Cyclosporine Protects the Heart during Aortic Valve Surgery

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ABSTRACT

Background: Part of the myocardial damage occurring during cardiac surgery is a consequence of reperfusion injury. Cyclosporine, a potent inhibitor of the opening of the mitochondrial permeability transition pore, attenuates reperfusion injury in patients with acute ST-segment elevation myocardial infarction. This study investigated whether the administration of cyclosporine just before the aortic cross-unclamping would reduce myocardial injury in patients undergoing aortic valve surgery.

Methods: This study was a monocentric, prospective, randomized, single-blinded, controlled trial. Sixty-one patients, scheduled for elective aortic valve surgery, were randomly assigned (computer-generated randomization sequence) to receive either an intravenous bolus of cyclosporine (2.5 mg/kg, cyclosporine group, n = 30) or normal saline (control group, n = 31) 10 min before aortic cross-unclamping. The primary endpoint was the 72-h area under the curve for cardiac troponin I.

Results: Both groups were similar with respect to baseline characteristics and aortic cross-clamping duration. A significant 35% reduction of area under the curve for cardiac troponin I was observed in the cyclosporine group compared with the control group (242 ± 225 *vs.* 155 ± 71 arbitrary units, mean ± SD; mean difference, −86.2 ± 42.5; 95% CI, −172.3 to −0.1; $P = 0.03$). Cyclosporine beneficial effect remained significant after adjustment for aortic cross-clamping duration in each group (mean difference, −88 ± 34, 95% CI, −157 to −19; $P = 0.01$). None of the treated patients had significant side effects (odds ratio, 0.64; 95% CI, 0.16 to 2.55; $P = 0.52$).

Conclusions: Cyclosporine administration at the time of reperfusion protects against reperfusion injury in patients undergoing aortic valve surgery. The clinical benefit of this protection requires confirmation in a larger clinical trial. **(ANESTHESIOLOGY 2014; 121:232-8)**

PERIOPERATIVE myocardial infarct in patients undergoing cardiac surgery remains a challenging problem, resulting in increased morbidity and mortality.[1] During surgery under cardiopulmonary bypass (CPB), the aortic cross-clamping–unclamping induces a global myocardial ischemia–reperfusion sequence. Despite improvements in perioperative protective strategies, myocardial injury reflected through increased cardiac troponin I (cTnI) level is an independent risk factor of adverse outcomes.[2–4] Increased postoperative cTnI level is an independent predictor of 3-yr postoperative mortality.[3]

A significant part of the irreversible myocardial damage is a consequence of the reperfusion injury after prolonged ischemia, possibly through the opening of the mitochondrial permeability transition pore (PTP).[5] Cyclosporine, in addition to its immunosuppressive properties, is a potent inhibitor of PTP opening.[6] We recently demonstrated that cyclosporine, administered intravenously just before reperfusion, reduced the extent of myocardial injury in patients with acute ST-elevation myocardial infarction.[7]

What We Already Know about This Topic

- Cyclosporine, a potent inhibitor of the mitochondrial permeability transition pore, attenuates reperfusion injury in acute myocardial infarction patients
- The present study investigated whether the cyclosporine administration just before aortic cross-unclamping would reduce myocardial injury in patients undergoing aortic valve surgery in a prospective, randomized trial

What This Article Tells Us That Is New

- Cyclosporine administration at the time of reperfusion protects against reperfusion injury in patients undergoing aortic valve surgery as demonstrated by a significant reduction in cardiac troponin I compared with the control group

We hypothesized that cyclosporine, administered at the time of reperfusion in a pharmacological postconditioning protocol, would reduce myocardial reperfusion injury in patients undergoing cardiac surgery. To test this hypothesis, we performed a clinical trial evaluating whether the administration of cyclosporine at the onset of reperfusion (aortic

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cross-unclamping) could reduce the amount of postoperative cTnI release in patients undergoing aortic valve surgery.

Materials and Methods

This study was a prospective, randomized, single-blinded, placebo-controlled trial with two parallel arms conducted at the University Hospital Louis Pradel in Lyon, France. The trial was performed in accordance with the Declaration of Helsinki (revised version, 1996), the European Guidelines for Good Clinical Practice (version 11, July 1990), and French laws. The ethics committee of our institution approved the study protocol. Written informed consent was obtained from all patients before inclusion.

Study Population

Consecutive patients scheduled for aortic valve surgery, older than 18 yr, were eligible for enrollment. Patients were recruited through the preoperative anesthetics' consultation at our institution.

Exclusion criteria were emergency surgery, combined aortic valve and coronary surgery, significant coronary stenosis (>70%), left ventricular (LV) ejection fraction less than 40%, renal insufficiency (serum creatinine level ≥150 μmol/l), severe hepatic dysfunction, 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 before presentation, or preoperative treatment with nicorandil (an adenosine triphosphate–sensitive potassium channel opener), sulfonylurea (an adenosine triphosphate–sensitive potassium channel blocker), or rosuvastatine (because of pharmacokinetic interaction with cyclosporine).

Perioperative Procedure

Standard intraoperative monitoring consisted of 5-lead electrocardiogram, pulse oxymetry, frontal electroencephalography (BIS-monitor A2000®; Aspect Medical Systems, Norwood, MA), radial arterial and central venous pressure monitoring, capnography, and vesical temperature measurement.

Intravenous anesthesia was induced with etomidate (0.3 mg/kg), sufentanil (0.4 μg/kg), and cisatracurium (0.15 mg/kg) and maintained with continuous infusion of propofol (2 to 4 mg kg^{-1} h^{-1}) and sufentanil (0.5 to 1.0 μg kg^{-1} h^{-1}) as clinically required. Because of their potential myocardial postconditioning effects, halogenated volatile anesthetics were not used in this study.[8] After systemic heparinization (300 IU/kg, activated clotting time >400 s), the ascending aorta and right atrium were cannulated. A standard CPB with a disposable hollow-fiber membrane oxygenator and a roller pump (SV®, Stoeckert; Sorin Group, Munich, Germany) was started with a target output of 2.4 l min^{-1} m^{-2} of body surface area. Surgery was performed under mild hypothermia (>35°C). After aortic cross-clamping, cardioplegia was achieved with a cold (4°C) crystalloid solution. After aortic valve surgery, the heart was defibrillated after aortic unclamping if sinus rhythm did not resume spontaneously. Patients were extubated when pressure support ventilation was tolerated.

Experimental Protocol

Patients who met the enrollment criteria were randomly assigned to either control or cyclosporine group. Randomization was performed with the use of a computer-generated randomization sequence. Numbered, sealed envelopes that contained the study group assignment were opened after anesthesia induction. Patients were allocated randomly in a 1:1 ratio. There was no specific additional randomization scheme or stratification in this study.

Less than 10 min before aortic unclamping, patients in the cyclosporine group received an IV bolus injection of 2.5 mg/kg of cyclosporine (Sandimmune®; Novartis Pharma SAS, Rueil-Malmaison, France). Patients in the control group received an equivalent volume of normal saline. The dose of cyclosporine was chosen on the basis of our previous clinical study.[7] The timing of treatment administration was also concordant to Piot's study and based on the observation that the pharmacological treatment must be administered a few minutes before aortic cross-unclamping to be active (and present) at the onset of myocardial reperfusion.

Outcomes

The primary outcome was the 72-h area under the curve (AUC) for cTnI release. Secondary outcomes included extubation time, length of stay in intensive care unit (ICU) and hospital, Simplified Acute Physiology Score (the ICU scoring system measuring the severity of disease for patients admitted to ICU), and major adverse events occurring during hospitalization.[9] The study duration was limited to the hospital length of stay.

All adverse events during the hospital length of stay were collected. These adverse events were reported as follows: all-cause death, infection requiring IV antibiotic therapy, and any peri- and postintervention complications. They were reported within each group.

Biochemical and Echocardiography Analysis

Blood samples for the analysis of cTnI (ARCHITECT STAT Troponin I; Abbott, North Chicago, IL) were drawn after induction of anesthesia and 4, 8, 12, 24, 36, 48, and 72 h after aortic unclamping. The whole-blood concentration of cyclosporine was measured at ICU arrival and 24 h after aortic unclamping. Serum concentrations of creatinine and potassium were measured the day before surgery and 24, 48, and 72 h after aortic unclamping. Serum concentrations of bilirubin, γ-glutamyltransferase, and alkaline phosphatase were measured the day before surgery and 24 h after aortic unclamping.

Transthoracic echocardiography was performed in all patients before aortic valve surgery and at hospital discharge.

LV ejection fraction and LV mass index were measured during these imaging studies.

Sample Size and Statistical Analysis

Sample size calculation was performed according to the previous study by Piot *et al.*[7] Considering an expected 25% reduction in cTnI release with a statistical power of 80% and an α of 0.05 using a two-tailed test, we calculated a total sample size of 60 patients (30 per group). All analyses were performed by an independent expert unaware of the allocated treatment group.

The results are expressed as mean ± SD or median and interquartile range, depending on normal distribution as assessed by the Shapiro–Wilks test. There were no changes made to the primary outcome that was set to be the AUC for cTnI, at the beginning and end of the trial.

Statistical analyses were performed according to a modified intent-to-treat approach, to account for patient dropout as reported in figure 1.

Comparisons between both independent groups were performed using unequal-variance Student *t* test or Mann–Whitney U test for continuous variables as appropriate. Chi-square or Fisher exact tests were used as appropriate for categorical variable comparisons between groups. Because the AUC for cTnI distribution did not follow a normal distribution, we applied a data transformation with inversion according to the following formula: transformed AUC = 1/AUC. The transformed data followed a normal distribution.

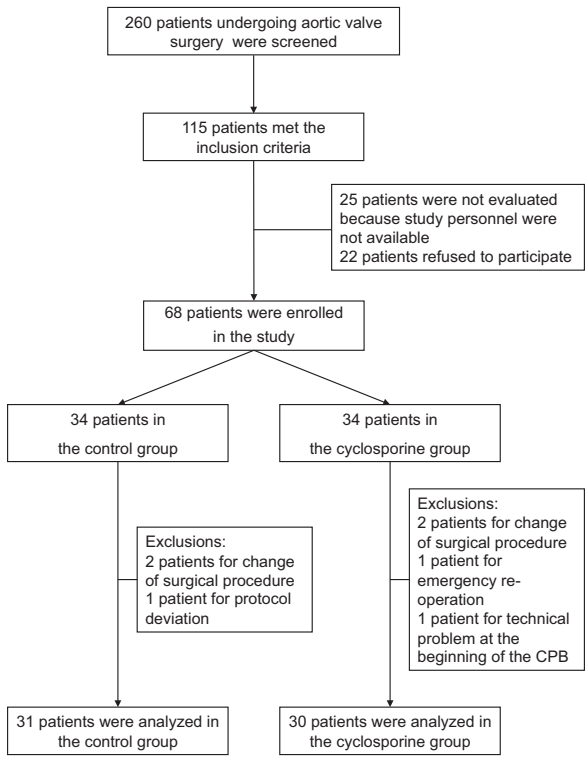

Fig. 1. Flow chart of the study population. CPB = cardio pulmonary bypass.

Comparison of AUC data was performed with a Student *t* test on the transformed data; however, for comprehension purposes, we left results expressed in terms of nontransformed AUC values.

The correlation between aortic cross-clamping duration and 72-h AUC for cTnI was performed using the Spearman test. To assess the effect of cyclosporine after adjustment for potential confounders, a multiple regression analysis was performed with treatment modality as a fixed factor and adding aortic cross-clamping duration, age, sex, body mass index, and LV mass in the model.

The differences in adverse event rate between the two study groups were assessed by univariate logistic regression analysis. All adverse events (all-cause death, infection requiring IV antibiotic therapy, and any peri- and postintervention complications) were reported within each group and added in a single clinical adverse event composite endpoint. Results were considered statistically significant at a *P* value less than 0.05. Statistical analyses were done using statistical software STATA SE 11.2 (StataCorp., College Station, TX). All authors have read and agreed to the article as written.

Results

Characteristics of the Study Population

From November 2008 to December 2012, 260 patients underwent aortic valve surgery in our institution; 115 of these patients met the inclusion criteria. Among them, 68 patients were enrolled in the study. After randomization, seven patients were excluded. Data are presented for 61 patients (fig. 1).

There were no missing data. No significant difference was seen between groups at baseline (table 1). Preoperative echocardiography showed no difference between groups regarding LV mass index. Intraoperative data such as CPB duration, aortic cross-clamping duration, and volume of cardioplegia were comparable (table 2).

After aortic cross-unclamping, spontaneous defibrillation occurred in a similar manner between groups. Weaning from CPB was easy in all patients, without any inotropic support necessity. Total amounts of anesthetics were similar between the two study groups (table 2).

Postoperative Myocardial Injury

The mean 72-h AUC for cTnI release after aortic unclamping was 242 ± 225 arbitrary units in the control group and was reduced to 155 ± 71 arbitrary units in the cyclosporine group (fig. 2). This protection afforded a significant 35% reduction of this surrogate marker of infarct size (mean difference, −86.2 ± 42.5; 95% CI, −172.3 to −0.1; $P = 0.03$).

There was a significant correlation, in the whole study population, between the 72-h AUC for cTnI release and the aortic cross-clamping duration ($R = 0.59$, $P < 0.0001$).

Multivariate analysis showed that the beneficial effect of cyclosporine on cTnI release remained significant after

Table 1. Baseline Patient Characteristics

Characteristics	Control Group (n = 31)	Cyclosporine Group (n = 30)	*P* Value
Age (yr)	62 ± 12	67 ± 11	0.13
Sex (M/F)	21/10	20/10	1
Body mass index	27 ± 5	28 ± 4	0.47
NYHA class	2.1 ± 0.5	2.0 ± 0.5	0.30
Logistic EuroSCORE (%)	3.4 ± 2.0	4.3 ± 2.3	0.11
LV ejection fraction (%)	64 ± 8	64 ± 13	0.95
LV mass index (g/m^2)	146 ± 38	146 ± 68	0.97
Creatinine clearance (ml/min)	92 ± 30	81 ± 28	0.15
Hypertension	13 (42)	11 (37)	0.79
Smoking	10 (32)	9 (30)	1
Dyslipidemia	11 (35)	13 (43)	0.61
Diabetes	2 (6)	4 (13)	0.42
Concomitant medications at inclusion			
β-blockers	7 (23)	7 (23)	1
Statins	8 (26)	11 (37)	0.42
Ca^{2+} channel blockers	3 (10)	4 (13)	0.71
ACE inhibitor/AR blocker	8 (26)	11 (37)	0.42
Diuretics	10 (32)	10 (33)	1
Platelet inhibitors	5 (16)	8 (27)	0.36
Insulin	2 (6)	0 (0)	0.49

Data are mean ± SD or number (%). Baseline characteristics were comparable between control and cyclosporine groups. Comparisons between continuous variables were performed with the use of unequal-variance Student *t* tests. Categorical variables were compared with Fisher exact or chi-square tests.

ACE = angiotensin-converting enzyme; AR = angiotensin II receptor; Logistic EuroSCORE = predicted mortality according to the logistic EuroSCORE; LV = left ventricular; NYHA = New York Heart Association.

adjustment for aortic cross-clamping duration (β = −88.0; 95% CI, −157 to −19; *P* = 0.01). The effect of cyclosporine on cTnI release remained significant after further adjustment on age, sex, and LV mass index (β = −113.3; 95% CI, −206.5 to −20.0; *P* = 0.02).

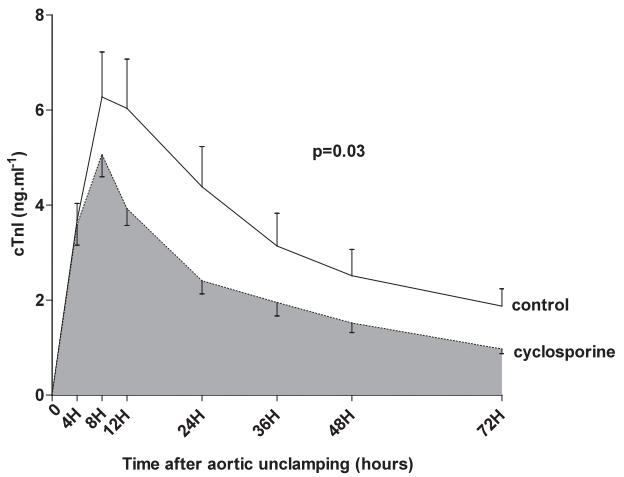

Fig. 2. Assessment of myocardial reperfusion injury by the 72-h area under the curve for cardiac troponin I (cTnI) release measurement. Cyclosporine administration resulted in a 35% reduction of myocardial reperfusion injury (*P* = 0.03). *T bars* denote SD.

Table 2. Intraoperative and Postoperative Patient Characteristics

Characteristics	Control Group (n = 31)	Cyclosporine Group (n = 30)	*P* Value
CPB duration (min)	68 ± 23	68 ± 22	0.98
Aortic cross-clamping duration (min)	54 ± 20	54 ± 19	0.94
Volume of cardioplegia (ml)	1,108 ± 405	1,083 ± 350	0.80
Surgery			
Aortic valve replacement	25 (81)	24 (80)	0.87
Bentall or David	6 (19)	6 (20)	
Total IV sufentanil (μg)	98 ± 36	105 ± 35	0.32
Total IV propofol (mg)	1,385 ± 507	1,287 ± 506	0.44
Extubation time (h)	5.1 ± 2.1	5.9 ± 2.7	0.19
SAPS II	22 ± 6	23 ± 6	0.37
LV ejection fraction (%)*	58 ± 11	60 ± 13	0.58
Creatinine clearance (ml/min)†	96 ± 31	90 ± 35	0.43
ICU LOS (h)	27.5 ± 20.5	28.1 ± 21.3	0.92
Hospital LOS (d)	9.2 ± 2.2	10.6 ± 4.2	0.12

Data are mean ± SD or number (%). Intraoperative and postoperative characteristics were comparable between control and cyclosporine groups. Comparisons between continuous variables were performed with the use of unequal-variance Student *t* tests. Categorical variables were compared with Fisher exact or chi-square tests.

* At hospital discharge. † At 72 h postoperatively.

CPB = cardio pulmonary bypass; ICU = intensive care unit; IV = intravenous; LOS = length of stay; SAPS II = Simplified Acute Physiology Score.

Other Endpoints

The whole-blood concentration of cyclosporine averaged 1,145 ± 487 ng/ml 1 h after aortic cross-unclamping and decreased to 78 ± 26 ng/ml 24 h later. None of the treated patients had significant side effects during or after the administration of cyclosporine. Biological measurements, such as bilirubin, γ-glutamyltransferase, or alkaline phosphatase, did not significantly differ between groups. Similarly, there was no creatinine clearance alteration between pre- and postoperative period, indicating that cyclosporine was well tolerated. In the postoperative period, the severity score of patients in the ICU, as assessed by the Simplified Acute Physiology Score, was comparable in the two groups (table 2).[9] Extubation time and ICU or hospital length of stay did not differ between groups. LV function, assessed by transthoracic echocardiography at hospital discharge, did not display any difference between groups (table 2). Adverse events occurred similarly in the two groups:

-sepsis with bronchitis and antibiotherapy: two cases in each group;
-pneumothorax: two cases in control group;
-sternal instability with reoperation necessity: one case in cyclosporine group;
-postoperative atrioventricular block: two cases in control group and one case in cyclosporine group.

One cyclosporine-treated patient died 3 days after surgery because of a complete atrioventricular block together with a temporary external pacing dysfunction. There were no significant differences between groups in the combined adverse event rate (odds ratio, 0.64; 95% CI, 0.16 to 2.55; $P = 0.52$).

Discussion

In this randomized controlled trial, cyclosporine IV administration 10 min before aortic cross-unclamping induced a statistically significant 35% reduction of the 72-h AUC for cTnI release in patients undergoing aortic valve surgery.

This is, to our best knowledge, the first study demonstrating the postconditioning effect of cyclosporine during cardiac surgery. Perioperative myocardial infarct remains a challenging problem resulting in postoperative cardiac morbidity and mortality. The amount of cTnI, an appropriate marker for the diagnosis of perioperative myocardial ischemia, is clearly an independent risk factor for adverse outcomes after cardiac surgery.[3,4]

The necessity of aortic cross-clamping induces a global myocardial ischemia–reperfusion injury, which is already attenuated by usual cardioprotective strategies such as cardioplegia and myocardial hypothermia. Patients scheduled for aortic valve surgery represent a relevant population to evaluate the detrimental effect of the aortic cross-clamping and the protective effect of a postconditioning-like intervention.[10]

Our patient population did not display any clinically significant coronary artery disease. Therefore, unlike coronary artery bypass grafting or mitral valve surgery, no direct myocardial damage (and subsequent confounding cTnI release) could be caused by surgery itself. One may question whether myocardial hypertrophy, often present in severe aortic stenosis, might facilitate subendocardial ischemia and enhance tissue damage after aortic cross-clamping. Echocardiography showed no statistically significant difference between the two groups regarding LV mass index, indicating that LV hypertrophy was not the reason for the difference in cTnI release in this population.

The current data also confirmed that aortic cross-clamping duration is a major determinant of myocardial injury. We observed a statistically significant correlation between the AUC of cTnI release during 72 h after surgery and the duration of global ischemia. This is in keeping with the observation that regional myocardial ischemia duration is a critical determinant of infarct size in experimental preparations.[11] Experimental evidence further suggests that ischemia duration also influences the protection afforded by ischemic postconditioning.[12–14] The current study suggests that it may also be true with cyclosporine pharmacological postconditioning.

Cyclosporine inhibits the PTP, a nonspecific channel situated in the inner mitochondrial membrane, by preventing the calcium-induced interaction of cyclophilin D with a pore component.[6] The PTP remains closed throughout ischemia, but opens at the time of reperfusion, triggered by mitochondrial calcium overload and overproduction of reactive oxygen species.[15,16] The opening of the PTP results in the membrane potential collapse, respiratory chain uncoupling, efflux of proapoptotic factors such as cytochrome c, and adenosine triphosphate hydrolysis. To date, the PTP precise molecular identity has not been elucidated, but cyclophilin D was shown to be a key component of this channel. Argaud *et al.*[17] demonstrated in an experimental model that cyclosporine inhibits PTP opening and prevents myocardial reperfusion injury after ischemia–reperfusion.

We previously demonstrated that the IV administration of cyclosporine immediately before reperfusion statistically significantly reduces the infarct size in patients with acute ST-elevation myocardial infarction.[7] The current study, based on a different pattern of myocardial injury occurring in a nonbeating model of CPB surgery, demonstrated a statistically significant 35% reduction of cTnI release. This difference remained significant after adjustment for aortic cross-clamping duration. This is concordant with results obtained in patients with ST-segment elevation myocardial infarction where cyclosporine given at the time of reperfusion significantly reduced the final infarct size, after adjustment for the myocardial area at risk's size.[7] It is worth noting that the 35% AUC for cTnI reduction observed with cyclosporine here in aortic valve surgery is similar to the infarct size reduction obtained in patients with ST-segment elevation myocardial infarction using either cyclosporine injection or angioplasty postconditioning induced by repeated inflation and deflation of the angioplasty balloon at the onset of coronary reperfusion.[7,18,19] This observation suggests that this reduction may correspond to the amount of irreversible damage due to reperfusion as compared with that due to ischemia.

Although our current study was not powered enough to evaluate the long-term benefit of cyclosporine, our previous study evaluating postconditioning in patients with ST-segment elevation myocardial infarction afforded persistent infarct size limitation at 6 months after treatment.[18,20] The question whether cyclosporine could afford similar beneficial effect in surgical conditions is still open and will need further analysis.

Another finding of our study is that a single dose of 2.5 mg/kg of cyclosporine administered at the time of reperfusion was safe during this short-term postoperative period. When compared with the control group, none of the treated patients had abnormal postoperative events or exhibited detectable signs of kidney toxicity. There are no clinical data showing that cyclosporine administered during cardiac surgery has a negative effect on the myocardium. This observation is concordant with our previous study in patients with ongoing acute myocardial infarction demonstrating that administration of a single dose of cyclosporine did not have any detrimental effect on LV remodeling.[7,21]

The principal limitation of this study was the small number of patients which does not allow us to perform powerful

analysis of long-term clinical benefit of cyclosporine. In addition, precise evaluation of myocardial oxygenation, such as blood gas analysis in the coronary sinus effluent at reperfusion, was not possible in this study. Even if CPB was conducted in the same way in all groups, we cannot exclude that these missing data could interfere with our results. Finally, the current study was not a double-blinded trial.

Another point of interrogation is the alternative treatments such as intralipid, which recently demonstrated a more effective protective effect, compared with cyclosporine, in experimental conditions.[22]

In summary, our study evaluated the effect of a single dose of cyclosporine in patients undergoing aortic valve surgery. The administration of cyclosporine before aortic cross-unclamping was well tolerated and associated with a significant reduction in postoperative cTnI release. These data and their clinical relevance require confirmation in a larger clinical trial.

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Competing Interests

The authors declare no competing interests.

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