RISK FACTORS OF INCOMPLETE DISTRIBUTION OF CARDIOPLEGIC SOLUTION DURING CORONARY ARTERY GRAFTING

From the Department of Cardiac Surgery, University of Florence, Florence, Italy, the Department of Cardiovascular Surgery, "La Sapienza" University of Rome, and the Istituto Superiore di Sanità, Ministero della Sanità, Rome, Italy.

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Address for reprints: Caretta Quintilio, MD, Via G. Giolitti 198, 00185 Roma, Italy.

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Myocardial distribution of cardioplegic solution infused by combined antegrade/retrograde routes was assessed with myocardial contrast echocardiography in 18 patients with chronic stable angina and three-vessel disease undergoing elective coronary artery bypass grafting. Overall myocardial opacification was significantly greater in retrograde than in antegrade cardioplegia ($77.7\% \pm 13.4\%$ versus $59.1\% \pm 15.7\%$; $p = 0.0009$). The difference was affected by collateral circulation, as pointed out by the significant interaction between coronary collateral circulation and percent of myocardial opacification after antegrade and retrograde cardioplegia ($p = 0.002$). When we performed multiple comparisons, in patients with good collaterals the opacification difference between antegrade and retrograde cardioplegia was not statistically significant ($66.4\% \pm 10.2\%$ versus $76.0\% \pm 15.2\%$; $p =$ not significant), whereas in patients with poor collaterals myocardial opacification during retrograde cardioplegia was significantly greater ($44.3\% \pm 15.0\%$ versus $81.2\% \pm 9.0\%$; $p < 0.02$). During antegrade cardioplegia, patients with poor collaterals showed a lower degree of myocardial opacification than patients with good collaterals ($44.3\% \pm 15.0\%$ versus $66.4\% \pm 10.2\%$; $p < 0.01$). Our results show that retrograde cardioplegia in patients undergoing elective coronary artery bypass grafting offers no advantage over antegrade cardioplegia when collateral circulation is well developed. On the other hand, conventional aortic root infusion may not provide adequate myocardial protection in the subset of patients with significantly narrowed or occluded coronary arteries and poor collaterals. (*J THORAC CARDIOVASC SURG* 1995;109:439-47)

Caretta Quintilio, MD, Paolo Voci, MD, Federico Bilotta, MD, Giampaolo Luzi, Flavia Chiarotti, BS, Maria Cristina Acconcia, MD, Corrado Mercanti, MD, and Benedetto Marino, MD, *Florence and Rome, Italy*

Clinical and experimental studies during coronary artery bypass grafting (CABG) have shown that cardioplegic solution infused antegradely may be nonhomogeneously distributed to myocardial segments supplied with obstructed or severely narrowed coronary arteries.¹⁻⁷ This limitation has been overcome by the use of the venous system of the heart as an alternative route for delivering cardioplegic solution.^{2, 7-14} However, the question regarding the more suitable route of delivery of the solution during coronary artery grafting is still being debated.^{6, 7, 15-24}

Myocardial contrast echocardiography is a safe and validated method to study the intramyocardial distribution of coronary blood flow during cardiac catheterization and coronary artery grafting,²⁵⁻³⁵ and it has been successfully used in association with cardioplegic techniques.^{25, 36-38}

The aim of the present study was to evaluate, with intraoperative myocardial contrast echocardiography, the risk factors of maldistribution of cardioplegic solution infused through the aortic

root and right atrium in patients undergoing elective CABG.

Patients and methods

Patient selection. Twenty-six patients (24 men and two women, mean age 54 ± 6 years) undergoing elective CABG for symptomatic chronic coronary artery disease were enrolled in this study. The study protocol was approved by the Ethical Committee of the University of Rome "La Sapienza" and informed consent was obtained from all patients. All patients underwent coronary angiography in accordance with the Judkins technique.³⁹ Coronary artery lesions causing a loss of 75% or more of cross-sectional area were considered significant stenoses.

Coronary collateral circulation was classified as proposed by Bruschke⁴⁰ and Hansen⁴¹ into two categories: good collaterals and poor collaterals. 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, the visualization of collaterals and epicardial arteries distal to an occlusion was faint or absent. Patients with evidence of aortic incompetence and/or patent foramen ovale were excluded from the study. Clinical and coronary angiographic findings are reported in Table I.

Table I. Clinical and coronary angiographic findings in 18 patients undergoing CABG with combined antegrade/retrograde cardioplegia

	Collateral circulation			
	Good		Poor	
	No.	%	No.	%
No. of patients	12	100.0	6	100.0
Clinical findings				
Age (mean $\pm$ SD)	52.7 $\pm$ 5.2		56.7 $\pm$ 5.8	
Sex				
Male	11	91.7	5	83.3
Female	1	8.3	1	16.7
Previous myocardial infarction				
No	7	58.4	3	50.0
Inferior	1	8.3	2	33.3
Anterior	1	8.3	1	16.7
Inferior and anterior	3	25.0	0	0.0
Hypertension	5	41.7	4	66.7
Diabetes	1	8.3	2	33.3
Coronary angiography findings				
Degree of coronary disease				
Three-vessel stenosis >75%	1	8.3	3	50.0
One vessel occluded + 2 vessels >75% stenosis	8	66.7	3	50.0
Two vessels occluded + 1 vessel >75% stenosis	3	25.0	0	0.0
Location of occlusion				
LAD occluded + 2 vessels >75%	3	25.0	1	16.7
LAD, RCA occluded + 1 vessel >75%	2	16.7	0	0.0
LAD, Cx occluded + 1 vessel >75%	1	8.3	0	0.0
Cx occluded + 2 vessels >75%	2	16.7	0	0.0
RCA occluded + 2 vessels >75%	2	16.7	1	16.7
RCA occluded + LM stenosis >75%	0	0.0	1	16.7
RCA occluded + LM >75% stenosis + LAD >75%	1	8.3	0	0.0

Differences between the groups of patients with good vs poor collateral circulation with respect to clinical and coronary angiographic finding were all not significant ($p = \text{NS}$). CABG, Coronary artery bypass grafting; SD, standard deviation; LAD, left anterior descending coronary artery; RCA, right coronary artery; Cx, circumflex coronary artery; LM, left main coronary artery.

Anesthetic technique. Anesthesia was induced with fentanyl (30 to 35 $\mu\text{g/kg}$), diazepam (0.25 to 0.5 mg/kg), and succinylcholine (1.5 mg/kg) and was maintained with fentanyl, droperidol, pancuronium bromide, and a 50% nitrous oxide and oxygen mixture.

Surgical technique. CABG was performed during cardiopulmonary bypass. All the patients were kept systemically hypothermic (25° to 28° C) throughout the procedure. A total of 97 grafts (average 3.7 ± 0.7 grafts per patient) were placed: 71 were of inverted saphenous vein and 26 of internal mammary artery. For saphenous vein grafting, the distal anastomosis was sutured first during aortic crossclamping. The proximal anastomosis was sutured on the partially crossclamped aortic root during the rewarming phase of the beating, nonworking heart.

Cardioplegia techniques. Myocardial protection was achieved by inducing topical hypothermia with iced saline slush and by administering cold (4° C) potassium crystalloid cardioplegic solution (a 30 mEq/L concentration of potassium chloride in the first dose and 15 mEq/L in retrograde cardioplegia and in all subsequent doses). All patients received combined antegrade and retrograde cardioplegia.

In the antegrade technique the cardioplegic solution was infused over 2 minutes via the aortic root at a pressure

of 70 to 80 mm Hg. Left ventricular venting was performed through the left atrium. In the retrograde technique the solution was administered via the right atrium, according to the method of Fabiani and associates.^{9, 10} The solution was infused at a pressure of 30 to 50 mm Hg during pulmonary artery clamping and right ventricular compression.

The overall cardioplegia dose (10 ml/kg) was equally divided between antegrade and retrograde delivery. Antegrade and retrograde cardioplegia was repeated every 20 minutes throughout the ischemic period.

Echocardiographic contrast agent. The echocardiographic contrast agent was prepared under sterile conditions 1 hour before the operation, according to a standardized protocol developed at the University of Rome "La Sapienza"⁴² based on guidelines for albumin sonication worked out at the University of Chicago.⁴³ The contrast material is nontoxic, does not impede blood flow through the capillaries,⁴⁴ and does not alter myocardial or systemic blood flow.⁴⁵

Imaging technique. All patients were monitored intraoperatively by single-plane transesophageal echocardiography. The probe was inserted after induction of anesthesia and tracheal intubation. Shortly after induction of

Fig. 1. Box plots of percent myocardial opacification for antegrade and retrograde cardioplegia, showing median and mean (*broken lines within the boxes*), first and third quartile (*bottom and top of the boxes*, respectively), and minimum and maximum of the observations (*upper and lower tails*).

anesthesia, color Doppler imaging was performed to rule out the presence of aortic incompetence and/or shunting at the level of the fossa ovalis.

The echocardiographic contrast agent was injected soon after hypothermic arrest, through a side branch of the cardioplegic conduit. Four contrast agent injections were scheduled for each patient, two of 2 ml during antegrade cardioplegia and two of 4 ml during retrograde cardioplegia. The first injection was performed during antegrade cardioplegia while the aortic valve and the left ventricle were being imaged, to rule out unexpected aortic regurgitation during aortic crossclamping. The second contrast injection was performed during antegrade cardioplegia while the left ventricle was being imaged in the short-axis view at the papillary muscle level, to evaluate myocardial opacification. The third injection was performed during retrograde cardioplegia while the interatrial septum was being imaged, to rule out right-to-left shunt at the level of the fossa ovalis. The fourth contrast injection was performed during retrograde cardioplegia while the left ventricle was being imaged in the short-axis view, to evaluate myocardial opacification.

Contrast echocardiography analysis. Contrast echocardiograms were recorded on magnetic tape and reviewed off-line by two independent observers. Planimetric measurements of myocardial opacification during both antegrade and retrograde cardioplegia were performed, and the percentage of myocardial opacification with respect to the total area of left ventricular myocardium was calculated.³⁷

Statistical analysis. Quantitative measurements were expressed as mean $\pm$ standard deviation. Categorical data were presented as the absolute frequency and the percent

frequency. Data on percent myocardial opacification were analyzed by analysis of variance with repeated measures, with sex, hypertension, diabetes, degree of coronary vessel disease, location of occlusion(s), and development of collateral circulation as between-subject factors (one in each analysis) and route (antegrade and retrograde) of delivery of cardioplegia solution as repeated-measures factor. Multiple comparisons were performed by applying the appropriate *t* test with Bonferroni's correction. Clinical and coronary angiographic findings in the patients with good and poor collateral circulation were compared by two-group *t* test for the quantitative variable and by Fisher's exact probability test for categorical variables. A *p* value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed with the BMDP package.⁴⁶

Results

Aortic incompetence was detected during intraoperative transesophageal color Doppler and contrast echocardiography in five of 26 patients (19.2%) and right-to-left shunt at the atrial level in three of 26 patients (11.5%); these eight patients were excluded from the analysis. The distributions of clinical and coronary angiographic findings in the remaining 18 patients (grouped by poor and good collateral circulation) were not significantly different (*p* = NS*) (Table I). In these patients overall

*NS = Not significant.

Table II. Results of analysis of variance with repeated measures

Variables	No. of patients	Myocardial opacification (%)		Main effect grouping factor	p Values	
		Antegrade (mean $\pm$ SD)	Retrograde (mean $\pm$ SD)		Main effect route of cardioplegic solution delivery	Interaction
Sex				NS	0.0139	NS
Male	16	58.3 $\pm$ 16.5	76.3 $\pm$ 13.2			
Female	2	65.5 $\pm$ 7.8	89.5 $\pm$ 12.0			
Previous myocardial infarction				NS	0.0057	NS
No	10	61.3 $\pm$ 15.3	79.1 $\pm$ 16.2			
Inferior	3	47.3 $\pm$ 20.4	77.7 $\pm$ 3.1			
Anterior	2	61.5 $\pm$ 20.1	78.5 $\pm$ 10.6			
Inferior and anterior	3	61.7 $\pm$ 19.7	72.7 $\pm$ 15.3			
Hypertension				NS	0.0013	NS
Yes	9	56.3 $\pm$ 16.1	76.3 $\pm$ 12.1			
No	9	61.8 $\pm$ 15.9	79.1 $\pm$ 15.3			
Diabetes				NS	0.0012	NS
Yes	3	52.3 $\pm$ 17.8	84.3 $\pm$ 12.1			
No	15	60.4 $\pm$ 15.6	76.4 $\pm$ 13.7			
Degree of coronary disease				NS	0.0042	NS
Three-vessel stenosis >75%	4	54.8 $\pm$ 17.9	84.3 $\pm$ 9.4			
One vessel occluded	11	57.0 $\pm$ 16.0	75.1 $\pm$ 15.0			
Two vessels occluded	3	72.3 $\pm$ 5.1	78.7 $\pm$ 12.7			
LM stenosis $\geq$ 75%				NS	0.0465	NS
Yes	2	56.5 $\pm$ 27.6	70.0 $\pm$ 14.1			
No	16	59.4 $\pm$ 15.1	78.7 $\pm$ 13.5			
LAD				NS	0.0017	NS
Stenosis >75%	11	58.7 $\pm$ 13.8	77.7 $\pm$ 13.6			
Occlusion	7	59.6 $\pm$ 19.7	77.7 $\pm$ 14.3			
Cx				NS	0.0199	NS
Stenosis >75%	15	57.9 $\pm$ 17.1	77.7 $\pm$ 13.6			
Occlusion	3	64.7 $\pm$ 2.9	78.0 $\pm$ 15.4			
RCA				NS	0.0019	NS
Stenosis >75%	11	55.7 $\pm$ 16.6	79.9 $\pm$ 13.3			
Occlusion	7	64.3 $\pm$ 13.8	74.3 $\pm$ 14.0			
Collateral circulation				NS	<0.0001	0.0024
Poor	6	44.3 $\pm$ 15.0	81.2 $\pm$ 9.0			
Good	12	66.4 $\pm$ 10.2	76.0 $\pm$ 15.2			

Interaction is referred to comparison between route of cardioplegia delivery (antegrade/retrograde) and levels of grouping factors. LM, Left main; LAD, left anterior descending coronary artery; Cx, left circumflex coronary artery; RCA, right coronary artery.

myocardial opacification was significantly greater during retrograde than during antegrade cardioplegia (77.7% $\pm$ 13.4% versus 59.1% $\pm$ 15.7; $p = 0.0009$; Fig. 1). This difference was affected by collateral circulation as pointed out by the significant interaction between coronary collateral circulation and percent myocardial opacification values with antegrade and retrograde cardioplegia administration ($F^{1, 16} = 12.95, p = 0.002$) (Table II, Fig. 2). In the presence of well-developed collateral circulation, multiple comparisons showed that percent myocardial opacification was greater during retrograde than during antegrade delivery of cardioplegic solution, but the difference was not significant (76.0% $\pm$ 15.2% versus 66.4% $\pm$ 10.2%; $p = \text{NS}$).

On the other hand, in patients with poor collaterals, myocardial opacification was significantly greater in retrograde than in antegrade cardioplegia (81.2% $\pm$ 9.0% versus 44.3% $\pm$ 15.0%; $p < 0.02$). When considering antegrade cardioplegia alone, myocardial opacification was significantly higher in patients with well-developed collateral vessels than in patients with poor or absent collaterals (66.4% $\pm$ 10.2% versus 44.3% $\pm$ 15.0%; $p < 0.01$).

Discussion

Myocardial ischemia, myocardial reperfusion, cardiopulmonary bypass, and intraoperative events may all cause myocardial injury; therefore successful resolution of pertinent questions on these elements

Fig. 2. Bar graph of percent myocardial opacification in 18 patients grouped by cardioplegia delivery (antegrade, retrograde) and angiographic evaluation of collateral circulation (poor, good). Correlations between and within groups are shown. See text for details.

will result in improved cardiac protection.^{21,22} The questions related to the intraoperative elements may be summarized in (1) optimization of the strategies currently used to perform cardiac operations, (2) use of new tools to make the operation safer, and (3) improvement in the knowledge of cardioplegia efficacy and distribution.^{21,22} Among these questions, the one related to delivery of cardioplegic solution is critical to the process of myocardial protection during CABG, and even though antegrade/retrograde cardioplegia has made remarkable strides in recent years, this issue is still being debated.^{6,7,15-24}

In the present report we focused on the factors that may be involved in maldistribution of cardioplegic solution during CABG. Before the 1990s myocardial distribution of cardioplegic solutions was monitored by thermography and by temperature probes that revealed the temperature differences in the myocardium.⁴⁷⁻⁵⁰ However, these monitoring techniques may be inadequate^{48,51-53} and are useless when normothermic cardioplegia is being used. Conversely, myocardial contrast echocardiography, recently introduced to evaluate myocardial perfusion, has been shown to be a useful tool for imaging antegrade and retrograde cardioplegia.^{25,36-38}

The optimal route of infusion of cardioplegic solutions during CABG represented an important issue in recent years. Antegrade cardioplegia has been demonstrated to be a safe and effective method for myocardial protection during elective CABG.^{6,18} However, the major disadvantage of aortic root cardioplegia is the nonhomogeneous

myocardial perfusion and cooling in the presence of severe coronary stenosis and/or occlusion.^{1-5,7} An adjunctive risk of incomplete myocardial perfusion during antegrade cardioplegia is chronic aortic insufficiency as an associated disease or transient valve incompetence inadvertently caused by aortic cross-clamping.^{2,5,6,12,38,54} To eliminate the interference of this risk factor, we excluded from the study patients showing aortic incompetence at transesophageal Doppler and contrast echocardiography.

On the other hand, retrograde delivery of cardioplegic solution through the venous system of the heart (coronary sinus, right atrium) has been reposed as an alternative way of myocardial protection allowing homogeneous distribution and cooling in myocardial areas supplied with occluded coronary arteries.^{2,7,9-13} However, more critical information on the pathophysiology of retroplegia through the coronary sinus is needed,^{22,23} and right atrial cardioplegia cannot be used in patients with either atrial septal defect or patent foramen ovale.^{6,9,10,38}

The results of our study confirm that the route of delivery of cardioplegic solution represents an important determinant for the adequacy of myocardial perfusion. In fact, overall myocardial opacification was significantly higher with retroplegia than with antegrade cardioplegia (see Fig. 1). However, another important role is played by the collateral circulation. In patients with chronic, stable angina, well-developed collateral vessels ensure homogeneous myocardial cooling that is independent of the route chosen for cardioplegic infusion.¹⁸ However, collaterals differ in terms of anatomy and flow

Fig. 3. *Top*, Selective left coronary arteriography showing obstruction (*arrow*) of left anterior descending coronary artery distal to the first septal branch. Collaterals from the circumflex to the left anterior descending beyond the obstruction are well visualized. *Middle*, Transesophageal echocardiography short-axis image of the left ventricle (*LV*) at the papillary muscle level before contrast injection. *Bottom*, During antegrade cardioplegia, the distribution of cardioplegic solution is homogeneous and the territory of the left anterior descending coronary artery is perfused.

pattern from the normal arterial vessels because they are characterized by marked endothelial cell proliferation and subintimal hyperplasia.^{55, 56} Thus even a well-developed collateral, despite maximal vasodilation after cardioplegic arrest,^{57, 58} represents a resistance to blood flow that is functionally comparable with a severe stenosis of a native coronary artery.⁵⁹ In our study the impact of collaterals on myocardial opacification was demonstrated by their interaction during antegrade and retrograde cardioplegia and by the lack of any significant gap between antegrade versus retrograde cardioplegia in the presence of good collaterals (see Table II, Fig. 2). The key role of collateral vessels is further demonstrated by comparing patients with poor versus good collaterals undergoing antegrade cardioplegia alone. In this subset of patients myocardial opacification was mainly related to poor versus good collaterals, rather than to obstructed vessels versus significantly narrowed vessels or to other nonanatomic risk factors (see Table II).

The results of our study confirm the following: (1) Retrograde cardioplegia provides greater myocardial opacification than antegrade cardioplegia; (2) well-developed collaterals ensure homogeneous myocardial distribution of cardioplegic solution, independent of the route chosen for infusion.

We conclude that when cold (4° C) potassium crystalloid cardioplegic solutions are being used in patients with chronic stable angina undergoing elective CABG, retrograde cardioplegia offers no advantage versus antegrade cardioplegia when a well-developed collateral circulation is present. On the other hand, conventional aortic root infusion may not provide adequate myocardial protection in the subset of patients with significantly narrowed or occluded coronary arteries and poor collateral circulation.

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