Does antegrade blood cardioplegia alone provide adequate myocardial protection in patients with left main stem disease?

Francesco Onorati, MD
Attilio Renzulli, MD, FECTS
Marisa De Feo, MD
Giuseppe Santarpino, MD
Rosario Gregorio, MD
Andrea Biondi, MD
Flavio Cerasuolo, MD
Maurizio Cotrufo, MD, FECTS

Dr Onorati

Background: The optimum route for cardioplegia administration in patients with severe coronary disease is still under debate. This study compared clinical, echocardiographic, and biochemical results in patients with left main stem disease treated with 2 different strategies of myocardial protection.

Methods: Between March 2000 and November 2002, 148 consecutive patients with left main stem disease undergoing coronary artery bypass grafting were divided into 2 groups according to the route of cardioplegia delivery: antegrade in 87 patients (group A) or antegrade followed by retrograde in 61 patients (group B). Electrocardiography, troponin I, MB-creatine kinase, and MB-creatine kinase mass were performed at 12, 24, 48, and 72 hours postoperatively. Echocardiography was performed preoperatively and before hospital discharge. Data were stratified in subgroups of patients with the following associated risk factors: left ventricular hypertrophy, diabetes, and right coronary stenosis.

Results: Groups were homogeneous in preoperative and intraoperative variables, apart from the higher incidence of unstable angina and severity of left main stem disease in group B. Hospital deaths, intensive therapy unit and hospital stay, perioperative acute myocardial infarction, and intraaortic balloon pump support were similar in both groups. Postoperative recovery of left ventricle ejection fraction and wall motion score index did not differ between the 2 groups. However, postoperative atrial fibrillation was higher in group A ($P = .015$), especially in patients with diabetes ($P < .0001$). Troponin I was significantly higher in group A from postoperative hours 12 to 72 ($P < .01$), and the same pattern was observed in patients with diabetes ($P < .001$), critical right coronary stenosis ($P < .001$), and left ventricle hypertrophy ($P < .001$).

Conclusion: The combined route of intermittent blood cardioplegia allows better results in left main stem disease. Such data are confirmed even in risk subgroups.

From the Department of Cardiothoracic and Respiratory Sciences, Second University of Naples, Naples, Italy.

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Address for reprints: Attilio Renzulli, MD, FECTS, Via Aquila 144, 80143 Napoli (E-mail: arenzul@tin.it).

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lthough Lillehei and associates¹ introduced coronary sinus perfusion into clinical use in 1956, it faded from clinical practice until Buckberg² introduced retroplegia into clinical practice, demonstrating that the efficacy of oxygenated blood cardioplegia is dependent on its complete and uniform distribution to the microvasculature of the heart. Progresses in the technique of myocardial protection showed that continuous warm cardioplegia could resuscitate the ischemic

myocardium, which is not possible with cold cardioplegia.³ In the last decade, myocardial protection with intermittent warm hyperkalemia blood cardioplegia has become a growing practice in cardiac surgery.⁴

Nevertheless, the preferential route of delivery of cardioplegia for myocardial protection in patients with severe coronary artery disease is still under debate. Although many cardiac surgeons suggest routinely the retrograde route of administration,^{5,6} others prefer the antegrade route.^{7,8} Such controversies arise from the large amount of clinical, biochemical, and histologic studies that have been performed during the last 2 decades. Several authors⁹ argue that experimental studies on retrograde cardioplegia performed in dogs may be of questionable relevance because of the differences in canine anatomy with predominant venous drainage by way of thebesian veins rather than the coronary sinus. Moreover, other investigators¹⁰ have found a larger number of thebesian veins and other venous channels in patients with a coronary atherosclerotic obstruction, and 70% of such patients can be shown to have increased coronary arteriovenous shunts.

Moreover, adequacy of myocardial protection may vary according to many other factors such as severity of coronary disease, composition, viscosity and temperature of the cardioplegic solution, time of infusion, and associated comorbidities (diabetes and left ventricular hypertrophy).

In addition to such findings, it has to be considered that modern on-pump myocardial revascularization in routine cases rarely requires more than 60 minutes of aortic cross-clamping; therefore, differences in clinical end points are difficult to ascertain.¹¹

Recently, troponin (Tn) I was shown to be a specific marker of cardiac damage with a higher specificity and a wider diagnostic window compared with creatine kinase (CK)-MB measurements.¹² Therefore, it is widely accepted that TnI should be able to detect even minor differences of myocardial ischemia.

This study evaluated the differences between 2 delivery routes of hyperkalemic intermittent warm blood cardioplegia in patients undergoing coronary artery bypass grafting (CABG) for left main stem disease.

Materials and Methods

Patient Selection

In January 2000, a postoperative protocol to evaluate perioperative myocardial damage after CABG was started. Twelve-lead electrocardiography (ECG), color Doppler echocardiography, and biochemical markers of myocardial damage such as MB-CK, MB-CK mass, and TnI were used to assess damage preoperatively and postoperatively.

Exclusion criteria were associated cardiac disease (valvular, aortic disease, and congenital pathology) or severe associated comorbidities (renal and hepatic failure, cancer, and autoimmune disease).

Between March 2000 and November 2002, 1610 consecutive patients undergoing first-time isolated CABG were enrolled in the study. Of these patients, 148 had a significant (>50%) left main stem disease and were divided into 2 groups (after informed consent was obtained) according to the route of cardioplegia administration. The study protocol was approved by the institutional review board.

The following criteria were used for definition of comorbidities: hypertension (systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, or ongoing treatment with any antihypertensive medication); insulin-dependent and non-insulin-dependent diabetes (fasting blood glucose levels > 140 mg/dL on at least 2 occasions or use of antidiabetic medication [oral drugs or insulin]); and right coronary artery stenosis (critical [>75%] obstruction in a right dominant coronary artery).

Anesthetic Technique

Anesthesia consisted of propofol infusion at 3 mg · kg · h and fentanyl administration at 0.10 mg every 20 minutes. Neuromuscular blockade was achieved with pancuronium bromide. Alfa-adrenergic drugs were used as required to maintain mean systemic pressure between 50 and 60 mm Hg.

Surgical Technique

Surgery was always performed by the same group of surgeons (no. 4). Assignment criteria to each surgeon were completely random, and the choice of myocardial protection technique was left to the surgeon. However, the combined route was more often preferred when unstable angina and left main stem stenosis greater than 90% were observed.

In all patients, CABG was performed through a median sternotomy. The left internal thoracic artery was harvested as a pedicle and anastomosed to the left anterior descending artery in all cases. The radial artery was always anastomosed to the ascending aorta. The right internal thoracic artery was harvested as a pedicle and never used as a free graft.

Heparin was administered at a dose of 300 IU/kg to achieve a target activated clotting time of 480 seconds or greater. Blood recovery with an autotransfusion device (Autotrans Dideco; Mirandola, Modena, Italy) was performed intraoperatively in all cases. A level of hemoglobin less than 8 g/dL indicated blood transfusion.

The standard cardiopulmonary bypass circuit was used: a Dideco tubing set, which included a 40- μ m filter, a Stockert roller pump (Stockert Instrumente, Munich, Germany), and a hollow fiber membrane oxygenator (Monolyth; Sorin Biomedica, Saluggia, Italy). The extracorporeal circuit was primed with 1000 mL of Ringer's lactate and 40 mg of heparin. Nonpulsatile flow with an output of 2.4 L · m² · min was used. Systemic temperature was kept between 32°C and 34°C. Proximal anastomoses were always performed with aortic partial clamping.

Myocardial Protection

Myocardial protection was always achieved with intermittent hyperkalemic blood cardioplegia as reported by Calafiore and colleagues.⁴

In 87 patients (group A), cardioplegia was administered through the aortic root every 20 minutes (500 mL of blood con-

taining 20 mEq/L of K^+ delivered into the aortic root at a pressure of 70 mm Hg and a temperature of 34°C for 3 minutes). In 61 patients (group B), after cardiac arrest was achieved with an antegrade infusion according to the previously mentioned protocol, the aortic root was vented and retrograde delivery of cardioplegia was commenced through an auto-inflating coronary sinus cannula at a flow rate of 200 mL/min for 2 minutes. Coronary sinus was cannulated with the blind technique through the lower portion of the right atrium, according to the method proposed by Gundry and colleagues.¹³ Coronary sinus pressure was monitored continuously by a separate pressure-monitoring line and maintained at less than 30 mm Hg throughout the procedure. The adequacy of cannula positioning was confirmed by observing distension of the posterior interventricular vein, maintaining coronary sinus pressure, and palpating the coronary sinus cannula. In group B, repeated doses lasting 3 minutes were administered every 20 minutes always by retrograde route alone. Warm reperfusion was never used in the present study.

ECG

Twelve-lead ECG was performed preoperatively, at admission in the intensive therapy unit, and then daily thereafter until hospital discharge. All patients underwent continuous ECG monitoring at least for the first 48 hours postoperatively. The incidence of dysrhythmias was recorded with transient ischemic events (ST segment elevation > 1 mm). ECG diagnostic criteria for perioperative myocardial infarction (MI) were new Q waves greater than 0.04 ms or a reduction in R waves greater than 25% in at least 2 leads or both.

Biochemical Analysis

Blood samples were always collected from the central venous line; the tip of the cannula was located in the lower part of the right atrium as confirmed by chest radiography postoperative control.

Determination of blood concentration of cardiac TnI, MB-CK, and MB-CK mass was conducted preoperatively before anesthetic induction and postoperatively at 12, 24, 48, and 72 hours.

The assays were performed using diagnostic kits provided by Beckman Coulter (Fullerton, Calif) for TnI (Access Immunoassay System, AccuTnI), MB-CK mass (Access Immunoassay System, MB-CK), and MB-CK (Synchron CX System).

Echocardiography

All studies were performed using a transthoracic Acuson Sequoia C256 echocardiography system (Acuson Corporation, Mountain View, Calif) with probe 3V2C, always by the same 2 physicians in a blind manner, preoperatively, at the time of hospital admission, and before hospital discharge. Left ventricle ejection fraction (EF), wall motion score index (WMSI), and indexed left ventricular mass were recorded. A value of indexed left ventricular mass greater than 125 g/m² indicated left ventricular hypertrophy.

Definition of Perioperative MI

Perioperative acute MI was defined according to the previously mentioned ECG criteria, new akinetic segment at echocardiography, and detection of peak TnI greater than 3.7 μ g/L or TnI concentration greater than 3.1 μ g/L at hour 12, as determined by Mair and colleagues.¹⁴

Inotropic Support

Inotropic support was defined as low dose when enoximone or dobutamine was administered at a dosage less than 5 μ g · kg · min, as medium dose when dobutamine or dopamine was administered at dosages between 5 and 10 μ g · kg · min for more than 6 hours postoperatively, and as high dose when epinephrine was added to dobutamine or dopamine administered at a dosage greater than 10 μ g · kg · min.

Statistical Analysis

Statistical analysis was performed with the SPSS program for Windows, version 10.1 (SPSS Inc, Chicago, Ill). Continuous variables are presented as mean $\pm$ SD, and categorical variables are presented as absolute numbers or percentage. Data were checked for normality before statistical analysis. Normally distributed continuous variables were compared using the unpaired *t* test, whereas the Mann-Whitney *U* test was used for those variables that were not normally distributed. Categorical variables were analyzed using the χ^2 square test or Fischer's exact test.

Study Limitations

An ideal comparison between 2 treatments should be performed on the basis of a prospective randomized study. Although the study was prospectively designed, no real randomization was performed. CABG procedures were always performed by the same group of surgeons (no. 4), but the option to add retrograde cardioplegia was the surgeon's choice.

Moreover, the 2 groups were not homogeneous for severity of left main lesion and incidence of unstable angina. Such differences, however, cannot be considered as bias because patients with the worst coronary lesions and clinical conditions were preferentially treated with the combined route.

Finally, randomized study in a single-center experience may carry some bias, especially concerning the techniques of myocardial revascularization.

Results

Groups proved homogeneous in most of the preoperative characteristics, as reported in Table 1. Intraoperative characteristics are shown in Table 2.

There were no differences between the 2 groups in terms of intensive care or hospital stay (Table 2). There were 3 hospital deaths, 2 in group A (pneumonia and multi-organ failure) and 1 in group B (mesenteric infarction) (*P* = .402). Two patients in each group developed postoperative MI (*P* = .547).

Two patients in group A and 1 patient in group B required postoperative intra-aortic balloon pump (*P* = .402); however, enzymatic release, ECG pattern, and echocardiographic evaluation did not show any data indicative of perioperative MI. Mechanical assistance was discontinued in all cases within 48 hours after the operation.

The number of patients who did not require any inotropic support at all was statistically higher in the group with combined cardioplegia; furthermore, there was no difference between the 2 groups in regard to the number of

TABLE 1. Preoperative characteristics

	Group A	Group B	P
No. of patients	87	61	
Mean age	58.9 ± 9.9	58.6 ± 15.1	.884
Sex (M/F)	74/13	54/7	.164
Euroscore	3.6 ± 2.2	4.0 ± 2.0	.228
Diabetes	29	26	.07
Hypertension	63	41	.114
Unstable angina	45 (51.7%)	44 (72.1%)	.006
AMI < 4 weeks	20	19	.08
Left main stem 50%-75%	72 (82.7%)	35 (57.4%)	.0001
Left main stem >75%	15 (17.2%)	26 (42.6%)	.001
Right coronary stenosis	32	22	.137
EF <40%	25	18	.145
Wall motion score index	1.43 ± 0.36	1.63 ± 0.26	.0001
Preoperative EF	51.5 ± 8.7	51.2 ± 10.1	.098
Indexed left ventricular mass >125 g/m ²	30	25	.099

EF, Ejection fraction; AMI, acute myocardial infarction.

TABLE 2. Intraoperative characteristics.

	Group A	Group B	P
Aortic crossclamp time	39.2 ± 14.3	41.6 ± 11.9	.294
Cardiopulmonary bypass time	72.9 ± 25.3	75.1 ± 18.1	.559
No. of diseased vessels	3.2 ± 0.9	3.2 ± 0.8	.422
No. of grafts	3.3 ± 0.8	3.3 ± 0.9	.855
Complete arterial revascularization	12 (13.8%)	15 (24.6%)	.129
No. of left ventricle defibrillation	4 (4.5%)	5 (8.2%)	.287
Inotropes low dose	31 (35.7%)	23 (37.7%)	.465
Inotropes medium dose	21 (24.1%)	8 (13.1%)	.07
Inotropes high dose	10 (11.5%)	0	.004
No inotropes	25 (28.7%)	30 (49.2%)	.009
Intra-aortic balloon pump	2 (2.3%)	1 (1.6%)	.402
Perioperative Q AMI	2 (2.3%)	2 (3.2%)	.547
Atrial fibrillation	30 (34.5%)	10 (16.4%)	.015
Transient atrioventricular block	-	-	-
Intensive therapy unit stay	2.9 ± 1.3	3.3 ± 2.4	.144
In-hospital stay	8.7 ± 1.9	8.2 ± 3.0	.267
Postoperative EF	54.3 ± 6.8	54.7 ± 8.2	.291
Postoperative wall motion score index	1.15 ± 1.18	1.13 ± 0.12	.202

patients requiring medium- and low-dose inotropic support. More patients who underwent antegrade cardioplegia delivery alone required a high dose of inotropic support (Table 2).

There were no patients demonstrating postoperative atrioventricular block. On the contrary, the prevalence of postoperative paroxysmal atrial fibrillation was higher in group A, as shown in Table 2. However, all patients were discharged with normal sinus rhythm, and no complications of atrial fibrillation were recorded during the hospital stay. In subgroups of patients with diabetes, postoperative atrial fibrillation was recorded more frequently in patients treated with antegrade cardioplegia alone (group A 19/29, 65.5% vs group B 5/32, 15.6%; $P < .0001$).

Figure 1. Assay of biochemical markers in overall population.

The biochemical results are reported in Figure 1. Enzyme assays showed statistically higher values in patients who underwent antegrade cardioplegia alone in terms of TnI starting from postoperative hours 12 to 72 (hour 12: 1.83 ± 0.81 ng/mL vs 1.17 ± 0.68 ; hour 24: 1.66 ± 1.32 vs 0.92 ± 0.58 ; hour 48: 1.45 ± 1.59 vs 0.77 ± 0.72 ; hour 72: 1.15 ± 1.65 vs 0.50 ± 0.64). This was confirmed by MB-CK mass at hour 12 (27.1 ± 47.5 ng/mL vs 12.7 ± 22.3); however, such enzyme release never fulfilled the criteria of perioperative MI.¹³

By stratifying the population in subgroups according to some preoperative risk factors (Figure 2), the TnI pattern proved statistically higher in antegrade cardioplegia alone at 12, 24, 48, and 72 hours postsurgery in patients with diabetes (hour 12: 2.3 ± 0.5 ng/mL vs 1.0 ± 0.5 ; hour 24: 2.2 ± 1.7 vs 0.7 ± 0.4 , hour 48: 1.9 ± 1.1 vs 0.5 ± 0.4 ; hour 72: 1.9 ± 2.3 vs 0.2 ± 0.2). The same pattern of TnI course was also demonstrated in subsets of patients with critical right coronary stenosis (hour 12: 2.3 ± 0.3 ng/mL vs 1.1 ± 0.7 ; hour 24: 2.0 ± 1.0 vs 0.8 ± 0.6 ; hour 48: $2.2 \pm$

1.9 vs 0.6 ± 0.6 ; hour 72: 1.8 ± 2.2 vs 0.4 ± 0.6) and in patients with left ventricle hypertrophy (hour 12: 1.8 ± 0.7 ng/mL vs 1.1 ± 0.6 ; hour 24: 1.7 ± 1.2 vs 0.9 ± 0.6 ; hour 48: 1.7 ± 2.1 vs 0.7 ± 0.5 ; hour 72: 1.5 ± 2.1 vs 0.5 ± 0.6).

In regard to echocardiographic data, both types of myocardial protection demonstrated a mild improvement in left ventricle EF (group A: preoperative EF, $51.5\% \pm 8.7\%$; postoperative EF, $54.3\% \pm 6.8\%$; $P < .0001$; group B: preoperative EF, $51.2\% \pm 10.1\%$; postoperative EF, $54.7\% \pm 8.2$; $P < .0001$) and left ventricle WMSI (group A: preoperative WMSI, 1.43 ± 0.36 ; postoperative WMSI, 1.14 ± 0.17 ; $P < .0001$; group B: preoperative WMSI, 1.63 ± 0.26 ; postoperative WMSI, 1.13 ± 0.12 ; $P < .0001$).

Discussion

The infusion of cardioplegic solution through the aortic root produces very quick diastolic arrest and good preservation of myocardial function. However, when advanced coronary disease is considered, it can result in an uneven distribution and, consequently, delayed functional recovery.¹⁵ Therefore, myocardial areas distal to complete coronary artery occlusion are poorly protected by antegrade cardioplegia. This can lead to myocardial injury and depressed postoperative left ventricular function.

Experimental studies have shown that in the presence of coronary occlusions, retrograde cardioplegia results in better distribution, myocardial cooling, and more complete recovery of function in the areas beyond the occlusion.^{16,17} However, veno-venous shunts and thebesian channels draining into the ventricular cavity may limit retrograde distribution of cardioplegia.³

Therefore, some authors have shown no clear advantage in myocardial protection of retrograde versus antegrade cardioplegia.¹⁵ Such findings, together with some drawbacks associated with retrograde perfusion, such as myocardial edema and coronary sinus rupture, caused many investigators to support the antegrade route alone even in patients with severe coronary artery disease.^{18,19}

Most of the conclusions were proven for cold crystalloid cardioplegia, in which the low viscosity of the solution may provide adequate peripheral distribution even in critical proximal stenoses.⁵

Technical problems can be circumvented by the technique of transatrial insertion of a balloon-tipped catheter that maintains pressure in coronary sinus of less than 50 mm Hg.¹³ Furthermore, blind cannulation of coronary sinus is simple and avoids the use of bicaval cannulation and right atriotomy.

The advantages of retrograde blood cardioplegia perfusion are the establishment of aerobic arrest; protection in areas distal to acute MI, ungraftable vessels, and acute occlusion; and elevation of the heart rate and dissection of coronary arteries while administering cardioplegia.^{20,21}

TnI assay in diabetics

TnI assay in LV hypertrophy

TnI assay in right coronary stenosis

Figure 2. Subgroup analysis according to risk factors.

Currently, crossclamp time rarely exceeds 60 minutes in routine practice; therefore, clinical end points are difficult to ascertain and require large series of patients.¹¹

During the past decade, the myocardial isoforms of Tns have been introduced in these terms, overcoming the biochemical limitations of CK-MB and myoglobin measurements. On the other hand, the detection of TnI is completely specific for myocardial damage. Cumulative data²² indicate TnI levels are detectable 3 to 6 hours after the onset of myocardial injury; moreover, TnI levels peak at approximately 12 to 16 hours and can remain elevated for 4 to 9 days post-acute MI. Therefore, it is widely accepted that TnI should be able to detect even minor differences of myocardial ischemia.²³

According to these data, postoperative TnI assay should be considered the gold standard test in studies concerning postoperative incidence of MI and in the assessment of the adequacy of myocardial protection.

The results of our study, although not randomized, indicate that combined delivery of blood cardioplegia shows a significantly lower level of postoperative TnI until the fourth postoperative day. Such biochemical findings are further supported by a significantly lower release of MB-CK mass at 12 hours postoperatively.

Although major clinical end points such as hospital mortality, postoperative MI, intensive therapy unit and hospital stay, and intra-aortic balloon pump support did not reach statistically significant differences between the 2 groups, the requirement of postoperative inotropic support was higher in group A. The incidence of postoperative atrial fibrillation, although not strictly a specific marker of adequate myocardial protection, was higher in group A.

Right ventricular protection was very often presented as a potential limitation of coronary sinus cardioplegia according to whether there was flow through the capillaries or through the extensive veno-venous collateral and into the ventricular chambers through the thebesian veins.²⁴ Specifically, deficits in the delivery of cardioplegia to the posterior septum and the right ventricle have been noted. In the warm arrested state, these regional deficits could result in metabolically active myocardium, with subsequent inadequate oxygen, substrate delivery, and warm ischemia.²⁵

Conversely, some authors^{26,27} have demonstrated that retrograde cardioplegia delivery compared with antegrade cardioplegia delivery is associated with similar right ventricle performance, and that there are no differences in outcome, hemodynamic indices, or enzyme data.

In the present study, Tn release showed lower levels in patients with the combined route of administration even in the subgroups of patients with proximal right coronary stenosis, in whom antegrade delivery would not compensate for the potential deficiencies of retrograde delivery as reported by some authors.⁹ Therefore, the present study confirms that the retrograde route is the only potential route for distal delivery of cardioplegia in patients with severe coronary artery disease involving the left main and right coronary arteries.

Moreover, the sub-endocardium is the most vulnerable region of the heart to ischemia, particularly in the hypertrophied ventricle. Another interesting finding of our study is the significantly lower release of TnI and MB-CK mass even in patients with left ventricle hypertrophy. Such data are consistent with others who showed better protection of the hypertrophied ventricle with retrograde cardioplegia.²⁸ Finally, the finding of a significantly lower TnI release and incidence of postoperative atrial fibrillation in the subgroup of diabetic patients who underwent combined delivery of

cardioplegia supports the hypothesis that patients with extensive coronary disease and impairment of coronary microcirculation (as reported in diabetes) may greatly benefit from myocardial protection strategy. Such data are supported by the hypothesis of Buckberg and colleagues²⁹ and Gates and colleagues³⁰ that retrograde blood cardioplegia perfuses some capillaries that are not perfused by antegrade blood cardioplegia alone.

Conclusion

The present study confirms that TnI is a good biochemical marker to evaluate differences in strategies of myocardial protection, whereas MB-CK and MB-CK mass can be used only for the diagnosis of MI. In patients with left main stem disease undergoing on-pump CABG with blood intermittent cardioplegia, the combined route of administration allows better results in terms of TnI release. Such results are confirmed even in subgroups of patients with increased ventricular mass and impaired microvascular circulation resulting from diabetes, who generally need a higher degree of myocardial protection.

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