and 34 patients (ILPL) versus 35 patients (control) were included for final analysis (Fig. 1). No significant difference was found between the 2 groups in terms of baseline characteristics or clinical data except body mass index (kg/m^2) (23.56 ± 2.58 vs 21.38 ± 4.70, P=.02) (Table 1). Intraoperative data and postoperative outcomes are illustrated in Table 2.

3.2. Primary end points

Plasma levels of cTnT and CK-MB measured after the procedure in the ILPC and control groups were higher than baseline levels, respectively ($P < .01$ for all time points). However, the levels of
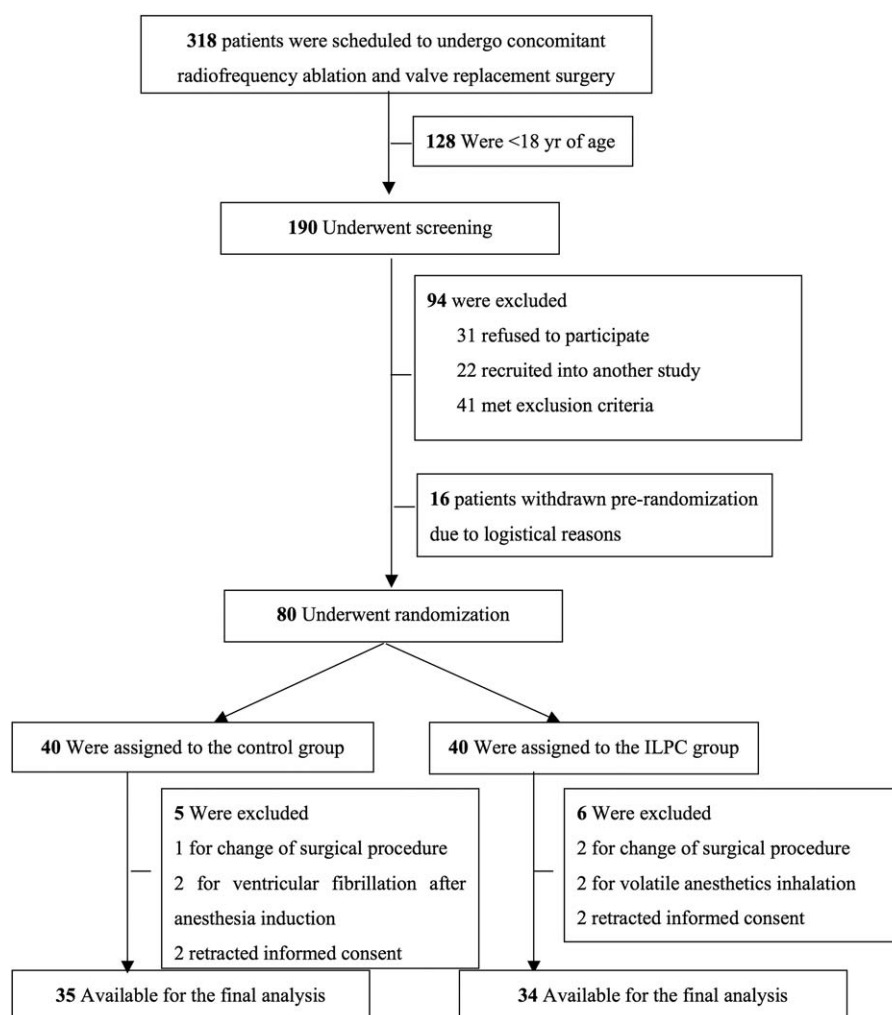

Figure 1. Study profile.

Table 1

Baseline patient characteristics.

Characteristics	Control (n=35)	ILPC (n=34)
Age, y	53.71 ± 10.05	52.00 ± 7.97
Sex, M/F	9/26	10/24
Body mass index, kg/m^{2*}	21.38 ± 4.70	23.56 ± 2.58
Smoking	7 (20.0%)	9 (26.5%)
NYHA class	2.89 ± 0.32	2.88 ± 0.33
EuroSCORE	5.15 ± 1.82	3.78 ± 1.09
SBP, mm Hg	120.23 ± 11.80	114.47 ± 15.72
DBP, mm Hg	76.29 ± 11.63	71.82 ± 9.92
LVEF, %	56.53 ± 11.17	60.76 ± 7.92
>55%	21 (60%)	23 (68%)
35–55%	13 (37%)	11 (32%)
<35%	1 (3%)	0 (0%)
Baseline cTnT, ng/L	10.88 ± 4.94	11.36 ± 9.29
Baseline CK-MB, ng/mL	1.45 ± 0.50	1.61 ± 1.11
History		
Hypertension	4 (11.4%)	2 (5.9%)
Diabetes	1 (2.9%)	0 (0%)
Stroke	4 (11.4%)	1 (2.9%)
Dyslipidemia	19 (54.3%)	13 (38.2%)

Dichotomic data are presented as number (%); continuous data are presented as mean (standard deviation). No significant difference was found between the 2 groups except body mass index. CK-MB = creatine kinase-MB, DBP = diastolic blood pressure, ILPC = intralipid postconditioning, LVEF = left ventricle ejection fraction, SBP = systolic blood pressure.
* $P < .05$.

Table 2

Intraoperative patient data and outcome data.

Characteristics	Control group (n=35)	ILPC group (n=34)	P
Type of surgery			
MVR	27 (77%)	26 (76%)	.947
AVR	1 (3%)	5 (15%)	.081
MVR + AVR	7 (20%)	3 (9%)	.187
Cardio pulmonary bypass duration, min	133 ± 27	123 ± 27	.138
Aortic cross-clamping duration, min	88 ± 25	78 ± 23	.1
Surgery duration, min	244 ± 42	244 ± 42	.964
Volume of cardioplegia, mL	2280 ± 489	2315 ± 721	.82
Lowest temperature, °C	32.9 ± 0.3	32.9 ± 0.3	.705
Total IV propofol, mg	991 ± 370	1045 ± 391	.57
Total IV sufentanil, μg	310 ± 60	295 ± 62	.32
Ventricular fibrillation after aortic unclamping	4 (11.4%)	4 (11.8%)	.96
Inotrope requirement over 48 h	18 (51.4%)	9 (26.5%)	.034
Left ventricle ejection fraction, %*	55.03 ± 10.12	60.74 ± 7.56	.011
>55%	22 (63%)	17 (50%)	.281
35–55%	12 (34%)	17 (50%)	.186
<35%	1 (3%)	0 (0%)	—
Atrial fibrillation recurrence			
At discharge	0 (0%)	2 (5.9%)	.15
1-mo after surgery	1 (2.8%)	2 (5.9%)	.98
3-mo after surgery	2 (5.7%)	3 (8.8%)	.978
6-mo after surgery	2 (5.7%)	4 (11.7%)	.642
Extubation time, h	27.19 ± 16.12	20.08 ± 13.91	.056
ICU length of stay, h	77.45 ± 71.25	62.26 ± 76.64	.40
Hospital length of stay, d	13.8 ± 4.1	13.9 ± 4.4	.34
Complications*			
Infection	5 (14.3%)	5 (14.7%)	.96
Renal dysfunction	1 (2.9%)	1 (2.9%)	.983

AVR = aortic valve replacement, ICU = intensive care unit, ILPC = intralipid postconditioning, MVR = mitral valve replacement.
* At hospital discharge.
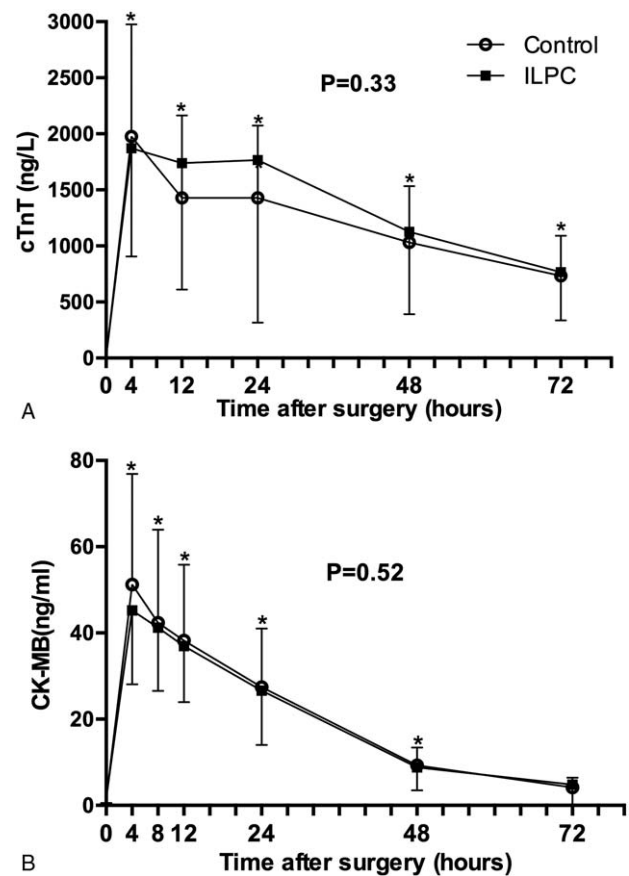
Figure 2. The 72-hour AUC for cTnT (A) and CK-MB (B) values after surgery. The cTnT release ($P = .33$) and the CK-MB release ($P = .52$) were comparable between the ILPC group and the control group. *Within a group, values were significantly different with baseline ($P < .05$). T bars denote standard deviation. AUC = area under the curve, cTnT = cardiac troponin T, CK-MB = creatine kinase-MB, ILPC = intralipid postconditioning.

cTnT and CK-MB were similar in the ILPC group compared to the control group at each time point after the surgery. The 72-hour AUC for cTnT release after surgery was comparable between the ILPC group (92163.9 ± 56902.4 arbitrary unit) and the control group (80930.7 ± 36849.4 arbitrary unit) (mean difference −11233.3; 95% CI: −34331.2 to 11864.7, $P = .33$). Similarly, the 72-hour AUC for CK-MB release of these 2 groups showed no significant difference (1406.5 ± 473.8 arbitrary unit vs 1489.7 ± 590.5 arbitrary unit, mean difference 83.2; 95% CI: −171.6 to 337.9, $P = .52$) (Fig. 2).

3.3. Secondary endpoints

The clinical outcomes are displayed in Table 2. The rate of inotrope requirement over 48 hours was lower (26.5% vs 51.4%, $P = .034$) and LVEF at discharge (60.74% ± 7.56% vs 55.03% ± 10.12%, $P = .011$) (Fig. 3) was higher in the ILPC group than that in the control group, while the extubation time and length of stays in ICU and hospital did not differ between 2 groups. A total of 2 patients (5.7%) in the control group and 4 patients (11.7%) in the ILPC group had early AF or atrial flutter within 6 months follow-up. The AF recurrence rate was similar in the ILPC group compared to the control group during the follow-up. Complications occurred similarly in the 2 groups during hospitalization. There was no major complication, such as infective endocarditis,
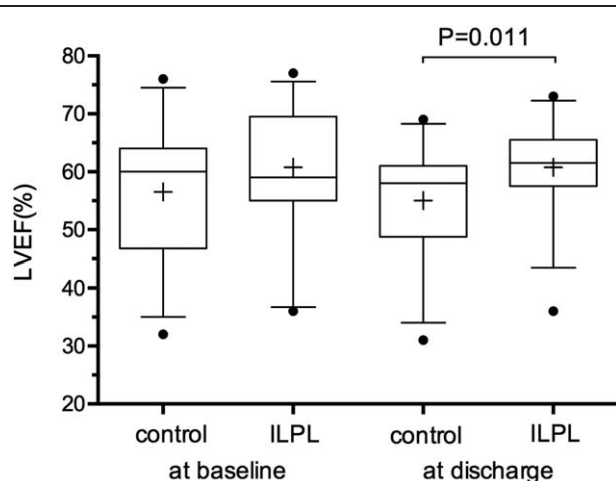
Figure 3. LVEF values are shown as mean (cross in the box), median (line in the box), 75% and 25% percentiles (upper and lower edge of the box), 95% and 5% percentiles (horizontal line of the "T" and reversed "T," respectively), maximum and minimum value (dot above and below 95% and 5% percentiles).

stroke, myocardial infarction, hepatic function failure, or death at discharge.

The blood lipids tests including triglyceride, total cholesterol and low density lipoprotein and biological measurements of renal function including serum creatinine and blood urea nitrogen increased significantly in the ILPC group compared with that in the control group at 24 hours after surgery but still in the normal range and became similar at discharge between 2 groups. Biological measurements of hepatic function at baseline, 24 hours after surgery or at discharge did not significantly differ between 2 groups (Table 1S, http://links.lww.com/MD/C63).

4. Discussion

In this randomized controlled trial, it was observed that plasma levels of cTnT and CK-MB were elevated in both the ILPC group and the control group after the valve replacement surgery with concomitant RFA; ILPC after ablation could not mitigate the postoperative elevation of cTnT and CK-MB release following myocardial injury or decrease the AF occurrence; ILPC resulted in beneficial effects on cardiac function determined by the rate of inotrope requirement over 48 hours and LVEF at discharge.

Up to 30% to 50% patients with RHD present with AF,[1] which is related to increased risk of thromboembolism, heart failure, and mortality.[2–4] Valve replacement surgery combining with the surgical ablation has become an effective therapeutic option of RHD associated with AF.[16] However, both CPB and RFA produce myocardial damage induced by the I/R injury and a thermal necrosis of the atrial myocardium, respectively.[6,17] Our study demonstrated elevated levels of cTnT and CK-MB following the valve replacement surgery with concomitant RFA. The 72-hour AUC for cTnT and CK-MB release were about threefold and 1.5-fold higher compared to our recent study which reported the same biomarkers release in patients undergoing isolated valve replacement surgery without ablation,[10] which suggests that the amount of cardiac biomarkers release caused by the thermal injury related to the RFA procedure is large and detectable within the background of biomarker release during CPB following I/R injury.

Our recent study reported the cardioprotective effects of intralipid against the I/R injury following CPB in isolated valve replacement surgery without ablation,[10] and in the present study, we administered the same dose of intralipid just before reperfusion in patients undergoing valve replacement surgery with concomitant ablation. The ischemia–hypoxia of myocardium before aortic cross-unclamping could lead to insufficient fatty acids oxidation, and the toxic fatty acids metabolites could accumulate in cardiomyocytes and cause cardiac lipotoxicity.[18,19] As a consequence, the intralipid was administration just before reperfusion to avoid the lipotoxicity following insufficient fatty acids oxidation during hypoxic–ischemic stage. In the present study, the findings showed that ILPC neither attenuate the myocardial injury documented by the increase in cTnT and CK-MB after RFA and CPB nor result in a lower risk of AF recurrence. Several clinical trials and animal studies reported the cardioprotective effects of intralipid against the I/R injury following CPB, which possibly through inhibiting mitochondrial permeability transitioning pore (mPTP) opening.[10,20,21] The opening of mPTP is considered to be a critical determinant of cardiomyocyte death in acute I/R injury, which results in cellular apoptosis and necrosis through an increase in mitochondrial membrane permeability.[22,23] However, RFA produces myocardial damage by means of a thermal-induced coagulative necrosis of the atrial myocardium, and upregulation of IL-6 and hs-CRP values suggests inflammatory processes after ablation.[6,7] A recent animal study showed that intralipid could mitigate limb I/R injury in rats through attenuation of local inflammatory mediators and the subsequent systemic inflammatory response.[11] However, our negative findings suggest that ILPC seem not to provide cardioprotective effect against myocardial damage following RFA as a result of the localized myocardial necrosis and the effect of intralipid against myocardial I/R injury is undetectable within the background of massive biomarker release following ablation. And the similar myocardial damage might be the reason for the comparable incidences of AF recurrence between the ILPC group and the control group. Besides, there are no published data about the cardioprotective role of intralipid on release of cardiac injury biomarkers after surgical ablation of AF and further related studies are needed.

Contrary to the findings in cardiac injury biomarkers release, our study found ILPC resulted in beneficial effects on cardiac function determined by the rate of inotrope requirement over 48 hours and LVEF at discharge, and they also contradicted those of our previous study.[10] The cardioprotective effect of intralipid regarding to the cardiac function is likely explained by the regulated preference for lipid over glucose to myocardium metabolism, as the vitro experimental studies reported that intralipid can restore myocardial contractions from bupivacaine-induced asystole and improve cardiac performance after I/R in isolated hearts.[24,25] The speculation would be strengthened if we focus on the examination of myocardial lipid utilization. In addition, one implication that needed to be addressed was the different levels of LVEF between 2 groups at baseline. A low preoperative ejection fraction (<50%) was in 9 (26%) of 35 patients in the control group and 2 (6%) of 34 patients in the ILPC group. Also, the LVEF at discharge did not alter significantly compared to baseline within groups (55.03% vs 56.53% in the control group and 60.74% vs 60.76% in the ILPC group). Hence, the potential selection bias might be the reason for the LVEF improvement and beneficial effects of intralipid on cardiac function need to be concluded cautiously.

Intralipid is a safe fat emulsion and widely used as a vehicle for different drugs.[21] In the present study, there were significantly differences of the blood lipids tests (including triglyceride, total cholesterol, and low density lipoprotein) and biological measurements of renal function (including serum creatinine and blood urea nitrogen) between 2 groups at 24 hours after surgery but still in the normal range. However, the values were rather statistically significant than meeting the diagnostic criteria of dyslipidemia or renal insufficiency. Hence, similar to our previous study, a single dose of 2 mL/kg of 20% intralipid administered was found to be safe with no related adverse effects.

One important limitation of this clinical study was that it was difficult to achieve in an optimal manner of double blinding because intralipid is white emulsion. However, all patients and staff involved in the study but the investigator giving the interventions were blinded to treatment allocation. Besides, early AF recurrence had been detected in 6 (8.7%) patients, 2 patients from the control group and 4 from the ILPC group within 6 months follow-up. The rate of freedom from AF at 6 months was higher than that reported in related studies (91.3% vs 66%–74%).[1,14,26] However, the present study is a single center, assessor-blinded trial without Holter for monitoring recurrent AF after ablation, which might have result in missing some patients with asymptomatic AF recurrence in nonfollow-up day. This limitation and the small number of patients might be the reason for the low recurrence of AF. In addition, results of the present study did not measure the level of inflammatory mediators such as IL-6 and hs-CRP, and cannot demonstrate a correlation between intralipid administration and myocardial injury following inflammatory mediators elevation after ablation. However, it is worth mentioning that extracorporeal circulation also has an effect on the inflammatory status, as a consequence, even though the elevation of inflammatory mediators were documented, the results would be confounded by the massive release of inflammatory mediators following systemic inflammatory response during CPB.[27]

In conclusion, there was no observed beneficial effect of intralipid before reperfusion on myocardial injury documented by the cardiac biomarkers of cTnT and CK-MB in patients undergoing valve replacement surgery with concomitant RFA, and the effect of ILPC against myocardial I/R injury is undetectable within the background of massive biomarker release following ablation as a result of the localized myocardial necrosis. Besides, there are no other published data about the cardioprotective role of intralipid in patients undergoing valve replacement surgery with concomitant ablation and benefits of this protection need further studies to validate.

5. Author contributions

All authors took part in all stages of the study, from design to writing and editing the manuscript. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

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