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A Practical and Effective Approach for the Prevention of Ischemia-Reperfusion Injury after Acute Myocardial Infarction: Pressure-Regulated Tepid Blood Reperfusion

Ozer Selimoglu, MD, Murat Basaran, MD, Hamiyet Ozcan, MD, Eylul Kafali, MD, Murat Ugurlucan, MD, Cuneyt Ozcelebi, PhD, Noyan Temucin Ogus, MD

Cardiovascular Surgery Clinic, Goztepe Safak Hospital, Istanbul, Turkey

ABSTRACT

Background. The prevention of perioperative ischemia-reperfusion injury is of critical importance, and this issue becomes more important in patients undergoing an early emergent revascularization procedure after an acute myocardial infarction. In this study, we sought to test the hypothesis that our simplified pressure-controlled initial reperfusion technique would be protective against ischemia-reperfusion injury in this subgroup of patients.

Methods. The data of 20 patients (group I) who underwent an emergent coronary artery bypass grafting procedure were analyzed and compared with the results of 37 patients (group II) underwent an innovative reperfusion technique. In group I patients, the operation was carried out using standard techniques. In group II, after the completion of all anastomoses, reperfusion was initiated before rewarming with a pressure of 20 to 25 mmHg and continued for a 2-minute period. Systemic blood pressure was then gradually increased to 40 mmHg and the aortic root was perfused at this pressure for another 2-minute period. Following the completion of the second low-pressure reperfusion period, cardiopulmonary bypass flow was regulated to preoperatively calculated values until systemic temperature reached 37°C.

Results. Both groups showed significant differences in terms of cardiac output, arrhythmia rates, and biochemical parameters. Spontaneous sinus rhythm recurred more frequently in group II ($P < .01$, 86% versus 45%). Atrial fibrillation attacks were observed in 5 and 3 patients in groups I and II, respectively. All patients were medically converted to sinus rhythm with amiadarone and/or β-blockers. Persistent electrocardiographic changes indicating postoperative myocardial infarction occurred in 5 patients in group I and in 1 patient in group II ($P = .003$). Postoperative enzyme levels were found to be lower in group II patients and the differences became statistically significant at the end of 24 hours.

Conclusion. These results indicate that our controlled initial reperfusion technique is effective in the prevention of ischemia-reperfusion injury. We advocate the use of this innovative technique as an alternative to complex controlled aortic root reperfusion with the guidance of the early promising results of this study.

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Correspondence: Murat Basaran, Fahrettin Kerim Gokay Caddesi, Goztepe Safak Hastanesi, Kadikoy, Istanbul, Turkey; 90216-565-44-44; fax: 90216 44-99-133 (e-mail: dr_murat_basaran@yahoo.com).

INTRODUCTION

In recent years, great advancements have been made in the management of cardiac patients and surgical outcomes have constantly improved. However, despite the increasing number of cardiac centers reporting better results over the last decade, an early emergent revascularization procedure after an acute myocardial infarction (MI) is still perceived to be a major and important risk factor for operative morbidity and mortality. In this subset of patients, immediate survival is decreased because of the risk of perioperative ischemia-reperfusion injury. Therefore, every attempt has been focused on the prevention of this complication, and various studies have evaluated the efficacy of different methods in achieving myocardial protection in this subset of patients [Yan 1985; Li 1998; Fogelson 2000; Holman 2000; Davies 2005]. On the basis of current understanding of the pathogenesis of reperfusion injury, numerous therapies have been proposed to reduce infarct size and improve ventricular function. Most research on this issue is usually related to controlled reperfusion models and the effects of enriched solutions. However, the need for additional supplements and technical difficulties encountered in the perioperative period may attenuate the application of these techniques in clinical practice. Another controversial issue arises from the question of optimal timing for surgical intervention. In the current surgical era, there is a general tendency of deferring coronary artery bypass grafting procedure after an acute MI because of disappointing results associated with an early revascularization procedure [Edwards 1990; Schlensak 1999]. However, there is an important group of patients still requiring an emergent operation after an acute MI because of the presence of critical stenosis in other myocardial territories. Therefore, in the clinical practice, we need more practical methods affording myocardial protection without requiring complex technical equipments. In this report, we present our novel method of controlled initial reperfusion technique and

sought to test our hypothesis that our technique would be protective against ischemia-reperfusion injury in patients undergoing an emergent coronary artery bypass grafting procedure.

MATERIALS AND METHODS

Fifty-seven consecutive patients who had been emergently operated following an acute MI between April 1999 and April 2005 were included in this prospective study. The institutional ethics committee approved the clinical study, and informed consents were obtained from each patient or family. The patients included in the study were randomly divided into 2 groups: group I (n = 20) patients did not receive a special protocol during the entire reperfusion period and group II (n = 37) patients received a simplified controlled initial reperfusion. Preoperative demographic data of all patients are summarized in Table 1.

Anesthesia

All patients received 5 mg of oral diazepam and intramuscular midazolam (0.1 mg/kg) for premedication. Intravenous lines and radial artery catheters were placed, and all patients were monitored by the BIS Monitoring System (A-2000 Bispectral Index; Aspect Medical Systems, Newton, MA, USA). Induction of anesthesia was achieved with intravenous fentanyl (3 μg/kg), propofol (2 mg/kg), and vecuronium (0.1 mg/kg). Intermittent boli of fentanyl and continuous inhalation anesthetics (isoflurane, rate of 4 L/min in oxygen) were used for maintenance.

All operations were performed through a standard median sternotomy incision with aortic and 2-stage venous cannulations. Heparin was given at a dose of 300 IU/kg to achieve a target activated clotting time of 480 seconds or more. The coronary sinus was also cannulated to give retrograde cardioplegia and draw blood samples during the operation.

Table 1. Demographic Data of the Patients

	Group I	Group II
Age range, y	57-71	37-74
Age mean, y	62 ± 4.4	66 ± 5.6
Male	14 (70%)	27 (73%)
Hemodynamically stable	7 (35%)	16 (43%)
Hemodynamically unstable	2 (10%)	4 (10.8%)
Previous ventricular fibrillation	2 (10%)	6 (16.2%)
Preoperative IABP	1 (5%)	4 (10.8%)
Preoperative inotropic support†	3 (15%)	5 (13.5%)
One-vessel disease	2 (10%)	3 (8.1%)
Two-vessel disease	2 (10%)	3 (8.1%)
Triple-vessel disease	16 (80%)	31 (83.7%)
Left main disease‡	2 (10%)	4 (10.8%)
Mean left ventricle performance score	18 ± 4.9	18.4 ± 5.3
Severe LVD§	3 (15%)	6 (16.2%)

*IABP indicates intra-aortic balloon pump; LVD, Left ventricular dysfunction.

†Requirement of inotropic support more than 8 μg/kg per minute.

‡Left main disease >85%.

§Ejection fraction <25%, CK-MB levels >25 UI.

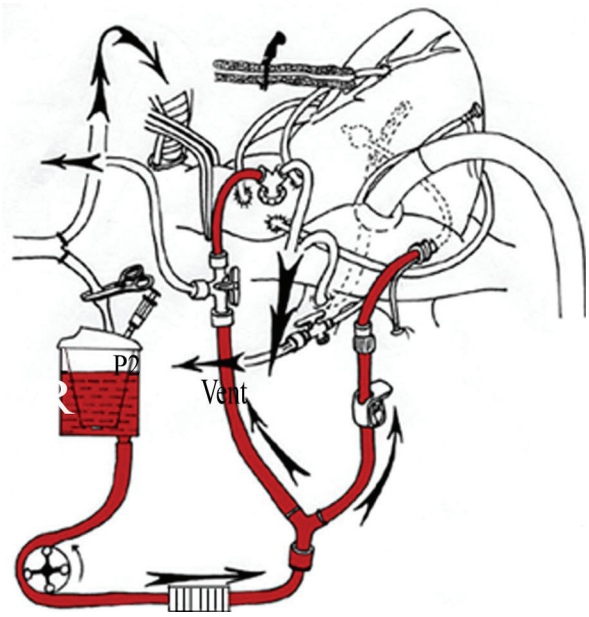
All procedures were carried out under aortic cross clamping at moderate hypothermia (28°C). The cardiopulmonary bypass (CPB) circuit was primed with 1 L of Ringer's lactate solution, 150 mL of 20% mannitol, and packed red blood cells calculated to provide a hematocrit value of >20% during cooling and 25% during rewarming periods. A level of hematocrit below these levels suggested blood transfusion. Management of CPB included systemic temperature drift to 28°C, α-stat pH management, targeted mean perfusion pressure between 50 and 80 mmHg, and pump flow rates of 2.0 to 2.4 L/min^{-1} per m^{-2}. A standard CPB circuit consisting of a pulsatile function roller, perfusion cardiopulmonary pump, and a hollow fiber membrane oxygenator was used. To induce cardiac arrest, all patients had 20 mL/kg^{-1} of isothermic blood cardioplegia given in an antegrade fashion via an aortic root cannula (Medtronic, Minneapolis, MN, USA). Induction cardioplegia solution consisted of isothermic blood, potassium chloride (30 mEq/L), sodium bicarbonate (10 mEq/L), and diltiazem (5 mg/L). In all patients, maintenance of cardiac arrest was achieved with retrograde blood cardioplegia consisting of isothermic blood, potassium chloride (6-10 mEq/L), sodium bicarbonate (5 mEq/L), and diltiazem (5 mg/L). A reservoir made of a 1000-mL crystalloid cardioplegia bag was filled with blood obtained with the aid of a Y line from the aorta. Perfusate additions were mediated with a stop-cock attached to this bag. Our experiences reveal 30 mmHg pressure could be obtained in the coronary sinus by hanging the cardioplegia bag 70 cm over the patient's chest, and we did not apply any coronary pressure measurements during retrograde cardioplegia application.

All patients underwent left internal thoracic artery for left anterior descending artery bypass, and remaining coronary revascularizations were performed with autologous saphenous vein grafts. The left internal thoracic artery was prepared following urgent initiation of CPB in patients transferred to the operating theater with cardiac failure.

In both groups, both distal and proximal anastomoses were performed with a continuous suture technique while the aortic cross clamp was still on. In group I, the aortic cross clamp was removed following the completion of the proximal anastomosis. Perfusion and rewarming was continued until body temperature reached 37°C, while group II patients received controlled initial reperfusion at tepid temperatures (28°C). After the operation, all patients were transferred to the intensive care unit and extubated under optimal parameters. Anesthetic medications were not reversed and left to spontaneous metabolization. Intramuscular injections were avoided to prevent interference with cardiac enzyme levels.

Reperfusion Technique in Group II

After the termination of all anastomoses, the aortic cross clamp and bulldog clamp on the left internal mammarian artery were removed while the temperature was still 28°C, and the first reperfusion period was initiated with a pressure of 20 to 25 mmHg. The first reperfusion period continued for a



Schematic drawing of the controlled reperfusion technique. The aortic cross clamp and bulldog clamp on the left internal mammarian artery are removed while the temperature is still 28°C. The first reperfusion period was initiated with a pressure of 20 to 25 mmHg. The first reperfusion period continued for a 2-minute period at this low pressure. Then, systemic blood pressure was gradually increased to 40 mmHg and the aorta was perfused at this pressure for another 2-minute period.

2-minute period at this low pressure. Systemic blood pressure was then gradually increased to 40 mmHg and the aorta was perfused at this pressure for another 2-minute period. Following the completion of the second low-pressure reperfusion period, CPB flow was regulated to a preoperatively calculated value until systemic temperature reached 37°C. During this period, the heart chambers were relatively free from circulation and hypothermic diastolic arrest was continued or 5 to 6 low-rate depolarization and poor contractions per minute might have occurred. Ventilation did not start immediately after the removal of the aortic cross clamp in order to avoid volume overload of the left ventricle; no patients required left ventricular venting. Ventricular fibrillation occurred rarely, and if it occurred, we reversed to diastolic arrest or low-intensity hypothermic-bradycardic contractions with defibrillation. After initiation of rewarming, both heart rate and strength of contractions increased gradually . The time until the optimum heart rate and strong contractions were achieved was recorded as the "recovery period". A schematic of the application of the technique is shown in the Figure.

Measured Parameters

(1) Two hours before the operation and at postoperative 24th, 48th, and 96th hours, SGOT, LDH, CK, and CK-MB levels were measured.

(2) After the removal of the aortic cross clamp, at the end of reperfusion period, and at the end of the recovery period, calcium, pO_2, pCO_2, O_2 saturation, and pH levels (Nova Stat Profile 9; Nova Biomedical, Waltham, MA, USA) were measured from coronary sinus and systemic arterial blood samples.

(3) The incidence of ventricular fibrillation until the end of the recovery period was recorded.

(4) The time interval until achieving normal sinus rhythm and strengthened cardiac contractions was recorded (time required for the completion of recovery period).

(5) Inotropic support and/or intra-aortic balloon pump requirements at the end of weaning from CPB were recorded.

(6) Pulmonary capillary wedge pressure at the end of weaning from CPB and in the intensive care unit at the postoperative 2nd and 24th hours was measured.

Statistical Analysis

Data are expressed as mean ± standard error of the mean, and categorical variables are reported as percent. Results of the groups were compared with the Student *t* test and significance was measured with Tukey's significance method. A *P* value of <.05 was considered significant and a *P* value of <.001 was considered highly significant.

RESULTS

Mean time interval between acute MI and surgical intervention did not differ between the 2 groups (2.1 ± 0.5 days versus 1.9 ± 0.3 days, *P* = .3). Intraoperative and postoperative findings are shown in Table 2. Mean aortic cross-clamp and CPB times and mean number of anastomosis were not statistically different. Ventricular fibrillation during reperfusion and after rewarming occurred more frequently in

Table 2. Intraoperative and Postoperative Data of Both Groups*

	Group I	Group II	*P*
Mean aortic cross-clamp time, min	38 ± 15	40 ± 11	ns
Mean CPB time, min	73 ± 27	84 ± 38	ns
Mean number of anastomosis	3.4 ± 0.8	3.5 ± 0.6	ns
VF in 2 minutes of reperfusion	5 (25%)	2 (5.4%)	.01
VF after rewarming	8 (40%)	4 (10.8%)	.02
Spontaneous sinusal rhythm	9 (45%)	32 (86.4%)	<.01
Inotropic support	8 (40%)	7 (18.9%)	.03
IABP support	4 (20%)	1 (2.7%)	.01
ECMO support†	2(10%)	—	—
ECG abnormality‡	6 (30%)	1 (2.7%)	.01
Postoperative rhythm abnormality§	5 (25%)	3 (8.1%)	ns
Mortality	1 (5%)	—	—

*ns indicates not significant; CPB, cardiopulmonary bypass; VF, ventricular fibrillation; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; ECG, electrocardiogram.

†The requirement of CPB support more than 15 minutes after the completion of rewarming.

‡Conduction abnormalities, right or left bundle branch block, CK-MB elevation with R loss or pathologic Q.

§Ventricular arrhythmias, atrial fibrillation.

group I despite normothermia during and after reperfusion. Additionally, spontaneous sinusal rhythm recurrence was significantly higher in group II (86.4% versus 45%; $P < .01$). Electrocardiographic changes were evaluated as a sign of conductance system abnormality and myocardial reperfusion injury. Postoperative atrial fibrillation attacks were observed in 5 patients (25%) in group I and 3 patients (8%) in group II between the 2nd and 8th postoperative days ($P < .01$). All patients were medically converted to sinusal rhythm with amiadarone and/or β-blockers. Persistent electrocardiographic changes indicating postoperative MI occurred in 5 patients (25%) in group I and in 1 patient (2.7%) in group II ($P = .003$).

Table 3 shows the pH, O_2 saturation, pCO_2, and pO_2 blood levels obtained from the coronary sinus. Arterial blood gas samples did not significantly differ between the groups at any time. At the beginning and during the 2 minutes of reperfusion, there were nonsignificant differences; however, at the end of recovery period, pH, O_2 saturation, and pO_2 levels were found to be significantly higher in group I. Although not confirmed and speculative, we believe that this finding is related to a kind of shunt occurring in the microvascular circulation. Group I patients had increased O_2 and pO_2 levels at the coronary sinus blood samples that were a result of insufficient oxygen extraction by tissues. Serum levels of SGOT, LDH, CK, and CK-MB are presented in Table 4. There was a decrease in the postoperative enzyme levels of group II patients that reached statistical significance at the end of 24 hours in contrast to an increase observed in group I.

DISCUSSION

Although reperfusion is the prerequisite for the normalization of cardiac functions, it may itself lead to further myocardial injury. Therefore, the method of reperfusion is of crucial importance in determining the success of the emergent surgical intervention. Previous studies have documented that the initial phase of reperfusion should be gentle to avoid ischemia-reperfusion injury and hyperemia-induced myocyte edema [Okamoto 1986; Sawatari 1991; Allen 1993]. Furthermore, these studies suggested that high initial reperfusion pressure impairs the endothelial regulation of coronary vascular tone. In our animal experiment, we have previously shown that integrated cardioplegia could partially resuscitate the myocardium, and pressure-controlled reperfusion during the first 2 minutes is needed as an adjunct procedure [Us 2004]. In the light of this experience, we have developed a strategy of controlled initial reperfusion that can be used easily in clinical practice, and our results indicate that the controlled initial reperfusion with our simple method is also very effective in the prevention of ischemia-reperfusion injury.

Following reperfusion, several functional and metabolic changes occur in an acutely ischemic myocardium. When cardiomyocytes are reoxygenated after a prolonged period of energy depletion, formation of oxygen-free radicals, cytosolic calcium overload, and reactivation of energy production may lead to deleterious hypercontracture [Garlick 1987; Schlensak 1999]. Therefore, the initial reperfusion should maintain cardiac arrest and prevent this hypercontracture, allowing a brief interval during which ionic balance can recover more

Table 3. Coronary Sinus Levels of Physiologic Parameters*

	Group I	Group II	*P*
Coronary sinus levels (adjusted with body temperature)			
At the beginning of reperfusion			
pH	7.15 ± 0.14	7.05 ± 0.26	ns
O_2 saturation	66.4 ± 4.20%	67.3 ± 6.9%	ns
pCO_2	45.7 ± 4.09 mmHg	46.3 ± 3.85 mmHg	ns
pO_2	21.4 ± 3.6 mmHg	22.5 ± 3.9 mmHg	ns
A-V calcium difference	+0.26 ± 0.2 mmol/L	+0.25 ± 0.3 mmol/L	ns
At the end of 2 minutes of reperfusion after the removal of the aortic cross clamp			
pH	7.12 ± 0.19	7.17 ± 0.13	ns
O_2 saturation	50.0 ± 6.1%	51.6 ± 8.3%	ns
pCO_2	49.6 ± 4.0 mmHg	48.5 ± 5.9 mmHg	ns
pO_2	29.8 ± 5.2 mmHg	26.2 ± 4.5 mmHg	ns
A-V calcium difference	–0.2 ± 0.3 mmol/L	–0.1 ± 0.4 mmol/L	ns
After the completion of the recovery period			
pH	7.55 ± 0.18	7.36 ± 0.27	s
O_2 saturation	53.4 ± 4.5%	58.0 ± 5.0%	s
pCO_2	40.3 ± 6.8 mmHg	37.2 ± 2.4 mmHg	ns
pO_2	32.9 ± 4.0 mmHg	21.6 ± 3.1 mmHg	s
A-V calcium difference	–0.1 ± 0.2 mmol/L	–0.1 ± 0.3 mmol/L	ns

*ns indicates not significant; s, significant; A-V, the difference of ionized calcium levels between systemic arterial blood and coronary sinus.

Table 4. Preoperative and Postoperative Serum Enzyme Levels

Enzyme	Group I	Group II	*P*
SGOT, UI			
Preoperative	40 ± 4	39 ± 3	.54
2nd hour	44 ± 9	41 ± 5	.43
24th hour	56 ± 14	47 ± 8	.06
48th hour	72 ± 5	41 ± 9	.02
4th day	39 ± 16	32 ± 20	.56
LDH, UI			
Preoperative	492 ± 55	513 ± 32	.29
2nd hour	654 ± 82	627 ± 47	.22
24th hour	785 ± 172	615 ± 114	.04
48th hour	741 ± 156	543 ± 141	.03
4th day	541 ± 49	410 ± 125	.05
CK, UI			
Preoperative	584 ± 115	554 ± 92	.16
2nd hour	695 ± 139	601 ± 187	.07
24th hour	994 ± 247	812 ± 178	.05
48th hour	976 ± 196	740 ± 214	.01
4th day	632 ± 187	493 ± 230	.05
CK-MB, UI			
Preoperative	82 ± 11	79 ± 9	.37
2nd hour	98 ± 19	86 ± 21	.27
24th hour	103 ± 16	65 ± 16	.01
48th hour	86 ± 17	31 ± 12	.01
4th day	24 ± 8	26 ± 11	.40

normally during immediate reoxygenation. There are 3 main goals of controlled reperfusion [Okamoto 1986; Allen 1989; Schlensak 1999]: (1) to avoid "stunning," which occurs in almost all ischemic myocardium after aortic cross clamping and CPB; (2) to provide the optimal conditions for the recovery of myocytes exposed to reversible injury; and (3) the resuscitation and saving of myocytes that may die if left to their natural course.

Simplified pressure-controlled reperfusion has 2 main differences from the classical reperfusion method. The first difference is the use of systemic, low-pressure, and tepid blood lacking potassium. The application of the method at low temperatures was decided to decrease the automaticity of the heart and its energy demand. Furthermore, although the reperfusion periods are short, we sought to provide cerebral protection by hypothermia. Indeed, no patients developed signs or symptoms of cerebral ischemia in the postoperative period. In our technique, it is not necessary to substrate enriched solutions for reperfusion. Substrate addition usually requires additional equipment. These are emergent operations and sometimes it may not be possible to prepare these additional reperfusion systems.

Electromechanical silence during the first 2 or 3 minutes of reperfusion is important for homogenous delivery of blood. The principle of the pressure-controlled perfusion is the immediate restoration of ATP reserves during the first 2 minutes of electromechanical silence. In the simplified controlled reperfusion, electrical activities were not observed during the first 2 minutes of reperfusion and this may be related to the suppressive role of hypothermia and diltiazem. We observed diastolic arrest following 1 to 2 cardioversions in 5 patients in group II. Seldomly occurring bradycardic heart beats less than 5 to 6 beats per minute are due to hypothermia and diltiazem given directly to the coronary sinus together with cardioplegia. It has been observed that following the initiation of rewarming, regular spontaneous rhythm ensued and strength of contractions rapidly reached the maximum. Recurrence of normal sinusal rhythm and increase in the strength of contractions may be a sign of a clinical indicator of homogenous capillary flow. Thus, it is possible to state that success of recovery has a parallel relationship with the success of reperfusion [Rosenfeld 1987; Julia 1988]. Although the warming period was added to this period in group II, recovery time was significantly faster than in group I. This supports that capillary circulation has been protected during the early period of reperfusion despite initiation of tepid reperfusion in group II.

Myocytes and endothelial cells may act in different ways in case of energy depletion and reperfusion. Following reperfusion, myocytes may keep functioning properly up to an hour; however, they may end up in a process of necrosis and apoptosis during subsequent hours [Ambrosio 1989]. Ischemia followed by reperfusion produces a marked and selective impairment of endothelium-dependent responses in the coronary microcirculation [Quillen 1990]. A high-pressure reperfusion may cause endothelial cell swelling and myocyte edema, which in turn leads to compromised blood flow. Furthermore, the activated neutrophils and thrombocytes adhere to the damaged vessel wall and these events lead to microvascular obstruction [Mehta 1989; Nishida 1990; Vane 1990]. This cascade of events characterized with progressive hypoxia resulting in tissue injury is called "no re-flow phenomenon" and it presents itself as myocardial dysfunction. In our study, we did not have the opportunity to directly evaluate the endothelial cell functions. However, myocardial functions were investigated indirectly by assessing pulmonary capillary wedge pressure and inotropic agent/intra-aortic balloon pump requirement. In the postoperative period, there was a significant difference between the 2 groups in the incidence of low cardiac output. Thus, it can be easily stated that our technique is clinically effective in the prevention of no re-flow phenomenon and low cardiac output.

The optimal pressure of initial controlled reperfusion that provides homogeneous myocardial perfusion to avoid injury is a subject of considerable debate. Okamoto [1986] documented that coronary reperfusion with a pressure of 40 to 50 mmHg with normal blood provided better recovery of contractility. Li [1998] also demonstrated that in isolated pig hearts, perfusion at 40 cm H_2O provided better functional recovery, more coronary flow, less coronary vascular resistance, and lower magnitude of lactate release than perfusion at 80 cm H_2O. In the present study, therefore, we set the pressure of the initial reperfusion at 20 to 25 mmHg, and this level was associated with improved outcome in the clinical practice.

In conclusion, our results indicate that our controlled initial reperfusion technique is effective in the prevention of ischemia-reperfusion injury. We advocate the use of our innovative technique as an alternative to complex controlled aortic root reperfusion with the guidance of the promising results of the study.

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