Original Article

Limitations of Retrograde Continuous Tepid Blood Cardioplegia for Myocardial Remodeling

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Objective: We assessed potential limitations of retrograde continuous tepid blood cardioplegia (RCTBC) for myocardial remodeling, represented by hypertrophied and/or dilated myocardium in patients with severe cardiomyopathy following single aortic valve replacement.
Methods: The study was conducted on 91 patients who underwent initial single aortic valve replacement with tepid cardiopulmonary bypass (CPB) and RCTBC. Based on the postoperative maximum creatine phosphokinase (max CPK)-MB level, the patients were allocated to Group H (≥100 IU/mL) with severe cardiomyopathy or Group L (<100 IU/mL) to make intergroup comparisons of preoperative, intraoperative, and postoperative parameter values.
Results: Preoperative measurements were as follows: pressure gradient between left ventricle and aorta (ΔPG), 92.8±46.2 mmHg in Group H and 57.9±41.6 mmHg in Group L ($p<0.01$); implanted valve size, 21.0±2.2 mm in Group H and 22.8±2.2 mm in Group L ($p<0.01$); left ventricular end-diastolic volume (LVEDV), 155.7±73.3 mL in Group H and 224.3±101.5 mL in Group L ($p<0.01$). The rate of RCTBC flow rate increase did not differ between the groups (17.6% in Group H and 20.7% in Group L), while the rate of concomitant use of optional antegrade coronary perfusion was significantly lower in Group H (25%) than in Group L (37%) ($p<0.05$). Pre- and post-perfusion lactic acid levels in the myocardial protection solution measured every 30 min after aortic cross clamping were higher in Group H than in Group L.
Conclusion: The study suggests preoperative high ΔPG, small aortic root diameter, and low LVEDV, namely, concentrically hypertrophied myocardium, as risk factors for severe cardiomyopathy after RCTBC. RCTBC in patients with any risk factor should be accompanied by an increase in initial continuous perfusion flow and/or aggressive use of intermittent antegrade coronary perfusion. (Ann Thorac Cardiovasc Surg 2006; 12: 397–403)

Key words: retrograde continuous tepid blood cardioplegia, tepid cardiopulmonary bypass, aortic valve replacement, hypertrophied myocardium

Introduction

Advancements in myocardial protection techniques has made the largest contribution to improved outcomes of open heart surgery. At present, a more effective technique has been sought and discussed aggressively, especially for hypertrophied myocardium. Ten years have passed since our hospital introduced tepid cardiopulmonary bypass (CPB) and retrograde continuous tepid blood cardioplegia (RCTBC) first in 1994. Retrograde perfusion appears to provide a better subendocardial perfusion that is often affected by ischemia and to allow more reliable myocardial protection than that with antegrade perfusion in cases of severe coronary stenosis or left main trunk

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lesions. Safety of retrograde perfusion in open heart surgeries for other disorders is being established. We assessed potential limitations of RCTBC for myocardial remodeling represented by hypertrophied and/or dilated myocardium in patients with severe cardiomyopathy following single aortic valve replacement.

Methods

The study was conducted on 91 patients who underwent initial single aortic valve replacement in our hospital between January 1994 (when our hospital introduced tepid CPB with rectal temperature of 34˚C and RCTBC with myocardial protection solution of 34˚C) and March 2005. Age (mean ± standard deviation (SD)) was 61.3±11.6 years, and the male-female ratio was 2.1:1. CPB was established with blood perfusion from the ascending aorta to the superior and inferior vena cava. The ascending aorta was cannulated for antegrade infusion of myocardial protection solution, while blind cannulation of the right atrium was performed for retrograde coronary sinus infusion of myocardial protection solution. After aortic cross clamping, 700–1,000 mL of blood glucose-insulin-potassium (GIK) solution (high K-GIK containing 25 mEq/L of potassium) mixed with blood from CPB circuits at a ratio of 7:1 (Fig. 1) was infused antegradely to induce cardiac arrest. Subsequently RCTBC was initiated with low K-GIK containing 12 mEq/L of potassium at a rate of 150 mL/min with infusion pressure (coronary vein pressure) of 15–40 mmHg. In cases where cardiac arrest was not achieved rapidly or left ventricular overextension due to valve regurgitation was suspected, RCTBC with high K-GIK was immediately initiated after cardiac arrest was achieved, RCTBC with low K-GIK was instituted. Lactic acid levels in the myocardial protection solution were measured every 30 min before and after myocardial perfusion. Lactate concentrations were determined by measuring electrons generated during the oxidation process with an electrode consisting of an amperometric electrode body and membranes including an enzyme membrane (ABL700, Radiometer Copenhagen, Denmark), as shown below. The generated current is proportional to lactate concentrations in the sample. The limits of determination are 0–30 mmol/L (i.e., 0–270 mg/dL).

$$\text{Lactate} + O_2 + H_2O \rightarrow \text{pyruvate} + H_2O_2$$
$$H_2O_2 \rightarrow 2H^+ + O_2 + 2e^-$$

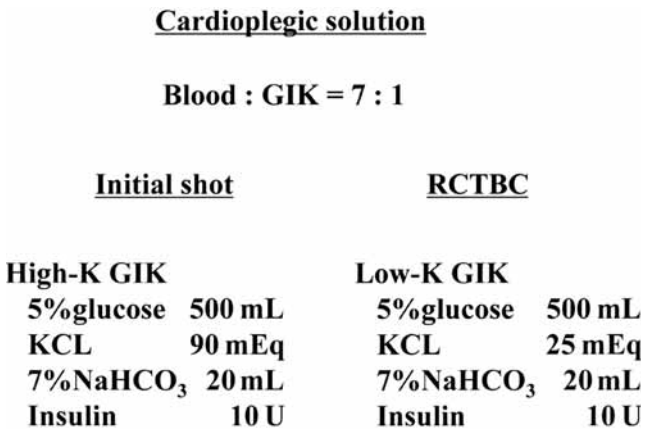

Fig. 1. Composition of myocardial protection solution.
We used GIK solution mixed with blood from cardiopulmonary bypass circuits at a ratio of 7:1.
GIK, blood glucose-insulin-potassium; RCTBC, retrograde continuous tepid blood cardioplegia.

When a 1-mEq/L elevation or more was noted, any of the following procedures was added: 1) a stepwise increase in RCTBC flow rates to 200 mL/min; 2) concomitant use of optional antegrade coronary perfusion (with 500 and 300 mL of GIK solution to the left and right coronary arteries, respectively); or 3) cooling down to rectal temperature of 32˚C (Fig. 2). Based on the postoperative maximum creatine phosphokinase (max CPK)-MB level, the patients were allocated to Group H (≥100 IU/mL) with severe cardiomyopathy or Group L (<100 IU/mL) to make intergroup comparisons of preoperative, intraoperative, and postoperative parameter values.

Statistical Analysis

Data expressed as the means±SD were analyzed with the Student's t test, chi-square for independence test, and Fisher's exact probability test. The level of significance was $p<0.05$.

Results

Group H consisted of 20 patients (22% of the total), of whom 15 had aortic valve stenosis and 5 had aortic valve regurgitation. Group L consisted of 71 patients (78% of the total), of whom 26 had aortic valve stenosis and 45 had aortic valve regurgitation. Preoperative measurements were as follows: pressure gradient between left ventricle and aorta (ΔPG) measured with cardiac cath-

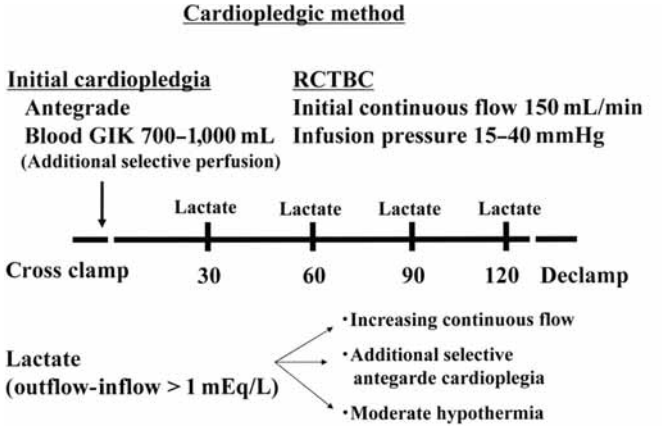

Fig. 2. Myocardial protection procedure in our hospital.
After aortic cross clamping, 700–1,000 mL of blood GIK solution (high K-GIK containing 25 mEq/L of potassium) was infused antegradely to induce cardiac arrest. Subsequently RCTBC was initiated with low K-GIK containing 12 mEq/L of potassium at a rate of 150 mL/min with infusion pressure (coronary vein pressure) of 15–40 mmHg. In cases where cardiac arrest was not achieved rapidly or left ventricular over-extension due to valve regurgitation was suspected, RCTBC with high K-GIK was initiated immediately, and after achievement of cardiac arrest, RCTBC with low K-GIK was instituted. Lactic acid levels in the myocardial protection solution were measured every 30 min before and after myocardial perfusion. When a 1-mEq/L elevation or more was noted, any of the following procedures was added: 1) a stepwise increase in cardioplegia flow rates to 200 mL/min; 2) concomitant use of optional antegrade coronary perfusion (with 500 and 300 mL of GIK solution to the left and right coronary arteries, respectively); or 3) cooling down to rectal temperature of 32˚C.
GIK, glucose-insulin-potassium; RCTBC, retrograde continuous tepid blood cardioplegia.

Table 1. Preoperative factors

	H	L	p value
Case	20	71	
Age (yr)	63.7±12.0	61.3±11.6	
Gender (M/F)	14/6	47/24	
BW (kg)	55.1±10.3	56.8±10.7	NS
BSA (m^2)	1.54±0.17	1.57±0.18	NS
Disease (S/R)	15/5	24/46	NS
Implanted valve size (mm)	21.0±2.2	22.8±2.2	<0.01
ΔPG (mmHg)	92.8±46.2	57.9±41.6	<0.01
IVSD (mm)	11.0±3.0	10.3±8.3	NS
PWD (mm)	11.0±9.0	10.8±9.0	NS
LVEDD (mm)	55.3±10.9	60.7±12.2	<0.05
LVESD (mm)	36.2±9.9	40.0±11.3	NS
LVEDV (ml)	155.7±73.3	224.3±101.5	<0.01
LVESV (ml)	58.9±47.9	84.4±54.2	NS
LVMI (g/m^2)	195.0±64.0	225.1±72.8	NS

Higher ΔPG, small aortic root diameter, and lower LVEDV were observed in Group H.
yr, years; M, male; F, female; BW, body weight; BSA, body surface area; S, aortic valve stenosis; R, aortic valve regurgitation; ΔPG, pressure gradient between left ventricular and aorta; IVSD, inter-ventricular septum dimension; PWD, posterior wall dimension; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVMI, left ventricular mass index; NS, not significant.

eterization, 92.8±46.2 mmHg in Group H and 57.9±41.6 mmHg in Group L (p<0.01); implanted valve size measured with echocardiography, 21.0±2.2 mm in Group H and 22.8±2.2 mm in Group L (p<0.01); left ventricular end-diastolic volume (LVEDV) measured with echocar-diography, 155.7±73.3 mL in Group H and 224.3±101.5 mL in Group L (p<0.01); and left ventricular mass index (LVMI) measured with echocardiography, 195.0±64.0 g/m^2 in Group H and 225.1±72.8 g/m^2 in Group L (Table 1).

The rate of RCTBC flow rate increase (number of patients with flow rate increase/total number of patients) did not differ between the groups (17.6% in Group H and 20.7% in Group L). While the rate of concomitant use of optional antegrade coronary perfusion (number of patients with concomitant use/total number of patients) was significantly lower in Group H (25%) than in Group L (37%)(p<0.05). The aortic cross clamp time was significantly longer in Group H (131.6±37.8 min) than in Group L (101.7±23.0 min)(p<0.01). No statistically significant differences were found between the groups in the aortic cross clamp release-withdrawal time (51.5±41.8 min in Group H and 40.5±22.2 min in Group L), the proportion of patients with return of spontaneous beat (50% in Group H and 57.7% in Group L), or the proportion of patients with intra-aortic balloon pumping (IABP)(5% in Group H and 4% in Group L)(Table 2). The postoperative CPK-MB level was significantly higher in Group H (282.0±178.6 IU/mL) than in Group L (37.2±21.0 IU/mL)(p<0.01).

Pre- and post-perfusion lactic acid levels in the myocardial protection solution were measured every 30 min after aortic cross clamping and were higher in Group H than in Group L, with no significant difference between the groups (Fig. 3).

Table 2. Peri- and postoperative factors

	H	L	p value
Valve (M/B)	10/10	54/16	
ACT (min)	131.6±37.8	101.7±23.0	<0.01
RCTBC flow-up (%)	17.6	20.7	NS
Additional selective perfusion (%)	25	37	<0.05
Spontaneous beat (%)	50	57.7	NS
Weaning time (min)	51.5±41.8	40.5±22.2	NS
IABP (%)	5	4	NS
Max CPK-MB (IU/mL)	282.0±178.6	37.2±21.0	<0.01

The ACT was significantly longer and the rate of concomitant use of optional antegrade coronary perfusion was significantly lower in Group H.
M, mechanical valve; B, bioprosthesis valve; ACT, aorta cross clamp time; RCTBC, retrograde continuous tepid blood cardioplegia; IABP, intra-aortic balloon pumping; max CPK-MB, maximum creatine phosphokinase-MB; NS, not significant.

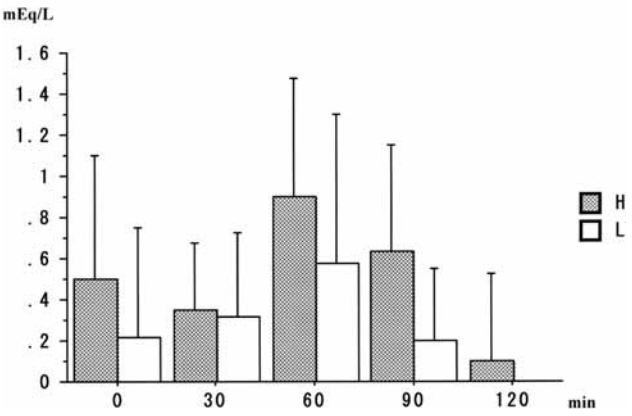

Fig. 3. Change of lactate (outflow-inflow).
Lactic acid levels in myocardial protection solution during aortic cross clamping before and after myocardial perfusion.
The levels were higher in Group H with no statistically significant difference between the groups.

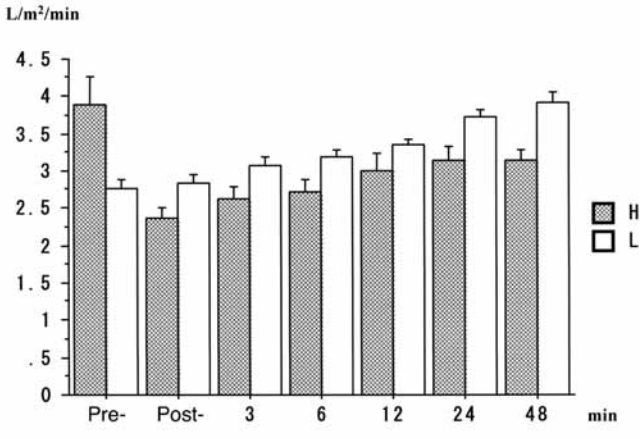

Fig. 4. Change of CI.
Time course of postoperative CIs.
The indexes immediately, 3 hours, and 6 hours after surgery decreased from baseline in Group H.
CI, cardiac index.

In Group H, cardiac indexes immediately, 3 hours, and 6 hours after surgery decreased from baseline (Fig. 4), but the cardiac function was favorably restored. However, 2 patients in Group H died in hospital early after RCTBC introduction because of postoperative low cardiac output syndrome or multiorgan failure.

When myocardial protective effects of RCTBC in the late postoperative period were assessed based on LVMI, myocardial remodeling was improved gradually even in Group H patients with severe cardiomyopathy (Fig. 5).

Discussion

Lichtenstein et al. proposed warm heart surgery based on the concepts of normothermic CPB at 37˚C and retrograde continuous warm blood cardioplegia (RCWBC) in 1991.[1] According to a report of clinical application of RCWBC by Salerno et al.,[2] our hospital has introduced normothermic CPB at 36˚C and RCWBC at 35˚C in the clinical practice since 1994. After introduction, our review of these approaches[3] revealed disadvantages such as graft vasospasm. This was attributable to vasoconstrictors used for correcting reduced systemic vascular resistance at ordinary temperature and difficulties in maintaining a favorable postoperative humoral balance with massive fluid infusion required. Menasche et al. suggested the relationship between systemic inflammatory reaction and reduced systemic vascular resistance, based on a sig-

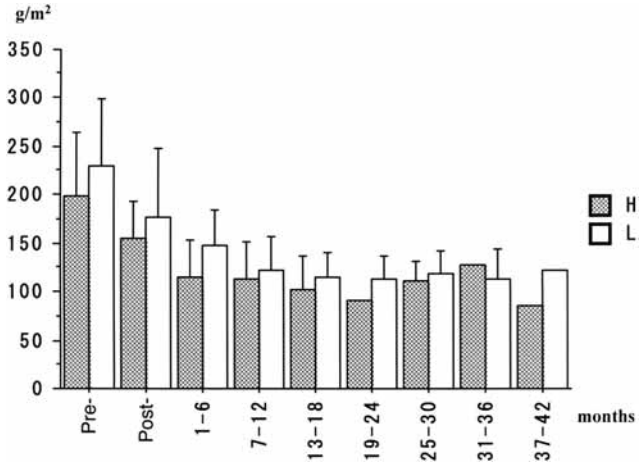

Fig. 5. Time course of LVMI.
Myocardial remodeling was improved gradually even in patients with severe cardiomyopathy.
LVMI, left ventricular mass index.

nificantly higher tumor necrotizing factor and interleukin 1 and 6 levels during normothermic CPB. It was recommended tepid cardioplegia at 34˚C, which could prevent the release of cytokines and thereby reduce vasoconstrictor be used.[4] Based on these findings, we have used tepid CPB. It was RCTBC at 34˚C since then.

While 80% of antegrade-delivered blood cardioplegia for explanted human hearts reached myocardial capillaries, 67.2% of retrograde-delivered blood cardioplegia was shunted through thebesian veins to the ventricles, and only 29.3% and 7.5% traversed the myocardium supplied by the left and right coronary arteries, respectively.[5] These results indicate some limitations of retrograde cardioplegia for right ventricular myocardial protection. Other reports suggest that the limitations can be solved with flow rate and perfusion pressure maintained at appropriate levels.[6,7] However, Tian et al. reported that retrograde cardioplegia provided significantly less myocardial capillary flow than did antegrade cardioplegia at the same perfusion rate.[8] Thus, retrograde myocardial protection requires an appropriate perfusion pressure maintained at higher flow rate than that with antegrade myocardial protection. Many studies explored optimal composition and temperature of myocardial protection solution, optimal flow rates, and optimal perfusion pressure levels.

A clinical study conducted by Yau et al. determined optimal flow rates and hemoglobin concentrations for continuous normothermic blood cardioplegia at 37˚C. This was to supply an appropriate amount of oxygen to cover myocardial oxygen consumption, using cardiac function and myocardial metabolism as indicators. It was demonstrated that continuous normothermic cardioplegia was safe when delivered at 80 mL/min or greater, with a hemoglobin concentration of at least 8.0 g/dL.[9] Ikonomidis et al. reported the necessity of at least 200 mL/min as the optimal flow rates for coronary bypass surgeries.[10] Salerno et al. reported that flow rates above 250 mL/min should not be used with consideration for coronary sinus damage, myocardial pressure-related damage, cellular edema, and intracardiac shunt.[11] They also reported that coronary vein pressure levels should not exceed a range of 40–55 mmHg.

In our hospital, RCTBC is initiated with a 34˚C myocardial protection solution perfused at a rate of 150 mL/min with infusion pressure (coronary vein pressure) of 15–40 mmHg. Lactic acid levels in the myocardial protection solution are measured every 30 min before and after myocardial perfusion. When a 1-mEq/L elevation or more was noted, any of the following procedures is added: 1) a stepwise increase in RCTBC flow rates to 200 mL/min; 2) concomitant use of optional antegrade coronary perfusion (with 500 and 300 mL of GIK solution to the left and right coronary arteries, respectively); or 3) cooling down to rectal temperature of 32˚C. Lactic acid monitoring is critical to prevent the disproportionate distribution of myocardial protection solution associated with retrograde characteristics. It is also useful for the early detection of catheter migration or intraoperative manipulation-related catheter dislodgment in the right atrium. In fact, we faced refractory arrhythmia and low cardiac output syndrome after aortic cross clamp release resulting from inadequate myocardial protection probably due to catheter misplacement. These experiences impressed the necessity of intraoperative lactic acid monitoring on us.

Usefulness of normothermic or RCTBC is shown in some reports[12–14] other than ours. In the present study, Group H patients with severe cardiomyopathy exhibited favorable time course of cardiac index despite a transient postoperative decrease and had improvements of myocardial remodeling in the late postoperative period. In the present context where safe myocardial protection with RCTBC is introduced to many cases of open heart surgery, the present study assessed the effects of RCTBC on remodeled myocardium in cases of severe cardiomyopathy characterized by volume overload-related dilated myocardium in aortic valve regurgitation patients and pressure overload-related concentrically hypertrophied

myocardium in aortic valve stenosis patients. The rate of RCTBC flow rate increase did not differ significantly between severe and non-severe cardiomyopathy patients, while the rate of concomitant use of optional antegrade coronary perfusion was significantly lower in severe cardiomyopathy patients. Lactic acid levels in the myocardial protection solution used for intraoperative monitoring were higher at each assessment point in severe cardiomyopathy patients than in non-severe patients. There was no statistically significant difference between the groups. The onset of severe cardiomyopathy in patients with mean lactic acid levels of 1 mEq/L or less suggests some difficulty with safe myocardial protection by current approaches for concentrically hypertrophied myocardium (with preoperative high ΔPG, small aortic root diameter, and LVEDV) with high coronary vascular resistance susceptible to poor subendocardial perfusion.

Menasche et al. performed retrograde cardioplegia for hypertrophied myocardium at higher flow rates.[15] Scorsin et al. reported that RCWBC with myocardial protection solution containing esmorol. This is an ultra-short-acting β-blocker, which is effective for the protection of hypertrophied myocardium.[16] Hayashida et al. reported that tepid blood cardioplegia at 29˚C reduced lactic acid production at the time of cross-clamp release and preserved postoperative left ventricular function favorably.[17] Recently, normothermic cardioplegia delivered continuous retrograde and intermittent antegrade has been applied to the clinical setting in place of a technique to induce cardiac arrest with antegrade coronary perfusion, and then maintain it with retrograde normothermic coronary perfusion alone. The combination technique is reported to reduce lactic acid production and to preserve adenosine triphosphate more effectively than the single technique.

In the present study, the rate of concomitant use of optional antegrade coronary perfusion, which has been introduced to our hospital, was low in severe cardiomyopathy patients. This finding suggests the necessity of aggressive use of optional intermittent antegrade coronary perfusion in combination with retrograde perfusion under intraoperative lactic acid monitoring for so-called concentrically hypertrophied myocardium characterized by the following preoperative parameter values: 1) high ΔPG (90 mmHg or more); 2) small root diameter (21 mm or less); and 3) low LVEDV (155 mL or less). Since lactic acid levels during aortic cross clamping were higher in severe cardiomyopathy patients than in non-severe patients with no statistically significant difference, an increase in initial continuous perfusion flow can be needed to prevent severe cardiomyopathy after RCTBC. Lactate is an anaerobic metabolite. It results from injury of the myocardium that is forced into anaerobic metabolism because of RCTBC perfusion failure. Lactate concentrations are thus regarded as an appropriate indicator of myocardial protective effects. In patients with severe cardiomyopathy, lactate concentrations tended to elevate but had no significant elevation. This finding suggests the presence of lactate that is not washed out by local circulation. The ACT should also be shortened further in patients with any of the above-mentioned risk factors.

Conclusion

The study suggests preoperative high ΔPG, small aortic root diameter, and low LVEDV, namely, concentrically hypertrophied myocardium, as risk factors for severe cardiomyopathy after RCTBC. Safe myocardial protection can be assured in most patients by maintenance of appropriate coronary vein pressure levels and flow rate control with lactic acid monitoring before and after the infusion of myocardial protection solution. However, RCTBC in patients with any risk factor should be accompanied by an increase in initial continuous perfusion flow and/or aggressive use of intermittent antegrade coronary perfusion.

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