Crystalloid Cardioplegia Route of Delivery and Cardiac Troponin I Release

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Background. Cardiac troponin I (CTn I) has been shown to be a marker of myocardial injury. Incomplete distribution of cardioplegic solution may be responsible for injury in jeopardized myocardial areas. The aim of this study was to compare CTn I release with respect to the route of delivery of crystalloid cardioplegia, either antegrade only or initially antegrade followed by retrograde cardioplegia for the remainder of the operation, in patients undergoing elective coronary artery bypass grafting.

Methods. Sixty patients were randomly assigned to one of two cardioplegia groups. Cardiac troponin I concentrations were measured in serial venous blood samples drawn just before cardiopulmonary bypass and after aortic unclamping at 6, 9, 12, and 24 hours and daily thereafter for 5 days. Analysis of variance with repeated measures was performed to test the effect of route of delivery, coronary disease, collateral circulation, risk of cardioplegia maldistribution, and number of grafts on release of CTn I.

Results. Compared with the antegrade route, the combined route offered no advantage in an unselected group of patients undergoing an elective first cardiac operation and having preserved left ventricular function. The CTn I concentration did not differ between groups for any of the samples considered. In patients with major left main coronary artery stenosis, CTn I release was significantly higher at hour 9 in the antegrade group than in the group with combined delivery.

Conclusions. A combined route of delivery of crystalloid cardioplegia is beneficial in patients with major stenosis of the left main coronary artery. Cardiac troponin I sensitivity is relevant in this study. Release of CTn I should be useful in determining the best form of myocardial protection for each patient.

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There are numerous strategies for intraoperative protection of the heart. Crystalloid versus blood cardioplegia, warm versus cold blood cardioplegia, antegrade versus retrograde delivery, and intermittent versus continuous perfusion are the main methods currently used. Cardiac troponin I (CTn I) has been shown to be a marker of myocardial injury [1]. Incomplete distribution of cardioplegic solution may be responsible for injury in jeopardized myocardial areas. Theoretically, CTn I should be sensitive to this injury. The aim of this study was to compare CTn I release with respect to the route of delivery of crystalloid cardioplegia, either antegrade only or initially antegrade followed by retrograde cardioplegia for the remainder of the operation, in patients undergoing elective coronary artery bypass grafting.

Patients and Methods

Patient Selection

Sixty patients (51 men and 9 women with a mean age of 63 ± 8 years) undergoing elective coronary artery bypass grafting for symptomatic disease were enrolled in this study. Patients were randomly assigned to one of two cardioplegia groups differentiated by route of administration. Coronary artery lesions causing a loss of 70% or more of cross-sectional area were considered to be major stenoses. For the left main coronary artery (LMCA), a loss of 50% was considered major. Patients with an ejection fraction of less than 0.30, those undergoing reoperation, or those with concomitant heart valve disease were not included.

Coronary collateral circulation was classified into two categories as proposed by Bruschke [2] and Hansen [3]. In patients with good collateral circulation, both collaterals and epicardial arteries distal to an occlusion or stenosis were well visualized. Conversely, in patients with poor collateral circulation, visualization of the collaterals and epicardial arteries distal to an occlusion was faint or absent.

Operative Technique

Cannulation for cardiopulmonary bypass was carried out in the usual fashion with a single-stage venous cannulation technique. Myocardial protection was achieved with cold, hyperkalemic crystalloid solution (modified St. Thomas' solution) and additional topical cooling. The left ventricle was vented by a catheter introduced through the right superior pulmonary vein. In patients assigned to the combined group, closed transatrial coronary sinus cannulation was performed as described by Arom and Emery [4]. During retrograde perfusion, coronary sinus pressure was measured through an in-line pressure

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transducer and maintained at less than 40 mm Hg by controlling the flow rate of the cardioplegic solution.

Cardioplegia Groups

Patients were randomly assigned to one of two cardioplegia groups. In the antegrade group, modified St. Thomas' solution was injected into the aortic root immediately after aortic cross-clamping and until cardiac arrest was achieved; the minimal amount was 700 mL. An additional dose of 150 mL was injected into the aortic root after each distal anastomosis except the last one.

In the combined group, 500 mL of cold cardioplegia was injected into the aortic root. The amount necessary to achieve cardiac arrest (minimum 200 mL) was given directly into the coronary sinus. An additional dose of 150 mL was injected into the coronary sinus after each distal anastomosis except the last. No additional cardioplegia was given through the vein grafts after completion of the distal anastomosis in either group.

Measurement of Cardiac Marker Proteins

Serial venous blood samples were drawn just before cardiopulmonary bypass, after aortic unclamping at 6, 9, 12, and 24 hours, and daily thereafter for 5 days. Cardiac troponin I concentrations were measured by a specific immunoenzymometric assay developed by ERIA Diagnostics Pasteur (Marne-la-Coquette, France). Each standard CTn 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. The concentration of the myocardial-specific isoenzyme of creatine kinase was measured at hour 6.

Electrocardiogram

A 12-lead electrocardiogram was recorded preoperatively, at 2 hours, postoperatively, and then daily thereafter until day 10. Diagnostic criteria for perioperative myocardial infarction (MI) were new Q waves of greater than 0.04 ms, a reduction in R waves of greater than 25% in at least two leads, and peak CTn I concentrations higher than 3.7 μg/L and a CTn I concentration greater than 3.1 μg/L at hour 12 or greater than 2.5 μg/L at hour 24 as determined by Mair and colleagues [5]. Acquired conduction defects were considered.

Statistical Analysis

The statistical analysis was performed with BMDP statistical software (BMDP Corp, Los Angeles, CA). One-way analysis of variance with repeated measures (BMDP 5V) was done to test the effect of route of delivery and time on CTn I release. Two-way analysis of variance with repeated measures was performed to test the effect of route of delivery, coronary disease, LMCA stenosis, collateral circulation, risk of cardioplegia maldistribution, and number of grafts on CTn I release. Multiple comparisons were carried out by applying the appropriate *t* test with Bonferroni's correction. Categoric data and quantitative variables were compared in Table 1 by the χ^2 test and the two-group *t* test, respectively. A *p* value of 0.05 or less was considered significant.

Table 1. Patient Profile by Group[a,b]

Variable	Antegrade (n = 30)	Combined (n = 28)
Mean age (y)	61 ± 8	65 ± 8
Sex ratio (M/F)	28/2	22/6
Body surface area (m^2)	1.87 ± 0.11	1.89 ± 0.16
Ejection fraction	0.59 ± 0.10	0.57 ± 0.9
Anterior preoperative MI	4	4
Inferior preoperative MI	12	10
Pump time (min)	68 ± 17	73 ± 16
Cross-clamp time (min)	36 ± 11	38 ± 9
Amount of cardioplegia (mL)	990 ± 210	1,070 ± 370
No. of grafts per patient	2.4 ± 0.6	2.4 ± 0.6
LIMA used	30	28
LIMA + RIMA used	15	10
Total amount of CTn I (μg)	5.6 ± 3.3	4.5 ± 2.5
Postoperative peak CK-MB (IU/L)	40 ± 16	41 ± 14
Operative mortality	0	1
Acquired RBB	2	1
Acquired LBB	0	1
Acquired AF	2	4

[a] Where applicable, data are shown as the mean ± the standard deviation. [b] There are no significant differences between groups for any variable.

AF = atrial fibrillation; CK-MB = myocardial-specific isoenzyme of creatine kinase; CTn I = cardiac troponin I; LBB = left bundle-branch block; LIMA = left internal mammary artery; MI = myocardial infarction; RBB = right bundle-branch block; RIMA = right internal mammary artery.

Results

No patient had aortic incompetence. No complication related to coronary sinus cannulation was noted. Two patients from the combined group were excluded from analysis because the retrograde cannulation could not be performed. Consequently, the analysis included 30 patients in the antegrade group and 28 in the combined group.

No patient had MI by electrocardiographic criteria or CTn I release. Twenty-two patients in the antegrade group and 19 in the combined group required no inotropic support. Four patients in the antegrade group and 3 in the combined group received dopamine hydrochloride (3 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and 4 patients in the antegrade group and 6 in the combined group required epinephrine (2 to 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$). The total amount of CTn I released was higher in patients requiring inotropic support (5.7 ± 3.7 μg) than in patients requiring no inotropic support (4.8 ± 2.6 μg) but not significantly so ($p = 0.20$). No patient in either group had need of an intraaortic balloon pump. In the combined group, 2 patients had mediastinal bleeding requiring reexploration as opposed to none in the antegrade group. One patient in the combined group had development of pneumonia followed by sepsis and multiple-organ failure, which caused death on postoperative day 14.

Preoperative, operative, and postoperative data are

Table 2. Results of Two-Way Analysis of Variance With Repeated Measures[a] for Cardiac Tropinin I Samples at Hour 9

Variable	Antegrade		Combined		*p* Values		
	No. of Patients	Mean ± SD	No. of Patients	Mean ± SD	Main Effect of Grouping Factor	Main Effect of Route of Delivery	Interaction
No. of diseased vessels					NS	NS	NS
Two	11	1.02 ± 0.62	12	1.28 ± 0.70			
Three	19	1.62 ± 0.71	16	1.29 ± 0.62			
LAD					NS	NS	NS
Stenosis	20	1.40 ± 0.72	16	1.25 ± 0.65			
Occlusion	9	1.49 ± 0.86	9	1.06 ± 0.63			
Cx					NS	NS	NS
Stenosis	16	1.73 ± 0.69	18	1.11 ± 0.43			
Occlusion	5	1.26 ± 0.58	3	1.34 ± 1.3			
RCA					NS	NS	NS
Stenosis	11	1.43 ± 0.84	7	1.35 ± 0.90			
Occlusion	13	1.45 ± 0.75	14	1.13 ± 0.58			
Collateral circulation					NS	NS	NS
Good	21	1.45 ± 0.91	18	1.15 ± 0.63			
Poor	9	1.40 ± 0.76	10	1.00 ± 0.47			
LMCA stenosis ≥50%					0.02	0.04	0.03
No	22	1.32 ± 0.73	16	1.22 ± 0.64			
Yes	8	1.65 ± 0.81	12	1.04 ± 0.68			
LMCA stenosis ≥50%					NS	NS	NS
With normal RCA	1	1.67 ± 0.00	3	0.94 ± 0.72		(Excluded from analysis)	
With RCA stenosis	2	1.73 ± 1.26	3	0.76 ± 0.39			
With RCA occlusion	5	1.62 ± 0.86	6	1.23 ± 0.80			
Risk of maldistribution					NS	NS	NS
Low	17	1.36 ± 0.77	15	1.05 ± 0.50			
High	13	1.47 ± 0.75	13	1.25 ± 0.79			
No. of grafts					NS	NS	NS
Two	19	1.26 ± 0.74	16	1.07 ± 0.72			
Three	9	1.68 ± 0.70	11	1.24 ± 0.58			
Four	2	...	1	...		(Excluded from analysis)	

[a] Coronary angiographic findings indicative of a high risk of cardioplegia maldistribution were defined by Menasché and associates [6] as a critical (≥50%) stenosis of the LMCA with total occlusion of the RCA or critical (≥70%) stenosis of the RCA with total occlusion of the left anterior descending or circumflex coronary artery.

Cx = circumflex coronary artery; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; NS = not significant; RCA = right coronary artery; SD = standard deviation.

shown in Table 1. The average volume of cardioplegia injected did not differ significantly between groups. The maximal dose of cardioplegia administered was 1,600 mL in the antegrade group and 2,000 mL in the combined group. The repartition of clinical (Table 1) and coronary angiographic (Table 2) data did not differ between groups. Figure 1 shows the time course of CTn I concentration according to delivery group. There were no significant differences for any samples. Table 2 shows the results of two-way analysis of variance with repeated measures for samples taken at hour 9. In all of the other samples, there were no significant differences in CTn I concentration by route of delivery, regardless of the grouping factor.

The two-way analysis of variance using LMCA disease and route of delivery revealed a significant difference at hour 9, as shown by the main effect of this grouping factor, the main effect of route of delivery, and the significant interaction of these two factors (see Table 2). Multiple comparisons with Bonferroni's correction showed that in patients with no major LMCA stenosis, CTn I release was equivalent in the antegrade and combined groups. Conversely, in patients with a major LMCA stenosis, CTn I release was significantly higher in the antegrade group than in the combined group ($p <$

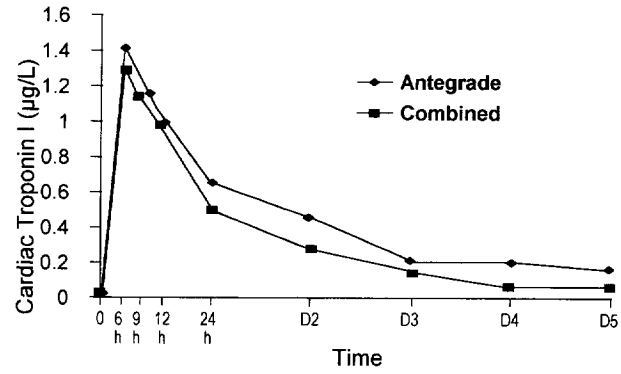

Fig 1. Time course of cardiac troponin I concentration by route of delivery. There were no significant differences for any samples.

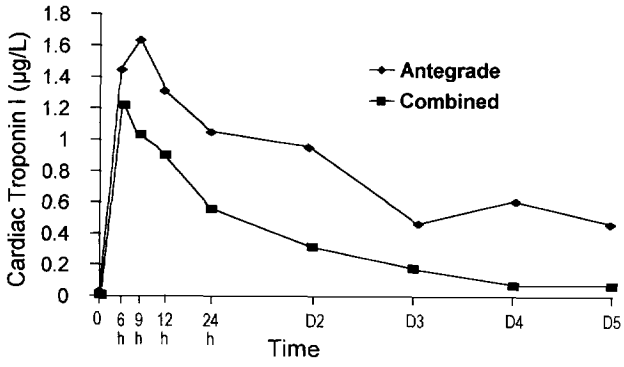

Fig 2. Time course of cardiac troponin I concentration in patients with a major stenosis of the left main coronary artery by route of delivery. The concentration at hour 9 was significantly higher ($p < 0.05$) in the antegrade group than in the combined group.

0.02). By pattern of the right coronary artery in patients with LMCA stenosis, the repartition of patients was not different between groups. There were too few patients with a normal right coronary artery and LMCA disease (see Table 2) to allow us to compare CTn I release in patients with LMCA disease by right coronary artery pattern.

Figure 2 shows the time course of CTn I concentration in patients with a major LMCA stenosis by route of delivery. The CTn I concentration at hour 9 was significantly higher ($p < 0.05$) in the antegrade group than in the combined group.

Comment

Cardiac troponin I has been shown to be a specific marker of cardiac damage: there is no cross-reactivity with the skeletal muscle isoforms, and it has been demonstrated that CTn I levels do not increase in a healthy population, in marathon runners, or as the result of muscular disease or a noncardiac operation [7–9]. The early sensitivity of CTn I in the diagnosis of acute MI is equivalent to that of myoglobin, the MB fraction of creatine kinase mass, creatine kinase isoform ratios, and cardiac troponin T [10]. The peak level of CTn I at hour 6 is higher in patients with perioperative MI than in patients without perioperative MI. The serum CTn I levels are lower in a perioperative non–Q-wave MI than in a perioperative Q-wave MI. Mair and associates [5] concluded that peak CTn I concentrations higher than 3.7 µg/L and that CTn I levels greater than 3.1 µg/L at 12 hours or greater than 2.5 µg/L at 24 hours after aortic unclamping indicate a high probability of perioperative MI.

Cardioplegic myocardial protection in patients with coronary artery disease is effective only if there is adequate delivery of cardioplegic solution beyond the coronary stenosis or occlusions [11]. For crystalloid cardioplegia, the route of delivery remains controversial: antegrade, retrograde, or combined? Grondin and coworkers [12], in an experimental study, showed that the presence of a critical coronary artery narrowing caused inadequate myocardial protection and poor recovery of regional left ventricular function when the antegrade route was used. Their results confirmed the conclusions of Hilton and associates [13]. Conversely, Savunen and co-workers [14] showed that ventricular septal temperature and left ventricular function were similar in an antegrade group and a combined group.

Inadequate distribution by the antegrade route of delivery distal to the occlusion led to use of the retrograde route. Arom and Emery [15] found that cardiac index, left ventricular stroke work index, and right ventricular stroke work index were better with the retrograde route than the antegrade route but not significantly so. Using myocardial contrast echocardiography, Quintilio and colleagues [16] showed a lower degree of myocardial opacification with the antegrade route than the retrograde route in patients with poor collateral circulation. Although Partington [17], Allen [18], and their associates demonstrated that retrograde cardioplegia does not adequately perfuse the right ventricle, Menasché and co-workers [19] concluded that retrograde coronary sinus cardioplegia does not cause detectable impairment of right ventricular function if the balloon catheter does not obstruct the terminal tributaries of the coronary sinus.

As the retrograde route of delivery could lead to potentially inadequate preservation of the right ventricle and delay cardiac arrest, the combined approach may have certain advantages. Menasché and colleagues [6] demonstrated the ability of the combined route to adequately preserve myocardial areas distal to complete chronic artery occlusions in a patient population at high risk for cardioplegia maldistribution. Conversely, for Savunen and co-workers [14], antegrade cardioplegia was at least as effective for myocardial protection as combined cardioplegia in patients with preserved left ventricular function who were undergoing elective coronary artery bypass grafting.

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 [20]. Using this technique could be cumbersome, confusing, and more time-consuming while the aorta is cross-clamped [15]. Barotrauma and coronary sinus rupture may occur [21]. Therefore, as the antegrade route appears sufficient for most patients [14], the combined route should be limited to select patients who are likely to benefit from this procedure. Using CTn I release, we tried to determine which patients fit this category.

Our criterion for evaluating the adequacy of myocardial protection was CTn I release. We [1] previously reported CTn I to be a marker of myocardial ischemia. In a group of 20 patients scheduled for aortic valve replacement and having normal coronary arteries, CTn I concentration at hour 6 was correlated to aortic cross-clamp time, whereas in 20 patients scheduled for coronary artery bypass grafting, there was no such relation because ischemia is multifactorial in such patients. In addition to cross-clamp time, two other factors must be considered: (1) Although revascularization may be as complete as possible, ischemic areas may remain, and (2) after the grafts are open, the consequences of reperfusion are uncertain. We thought that randomization might

balance out these two factors as well as aortic cross-clamp time between the two groups and therefore make it possible to show a difference in myocardial protection according to route of delivery if such a difference exists. Tables 1 and 2 confirm that randomization created two equivalent groups in terms of pertinent variables such as pump time, cross-clamp time, number of grafts, and coronary angiographic findings.

Our results showed that compared with the antegrade route, the combined route offered no advantage in an unselected group of patients who were undergoing an elective first cardiac operation and who had preserved left ventricular function. This conclusion confirms the results of Savunen and co-workers [14]. Two-way analysis of variance concerning CTn I release according to coronary angiographic findings and divided by route of delivery showed that the combined route of delivery is beneficial only in patients with a major LMCA stenosis. Cardiac troponin I release was not different with respect to route of delivery in patients divided by quality of the collateral circulation (good or poor); this finding does not concur with the conclusions of Noyez [22], Quintilio [16], and their associates. Coronary angiographic findings predictive of a high risk of cardioplegia maldistribution were defined by Menasché and colleagues [6] as a critical stenosis of the LMCA with total occlusion of the right coronary artery or critical stenosis of the right coronary artery with total occlusion of the left anterior descending or circumflex coronary artery. Release of CTn I was not different when risk of maldistribution was divided into two groups (low, high) examined by route of delivery. Although for each route of delivery, CTn I release was higher when there was a high risk of cardioplegia maldistribution, and CTn I release was higher in the antegrade group than in the combined group irrespective of the risk of maldistribution, these differences were not significant (see Table 2). Patients with acute coronary artery occlusion after failed balloon angioplasty or patients undergoing reoperation were not included in our study. The combined route would appear to be preferable for such patients [23].

Our study also confirms the sensitivity of CTn I release as a marker of myocardial injury. The time course of CTn I concentration is shown in Figure 1. Concentration is maximal at hour 9 and decreases steadily until postoperative day 5. In our previous study [1], CTn I levels peaked at hour 6, but the next sample was taken at hour 12 instead of hour 9.

The results of our study suggest that myocardial protection should be adapted to each patient individually with reference to his or her condition and disease. The combined route of delivery of crystalloid cardioplegia is beneficial in patients with a major stenosis of the LMCA. The CTn I sensitivity is relevant in this study. Release of CTn I should be useful to determine the best form of myocardial protection for each patient.

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