INTERMEDIATE LUKEWARM (20°C) ANTEGRADE INTERMITTENT BLOOD CARDIOPLEGIA COMPARED WITH COLD AND WARM BLOOD CARDIOPLEGIA

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Background: **In the field of intermittent antegrade blood cardioplegia, 3 levels of temperature are commonly used: (1) cold (8°C); (2) tepid (29°C); and (3) warm (37°C). Given the 21°C spread and the metabolic changes that can occur between cold (8°C) and tepid (29°C) cardioplegia, we thought it worthwhile to test a temperature halfway between the cold and tepid levels. The aim of this study was to test the quality of myocardial protection provided by intermediate lukewarm (20°C) cardioplegia by comparing it with cold and warm cardioplegia. Protection was assessed by measuring cardiac troponin I release.** ***Methods:*** **One hundred thirty-five patients undergoing coronary artery bypass grafting were enrolled in a prospective randomized trial comparing cold (8°C), intermediate lukewarm (20°C), and warm (37°C) antegrade intermittent blood cardioplegia. Cardiac troponin I concentrations were measured in serial venous blood samples.** ***Results:*** **The total amount of cardiac troponin I released was significantly higher in the cold group (4.7 ± 2.3 μg) than in the intermediate lukewarm (3.4 ± 2.0 μg) or the warm (3.1 ± 2.7 μg) groups. The cardiac troponin I concentration was significantly higher at hour 6 in the intermediate lukewarm group (1.23 ± 0.55 μg/L) than in the warm group (0.89 ± 0.50 μg/L).** ***Conclusions:*** **Intermittent antegrade intermediate lukewarm blood cardioplegia is appropriate and clinically safe. Cardiac troponin I release suggests that intermediate lukewarm cardioplegia is better than cold cardioplegia but less effective than warm cardioplegia in low-risk patients. We therefore recommend the use of warm cardioplegia in low-risk patients. (J Thorac Cardiovasc Surg 2000;119:610-6)**

Cardiac troponin I has been shown to be a sensitive and specific marker of ischemia during heart operations,[1] and we have used it to compare different methods of myocardial protection.[2-4] Effective myocardial protection is a compromise between two opposing strategies: (1) reducing metabolic need by cardiac arrest and lower myocardial temperature and (2) increasing myocardial temperature during cardiac arrest to increase the chances of immediate recovery of cardiac function. Cold crystalloid cardioplegia obviously reduces metabolic need, but this is not sufficient to provide adequate protection.[3] Warm reperfusion, which permits immediate recovery of cardiac function, improves myocardial protection induced by cold crystalloid cardioplegia.[4] There are 3 levels of temperature commonly used in intermittent antegrade blood cardioplegia: (1) cold (8°C); (2) tepid (29°C); and (3) warm (37°C). Given the 21°C spread and the metabolic changes that can occur between cold (8°C) and tepid (29°C) cardioplegia, we thought it worthwhile to test a temperature halfway between the cold and tepid levels: 20°C blood cardioplegia. The aim of this study was to test the quality of myocardial protection provided by intermediate lukewarm (20°C) cardioplegia by comparing it with cold and warm cardioplegia. To the best of our knowledge, no study to date has reported the quality of myocardial protection provided by blood cardioplegic solution delivered at 20°C. We designed a prospective randomized study by using 3 different tem-

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peratures of blood cardioplegia: cold, from 6°C to 8°C; intermediate lukewarm, from 18°C to 20°C; and warm, from 35°C to 37°C. Delivery was intermittent and antegrade, cardiopulmonary bypass was conducted at 37°C, and a *hot shot* was performed before aortic unclamping in all 3 groups. Cardiac troponin I release was the criterion used to evaluate the adequacy of myocardial protection.

Patients and methods

Patient selection. After approval by our institutional review board, informed consent was obtained from all eligible patients. One hundred thirty-five consecutive patients (111 men and 24 women; mean age, 65 ± 9 years) scheduled for first elective coronary artery bypass grafting were enrolled in a prospective randomized trial comparing cold (6°C-8°C), intermediate lukewarm (18°C-20°C), and warm (35°C-37°C) blood cardioplegia. Not included in this study were patients with aortic incompetence, patients requiring only one distal anastomosis, patients with an ejection fraction below 0.30, patients undergoing reoperation, and patients with concomitant heart valve disease or unstable angina. The study took place over a 9-month period, during which 216 patients were not included in the study for the reasons given above. Among these 216 patients, 71 requiring isolated coronary artery bypass grafting did not satisfy inclusion criteria. An independent data manager was responsible for supervising patient registration. A randomization list of consecutive random treatment assignments had been prepared in advance. This randomization list was transferred to a series of sealed envelopes, each containing the name of the next treatment on a card. Envelopes were opened sequentially as each patient entered the trial (ie, entered the operating room). Coronary artery stenoses causing a loss of 70% or more of the cross-sectional area were considered to be significant. For the left main coronary artery, a loss of 50% was considered significant.

Operative technique. Cannulation for cardiopulmonary bypass was carried out in the usual fashion with a single-stage venous cannulation technique and active normothermia (37°C). Consequently, the patients were rewarmed immediately after the onset of the cardiopulmonary bypass. The left ventricle was vented by a catheter introduced through the right superior pulmonary vein. The route of delivery was exclusively antegrade in all groups. Cardioplegic solution was injected into the aortic root immediately after aortic crossclamping and until cardiac arrest was achieved with a minimal amount of 700 mL. A dose of 400 mL was reinjected into the aortic root after each distal anastomosis, with the exception of the last anastomosis. No additional doses of cardioplegic solution were given through the vein grafts after completion of the distal anastomosis in any group. Proximal graft anastomoses to the aorta were performed with partial occlusion of the ascending aorta.

Cardioplegia groups. Cardioplegic solution was administered with the Dideco D514 delivery set (Dideco Inc, Mirandola, Italy), which mixes and cools or rewarms oxygenated blood with a modified St Thomas' Hospital solution, to which 4 g/L potassium was added in a 3:1 dilution. The temperature of cardioplegic solution depended on the group: 6°C to 8°C in the cold group, 18°C to 20°C in the intermediate lukewarm group, and 35°C to 37°C in the warm group. A 1-minute hot shot composed exclusively of 37°C oxygenated blood with a constant flow rate of 200 mL/min was performed immediately after the last distal anastomosis, once the thoracic artery or arteries were unclamped.

Measurements of cardiac marker proteins. Serial venous blood samples were drawn just before cardiopulmonary bypass and after aortic unclamping at 6, 9, 12, and 24 hours and daily thereafter for 5 days. Cardiac troponin I concentrations were measured by using a specific immunoenzymometric assay developed by Sanofi Diagnostics Pasteur (Marne-la-Coquette France). Each standard cardiac troponin I or test sample was incubated with monoclonal antibody 8E1 for 15 minutes. After washing, enzyme activity was measured after the addition of a substrate (tetramethylbenzydine). The reaction was stopped by adding H_2So_4, and the absorbance was read at 450 nm on the status spectrophotometer. Creatine kinase isoenzyme MB (CK-MB) was measured at hour 6.

Electrocardiogram. A 12-lead electrocardiogram (ECG) was recorded preoperatively, at 2 hours, and then daily postoperatively. ECG diagnosis criteria for perioperative myocardial infarction (MI) were new Q waves of greater than 0.04 ms and a reduction in R waves of greater than 25% in at least 2 leads. Cardiac troponin I diagnosis criteria for perioperative MI were cardiac troponin I peak concentrations of greater than 3.7 μg/L and cardiac troponin I concentrations of greater than 3.1 μg/L at 12 hours or greater than 2.5 μg/L at 24 hours, as determined by Mair and colleagues.[5]

Statistical analysis. Sample sizes were calculated for a 2-sided significance level ($\alpha = .05$ and power $1-\beta = .8$) to detect a difference of 0.4 μg/L in cardiac troponin I concentration between groups. The standard deviation of measurements of cardiac troponin I was based on a previous study.[1] The number of subjects required in each group was 40. Statistical analysis was performed with BMDP statistical software (BMDP Corp, Los Angeles, Calif). One-way analysis of covariance with repeated measures (BMDP 5V) was performed to test the effect of the type of cardioplegia and time on cardiac troponin I concentration. Categoric data and quantitative variables were compared by using the χ^2 test and 1-way analysis of variance, respectively. Values are expressed as means ± standard deviation.

Results

With regard to the preoperative and operative data (Table I), randomization produced 3 equivalent groups. Two (1.5%) patients died within 30 days. Both were from the intermediate lukewarm group. One of them died of perioperative MI at hour 4, and the other died of a postoperative stroke at day 28. One patient from

Table I. *Patient profile by group*

Variable	*Cold group (n = 45)*	*Intermediate lukewarm group (n = 45)*	*Warm group (n = 45)*	P *value*
Mean age (y)	64 ± 9	66 ± 9	64 ± 9	.4
Ejection fraction	0.55 ± 0.1	0.53 ± 0.1	0.55 ± 0.1	.4
Body surface area (m^2)	1.86 ± 0.18	1.85 ± 0.15	1.86 ± 0.16	.6
Anterior preoperative MI (n)	9	9	8	.95
Inferior preoperative MI (n)	15	14	15	.95
Distal anastomoses per patients (n)	2.5 ± 0.7	2.5 ± 0.6	2.3 ± 0.6	.15
LITA used (n)	12	14	15	.8
LITA and RITA used (n)	33	31	30	.8
Saphenous vein grafts (n)	27	30	25	.5
Sequential grafts (n)	6	8	4	.5
Crossclamp time (min)	38 ± 10	37 ± 13	35 ± 12	.6
Pump time (min)	60 ± 15	61 ± 19	56 ± 16	.4
Amount of crystalloid cardioplegic solution (mL)	360 ± 100	410 ± 150	370 ± 160	.15
Postoperative peak CK-MB (IU/L)	20 ± 8	17 ± 10	17 ± 13	.5
Total amount of CTnI (μg)	4.7 ± 2.3	3.4 ± 2.0	3.1 ± 2.7	.007
Postoperative stroke (n)	1	1	0	.6
30-day mortality (n)	0	2	0	.1

Where applicable, values are expressed as mean ± standard deviation. *MI*, Myocardial infarction; *LITA*, left internal thoracic artery; *RITA*, right internal thoracic artery; *CTnI*, cardiac troponin I.

Table II. *Angiographic data*

Variable	*Cold group*	*Intermediate lukewarm group*	*Warm group*	P *value*
LMCA stenosis ≥50%				.3
No	32	38	34	
Yes	13	7	11	
LMCA stenosis ≥50%				.2
With normal RCA	7	2	8	
With diseased RCA	6	5	3	
No. of diseased vessels*				.7
1	1	3	3	
2	11	10	13	
3	20	25	18	

LMCA, Left main coronary artery; *RCA*, right coronary artery.
*Stenosis of left main coronary artery excluded.

the cold group had a transient postoperative stroke. Two patients in the 20°C group required an intra-aortic balloon pump. One of them was the patient who died of perioperative MI at hour 4. One patient randomized in the cold group was mistakenly given warm cardioplegia. This patient was analyzed in the group to which he had been randomized. The blood samples of two patients in the warm group and one patient from the intermediate lukewarm group (dead at hour 4) were not drawn. Age, sex, preoperative ejection fraction, body surface area, the average number of distal anastomoses per patient, crossclamping time, and cardiopulmonary bypass time were equivalent in all groups. At least one thoracic artery was used in all patients. Sequential grafts were performed in 6 patients in the cold group, 8 patients in the intermediate lukewarm group, and 4 patients in the warm group ($P = .5$). The repartition of coronary angiographic data did not differ from one group to the other (Table II). Fig 1 shows the time course of cardiac troponin I concentration according to the type of cardioplegia. Cardiac troponin I concentration was significantly higher in the cold group at hours 6, 9, and 12 (1.86 ± 0.97 μg/L at hour 6, 1.20 ± 0.61 μg/L at hour 9, and 0.80 ± 0.47 μg/L at hour 12) than in the intermediate lukewarm group (1.23 ± 0.55 μg/L at hour 6, 0.80 ± 0.36 μg/L at hour 9, and 0.51 ± 0.23

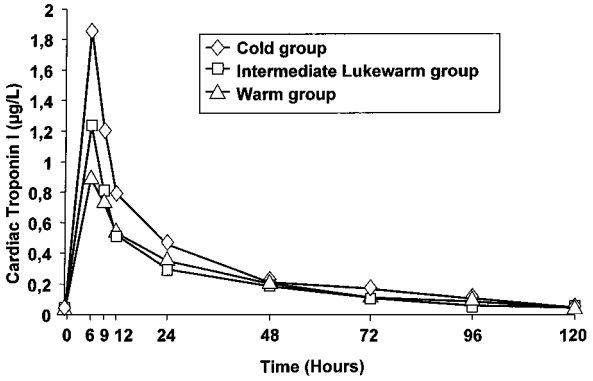

Fig 1. Time course of cardiac troponin I concentration according to type of cardioplegia. Cardiac troponin I concentration was significantly higher in the cold group at hours 6, 9, and 12 than in the intermediate lukewarm or the warm group. Cardiac troponin I concentration was significantly higher in the intermediate lukewarm group at hour 6 than in the warm group.

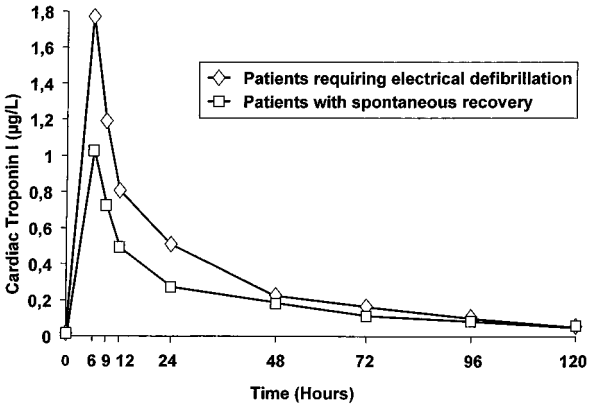

Fig 2. Time course of cardiac troponin I concentration according to cardiac rhythm recovery after aortic unclamping. Cardiac troponin I concentrations at hours 6, 9, 12, and 24 were significantly lower in patients with spontaneous return to sinus rhythm after unclamping of the aorta than in patients requiring electrical defibrillation.

µg/L at hour 12; $P < .001$ for the pattern) or the warm group (0.89 ± 0.50 µg/L at hour 6, 0.73 ± 0.60 µg/L at hour 9, and 0.54 ± 0.62 µg/L at hour 12; $P < .001$ for the pattern). Cardiac troponin I concentration was significantly higher in the intermediate lukewarm group at hour 6 (1.23 ± 0.55 µg/L) than in the warm group (0.89 ± 0.50 µg/L; $P = .005$). The total amount of cardiac troponin I released, estimated by the area under the corresponding curve (Fig 1), was significantly higher in the cold group (4.7 ± 2.3 µg) than in the intermediate lukewarm group (3.4 ± 2.0 µg; $P = .008$) or the warm group (3.1 ± 2.7 µg, $P = .005$). The total amount of cardiac troponin I released tended to be higher in the intermediate lukewarm group (3.4 ± 2.0 µg) than in the warm group (3.1 ± 2.7 µg, $P = .60$). Spontaneous return to sinus rhythm after aortic unclamping was significantly higher in the warm group (93%) than in the intermediate lukewarm group (75%, $P = .02$) or the cold group (9%, $P < .001$). Spontaneous return to sinus rhythm after aortic unclamping was related to a lower release of cardiac troponin I. The total amount of cardiac troponin I released in patients with spontaneous return to sinus rhythm after aortic unclamping was significantly lower (3.0 ± 1.75 µg) than in patients requiring electrical defibrillation (4.9 ± 2.9 µg, $P < .001$), irrespective of the group. Cardiac troponin I concentrations at hours 6, 9, 12, and 24 were significantly lower in patients with spontaneous return to sinus rhythm after unclamping of the aorta (1.0 ± 0.6 µg/L, 0.7 ± 0.4 µg/L, 0.5 ± 0.3 µg/L, and 0.3 ± 0.2 µg/L, respectively) than in patients requiring electrical defibrillation (1.7 ± 0.9 µg/L, 1.1 ± 0.6 µg/L, 0.8 ± 0.6 µg/L, and 0.5 ± 0.4 µg/L; $P < .001$ for the pattern; Fig 2).

In the intermediate lukewarm group, one patient who died had ECG evidence of perioperative MI. One patient in the warm group had cardiac troponin I evidence of perioperative MI. Thirty-seven patients in the cold group, 33 in the intermediate lukewarm group, and 36 in the warm group required no inotropic support ($P = .6$). Three patients from the cold group, 7 from the intermediate lukewarm group, and 9 from the warm group ($P = .2$) received either dopamine hydrochloride (3-5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) or dobutamine (3-5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Five patients from the cold group, 5 from the intermediate lukewarm group (including the 2 patients who required an intra-aortic balloon pump), and none from the warm group ($P = .07$) received epinephrine (0.2-0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The total amount of cardiac troponin I released was higher in patients requiring inotropic support than in patients not requiring inotropic support (4.5 ± 2.6 µg vs 3.6 ± 2.4 µg, $P = .08$). CK-MB concentration at hour 6 was equivalent in all groups.

Discussion

Most of the advantages of blood cardioplegia stated by Barner[6] are temperature dependent; they occur at 37°C and are probably less effective when the temperature is lowered. On the other hand, myocardial requirements increase as the temperature rises. Therefore the question arises as to what is the best compromise.

Three levels of temperature are commonly used in intermittent antegrade blood cardioplegia: (1) cold (8°C); (2) tepid (29°C); and (3) warm (37°C). Cold cardioplegia has been shown to impair mitochondrial state 3 respiration,[7] which is probably related to the delay of cardiac functional recovery.[8] Because we do not know at what temperature cardiomyocyte mitochondrial dysfunction begins to appear, an intermediate lukewarm cardioplegic solution needed to be tested. Given the 21°C spread and the metabolic changes that can occur between cold (8°C) and tepid (29°C) cardioplegia, we thought it worthwhile to test a temperature halfway between the cold and tepid levels. Intermediate lukewarm cardioplegia seemed likely to provide better myocardial protection than cold cardioplegia and, perhaps, warm cardioplegia. Buckberg and colleagues,[9] looking at oxygen consumption in canine hearts, suggested that cardioplegia need not be cold to be effective. However, lowering the temperature reduces oxygen consumption, and if mitochondrial energy generation is not impaired at 20°C, or at least less so than at 8°C, the result may be better myocardial protection.

Cold intermittent antegrade cardioplegia has been the benchmark for myocardial protection.[10] On the other hand, many studies[11,12] have demonstrated the interest of using antegrade intermittent warm blood cardioplegia. We therefore chose cold and warm cardioplegia to evaluate intermediate lukewarm cardioplegia. As tepid (29°C) and warm cardioplegia were likely to provide similar myocardial protection because their temperatures are very close, we thought that a comparison between 20°C and tepid cardioplegia was unnecessary. Two points led us to this opinion. First, Buckberg and colleagues'[9] results, as stated above, suggest that the difference in oxygen consumption should be very small when the temperature falls from 37°C to 29°C. This was confirmed by Hayashida and colleagues,[7] who showed that there was no significant difference in oxygen extraction and lactate or acid production between warm and tepid antegrade cardioplegia. Second, again because of the proximity of the temperatures, mitochondrial respiration preservation should be equivalent with both techniques, as confirmed by Hayashida and colleagues[8] in a second study.

Cardiac troponin I is a specific marker of myocardial damage.[13] We have already performed studies showing (1) the sensitivity of cardiac troponin I to myocardial ischemia[1,14] and (2) the interest of using cardiac troponin I to compare different methods of myocardial protection in cardiac surgery.[2-4] The aim of our present prospective randomized study was to test the quality of myocardial protection provided by intermediate lukewarm cardioplegia by comparing it with cold and warm cardioplegia and by using cardiac troponin I as the criteria for evaluating the adequacy of myocardial protection. To answer this question, we designed a study including 3 temperatures of blood cardioplegia delivery: cold, 6°C to 8°C; intermediate lukewarm, 18°C to 20°C; and warm, 35°C to 37°C. The following parameters were identical in all groups: (1) the route of delivery was exclusively antegrade; (2) delivery was intermittent; (3) cardiopulmonary bypass was conducted in active normothermia (37°C); and (4) a hot shot was performed before aortic unclamping. Cardiac troponin I release indicated that intermediate lukewarm cardioplegia provided better myocardial protection than cold cardioplegia and warm cardioplegia provided the best myocardial protection when compared with cold or intermediate lukewarm cardioplegia in an unselected group of patients undergoing an elective first cardiac operation and having preserved left ventricular function. It could be assumed that myocardial rewarming caused by normothermic bypass might impair myocardial protection in the cold and lukewarm groups. We think this is unlikely to occur because of the short time interval between two successive injections (average, 15 ± 3 minutes) and the fact that the ventricle was vented. However, because we did not measure myocardial temperature, we cannot disregard this hypothesis.

In the present study no significant differences in postoperative clinical results were found among warm, cold, and intermediate lukewarm cardiac protection with intermittent antegrade administration, except a rate of spontaneous return to sinus rhythm after aortic unclamping, which increased significantly with the 3 temperatures. However, we do not know whether spontaneous return to sinus rhythm expressed a better myocardial protection or whether electrical defibrillation resulted in an additional myocardial injury. A greater rate of spontaneous return to sinus rhythm with warm, as opposed to cold blood cardioplegia has already been reported.[15] In our series there was no significant difference in immediate postoperative dysfunction between groups, as indicated by the similar need for pharmacologic support in the three groups.

Antegrade intermittent warm and cold cardioplegia have already been compared in several studies. Calafiore and colleagues,[16] in a nonrandomized trial, showed that warm cardioplegia provided better clinical outcomes. Pelletier and colleagues[15] showed that there was no difference in clinical outcome, but that cardiac troponin T release and CK-MB mass concentration were lower in the warm group, suggesting better myocardial protection. Mezzetti and colleagues[17]

showed that warm cardioplegia protects the myocardium from ischemia-reperfusion injury better than cold cardioplegia. Conversely, Landymore and colleagues[18] showed equivalent results with both techniques. With respect to cardiac troponin I release, our data suggest that warm cardioplegia provided better myocardial protection than cold cardioplegia.

Interrupting warm blood cardioplegia is likely to lead to myocardial ischemia. Because it is often necessary to interrupt the infusion of cardioplegic solution to improve visualization of the surgical field, several studies have been performed to determine the maximum time of interruption. Yasuda and colleagues[11] showed that a 10-minute interruption was safe, whereas a 20-minute interruption caused cumulative ischemic injury in normal dog hearts. Lichtenstein and colleagues[12] showed that repeated interruptions of up to 13 minutes were unlikely to lead to adverse clinical results. For technical reasons, 4 of our patients from the warm group had an interruption of more than 20 minutes. Both the clinical outcome and cardiac troponin I release established that there was no adverse effect with one interruption of up to 23 minutes. Should more than one long interruption be needed, we think it wise to interrupt the procedure to allow another infusion.

The antegrade route of delivery may be impaired by coronary occlusions, whereas the retrograde route may be inhomogeneous. The combined route of delivery requires another set of tubing on the operating table to switch back and forth from one type of perfusion to the other. Using this technique could be cumbersome, confusing, and more time consuming while the aorta is crossclamped.[19] Our study confirmed the data from others[16] stating that the antegrade route of delivery appears sufficient for most patients. The combined route of delivery should be limited to select patients (eg, acute coronary occlusion or redo operations).

In terms of efficacy intermediate lukewarm cardioplegia appears to situate itself halfway between cold and warm cardioplegia. Cardiac troponin I release was significantly lower in the lukewarm group than in the cold group but significantly higher in the lukewarm group than in the warm group. Therefore intermittent antegrade lukewarm cardioplegia is a safe and efficacious method of myocardial protection with proven advantages when compared with cold blood cardioplegia in elective myocardial revascularization in patients with preserved ventricular function. Under these conditions, intermittent antegrade warm cardioplegia provided the best myocardial protection.

Two patients (1.5%) had a postoperative stroke, as is the average in published data. Our study did not confirm the adverse effect of normothermic cardiopulmonary bypass on neurologic outcome, as reported by Martin and colleagues[20] and denied by Engelman and colleagues.[21]

Conclusions

Intermittent antegrade intermediate lukewarm blood cardioplegia is appropriate and clinically safe. The release of cardiac troponin I suggests that intermediate lukewarm cardioplegia improved protection in low-risk patients when compared with cold blood cardioplegia. Conversely, cardiac troponin I release suggests that lukewarm cardioplegia is less effective for myocardial protection than warm cardioplegia. We therefore recommend the use of warm cardioplegia in low-risk patients.

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