SURGERY FOR ACQUIRED CARDIOVASCULAR DISEASE

REOPERATIVE CORONARY BYPASS SURGERY: EFFECT OF PATENT GRAFTS AND RETROGRADE CARDIOPLEGIA

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Objective: To determine the effects of patent or diseased aorta-coronary bypass grafts and retrograde cardioplegia on mortality during reoperative coronary bypass surgery.

Methods: We conducted a retrospective review of prospectively gathered data, supplemented by systematic chart review, of all patients (n = 744) undergoing reoperative coronary bypass surgery at our institution between 1990 and 1997. Independent predictors of survival were determined by step-wise logistic regression analysis.

Results: At least one patent or stenosed graft to the left anterior descending artery was present in 50% of patients, to the circumflex territory in 27% of patients, and to the right coronary artery territory in 33% of patients. The previous left anterior descending graft was a saphenous vein in 82% and a left internal thoracic artery in 18% of patients. In-hospital mortality occurred in 42 (5.6%) patients. Patent or diseased grafts of any coronary artery territory did not significantly increase the risk of mortality. Retrograde cardioplegia use increased in more recent years, was more frequent in patients with stenosed grafts, and was associated with improved survival. Independent predictors of mortality were as follows (with odds ratios and 95% confidence intervals in parentheses): failure to use retrograde cardioplegia (odds ratio 2.81; 1.28-6.20), New York Heart Association class (odds ratio 2.69; 1.25-5.81), peripheral vascular disease (odds ratio 2.60; 1.25-5.41), and left ventricular grade (2.07; 1.31-3.27).

Conclusions: In this series, patent or stenosed grafts were not associated with an increased risk of mortality during reoperative coronary bypass surgery, possibly because of increased use of retrograde cardioplegia in this patient group. We strongly recommend the routine use of retrograde cardioplegia during redo coronary bypass surgery. (J Thorac Cardiovasc Surg 2001;121:83-90)

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Reoperative coronary bypass grafting (redo-CABG) is an important clinical problem for cardiac surgeons. The number of redo-CABGs may be rising over time,¹ and the risk profile of patients undergoing reoperation is increasing.^{2,3} Several previous studies have demonstrated an increased risk for reoperation in patients with patent or diseased CABGs, particularly atherosclerotic saphenous vein grafts.⁴⁻⁷ Retrograde cardioplegia has been proposed as a method of decreasing the risk of redo-CABG.⁸⁻¹⁰

We undertook this study to determine (1) whether patent or diseased grafts increase the risk of mortality during redo-CABG and (2) whether retrograde cardioplegia mitigates this increased risk.

Methods

Preoperative, perioperative, and postoperative data were collected prospectively on all patients and entered into our institutional computerized registry. All patients undergoing redo-CABG (at least one prior CABG procedure) from 1990 to 1997 were identified. Patients undergoing concomitant valvular, aneurysmal, or extracardiac procedures were excluded.

A systematic chart review was performed on all redo-CABG patients identified ($n = 744$), with a focus on the status of previous CABGs. Previous grafts were classified as patent (no stenosis), stenosed (at least one stenosis $> 50\%$ of the luminal diameter), or occluded. Graft location was classified according to the three major coronary artery territories—left anterior descending (LAD), circumflex, and right coronary artery (RCA). Patients with more than one graft to a territory were assigned the highest risk present for that territory, where estimated risk was stenosed $>$ patent $>$ occluded. For example, a patient with one stenosed and one patent (non-stenosed) graft to the circumflex territory was considered to be in the stenosed circumflex group.

Anesthetic and surgical management. Pulmonary artery catheters and arterial cannulas were used for perioperative monitoring. Before 1995, our standard cardiac anesthetic consisted of high-dose fentanyl and midazolam for induction and isoflurane for maintenance. Since 1995, we have aimed for early extubation in all patients with an anesthetic consisting of low-dose fentanyl for induction and isoflurane and propofol for maintenance.¹¹

Access to the mediastinum was through a median sternotomy in nearly all patients. Femoral vessels were not routinely exposed. Arterial cannulation was performed via the ascending aorta or aortic arch. A single, two-staged right atrial cannula was used for venous drainage. The hematocrit value was maintained between 20% and 25% during cardiopulmonary bypass (CPB), pump flow rates between 2.0 and 2.5 L $\cdot$ min⁻¹ $\cdot$ m⁻², and mean arterial pressure between 60 and 80 mm Hg. Systemic body temperature was allowed to drift to 34°C, with active rewarming at the end of CPB.

The “no-touch” technique was used for dissection of mediastinal structures in patients with diseased grafts,¹⁰ with manipulation of diseased grafts being avoided before admin-

istration of cardioplegic solution. Diseased grafts were ligated and removed after cardioplegic solution was administered, except when a left internal thoracic artery (LITA) was being used to replace a large, noncritically stenosed vein graft to the LAD.¹² Coronary bypass anastomoses were performed during a single period of aortic crossclamping. We used the LITA to bypass the LAD in the majority of patients without a previous LITA graft. In those patients with a functioning previous LITA graft, a temporary clamp was applied to the LITA during administration of cardioplegic solution.

Myocardial protection. All patients received blood-based cardioplegic solution at a ratio of 4:1 (blood to crystalloid solution) before 1996 and 8:1 since 1996. Our crystalloid component consisted of potassium chloride and magnesium sulphate.¹³ Cardioplegia temperature and delivery technique were according to surgeon preference. Antegrade cardioplegia was administered via the aortic root at a pressure of 70 mm Hg. One liter of cardioplegic solution was given to achieve myocardial arrest, followed by repeated doses of 300 mL after each proximal anastomosis or every 20 minutes thereafter. When used, retrograde cardioplegia was administered almost continuously via a self-inflating coronary sinus catheter to a maximum flow of 200 mL/min or a maximum coronary sinus pressure of 40 mm Hg. “Combination” cardioplegia consisted of antegrade cardioplegia to achieve myocardial arrest followed by retrograde cardioplegia with or without antegrade perfusion of completed vein grafts.

Statistical analysis. All statistical analyses were performed with the SAS system (SAS Institute, Inc, Cary, NC). Categorical variables are expressed as percentages and were evaluated with χ^2 or Fisher exact tests where appropriate. Continuous variables are expressed as mean $\pm$ standard deviation (SD) and were evaluated by the Student t tests. Possible risk factors for in-hospital mortality were analyzed univariately (see the appendix). All variables suggested by the univariate analysis ($P < .25$) or those judged to be clinically important were entered into a stepwise multivariable logistic regression analysis model. The model with the best Hosmer-Lemeshow goodness-of-fit statistic and receiver operator characteristic curve was chosen, as previously described.¹⁴

Results

A total of 744 patients underwent redo-CABG at our institution between 1990 and 1997, representing 7.0% of the entire CABG population. The number of redo-CABGs performed per year, as well as the percentage of CABG procedures that were reoperative, remained relatively constant over this time period. The number of previous CABG procedures was one in 723 patients, two in 20 patients, and three in 1 patient. The mean ($\pm$ SD) interval between operations was 11.4 $\pm$ 4.9 years. The number of distal anastomoses per patient was 3.2 $\pm$ 1.0. At reoperation, the LITA was used to bypass the LAD in 494 (66%) patients. The mean aortic cross-clamp and CPB times were 68 $\pm$ 23 and 103 $\pm$ 36 minutes, respectively.

Fig 1. Prevalence of retrograde cardioplegia use (alone or in combination with antegrade cardioplegia) during redo-CABG surgery over time.

Table I. Incidence of in-hospital mortality according to previous graft status during redo-CABG (n = 744)

Territory	Status of previous graft (%)				P value
	None	Occluded	Stenosed	Patent	
LAD	10.7	3.8	7.3	4.7	.10
Circumflex	4.5	5.5	8.6	5.1	.5
RCA	4.8	7.0	4.0	3.5	.4

LAD, Left anterior descending coronary artery; RCA, right coronary artery.

A perioperative myocardial infarction occurred in 49 (6.6%) patients and postoperative low cardiac output syndrome occurred in 166 (22.3%) patients. An intra-aortic balloon pump was inserted in the operating room or postoperatively in 144 (19.4%) patients. Seventeen (2.3%) patients required re sternotomy for bleeding. Stroke occurred in 17 (2.3%) patients and deep sternal wound infection in 5 (0.7%) patients. In-hospital mortality occurred in 42 (5.6%) patients and is discussed in more detail below.

Previous graft status. A patent or stenosed graft to the LAD was present in 370 (50%) patients. The previous graft to the LAD was a saphenous vein in 82% of patients and a LITA in 18%. Previous saphenous vein grafts were more likely to be stenosed (40%) or occluded (50%) than LITA grafts (9% and 33%, respectively; $P < .001$). The LITA was injured during re sternotomy in 10 patients (12.5% of all patients with patent or stenosed LITA grafts), of whom 1 patient died. The right ventricle was injured during re sternotomy in 9 patients, of whom 2 died.

At least one patent or stenosed graft to the circumflex territory was present in 199 (27%) patients and to the

RCA territory in 246 (33%) patients. Previous grafts to the circumflex or RCA territory were saphenous veins in the vast majority of patients.

Table I displays mortality rates according to the status of previous grafts. We were unable to demonstrate a statistically significant effect of previous graft status—to the LAD, circumflex, or RCA territory—on mortality. Although the differences were not statistically significant, it appears that patients with no previous LAD graft had the highest risk of mortality, followed by patients with stenosed grafts to the circumflex and LAD coronary arteries.

Myocardial protection. As stated previously, the method of cardioplegia administration was at the discretion of the surgeon. Antegrade cardioplegia alone was used in 60% of patients, retrograde cardioplegia alone in 15%, and a combination of the two methods in 25%. The cardioplegic solution was warm ($>35^{\circ}\text{C}$) in 3% of patients, tepid (20°C - 35°C) in 8%, and cold ($<20^{\circ}\text{C}$) in 89%. Cardioplegic solution was administered intermittently in 67% of patients and near continuously in 33%.

Fig 1 displays the use of retrograde cardioplegia, either alone or in combination with antegrade cardio-

Fig 2. Use of cardioplegia delivery techniques according to the presence or absence of one or more stenosed grafts. Retrograde cardioplegia, alone or in combination with antegrade cardioplegia, was used more frequently in patients with stenosed grafts.

Fig 3. In-hospital mortality according to cardioplegia delivery technique.

plegia, over time. There was a significant increase in the use of retrograde cardioplegia for redo-CABG surgery over the period of this study ($P < .001$). We also examined the relationship between retrograde cardioplegia use and status of previous grafts. Fig 2 reveals that retrograde cardioplegia, alone or in combination with antegrade cardioplegia, was more likely to be used in patients with at least one stenosed graft ($P < .001$).

Retrograde cardioplegia, alone or combined, resulted in a significant reduction in mortality ($P < .05$, Fig 3). However, the use of retrograde cardioplegia did not significantly decrease the risk of myocardial infarction,

which occurred in 5.3% of antegrade procedures, 5.3% of retrograde procedures, and 7.8% of combined procedures ($P = .5$). Likewise, retrograde cardioplegia did not reduce the incidence of low cardiac output syndrome (21% for antegrade, 24% for retrograde, and 22% for combined, $P = .5$).

Predictors of mortality. Hospital mortality occurred in 42 (5.6%) patients. The association between mortality and each of the variables listed in the appendix was first analyzed univariately. Significant ($P < .05$) univariate predictors of mortality were female sex, increased age, urgent timing, Canadian Cardiovascular Society

Fig 4. Independent predictors of in-hospital mortality. *C.I.'s*, Confidence intervals; *NYHA class*, New York Heart Association heart failure class; *PVD*, peripheral vascular disease; *LV grade*, left ventricular ejection fraction, where grade I is 60% or more, grade II is 40% to 59%, grade III is 20% to 39%, and grade IV is less than 20%.

angina class, New York Heart Association heart failure class, increasing left ventricular dysfunction (left ventricular grade), peripheral vascular disease, systemic hypothermia during CPB, failure to use a LITA graft, and failure to use retrograde cardioplegia. The surgeon was also a significant univariate predictor of mortality ($P = .03$) before risk adjustment by multivariable techniques. Mortality rates for the 8 surgeons who performed more than 10 reoperative procedures ranged from 1.3% to 15%.

Fig 4 displays the independent predictors of mortality, as determined by multivariable logistic regression analysis. The risk factors for mortality, in decreasing order of magnitude, were failure to use retrograde cardioplegia, increasing New York Heart Association class, peripheral vascular disease, and increasing left ventricular dysfunction (left ventricular grade). After adjustment for these risk factors, the operating surgeon was not an independent predictor of mortality. The area under the receiver operator characteristic curve was 0.741 and the Hosmer-Lemeshow goodness-of-fit statistic was 0.611 for our logistic regression model, indicating good discrimination and precision.

Discussion

Redo-CABG is an important clinical entity. Previous studies have noted an increase in the prevalence of redo-CABG surgery over time as the age of our patient population increases.^{3,15,16} However, increasing use of arterial conduits¹⁷ and lipid-lowering agents¹⁸ may

result in a plateau in the number of reoperative procedures, a pattern we have noted in our own institution.²

Several investigators have noted an increased risk profile for redo-CABG patients over time.^{2,3,16} We recently examined 1230 consecutive redo-CABG patients over a 16-year period and found increased age, left ventricular dysfunction, severity of symptoms, extent of coronary artery disease, and urgent/emergency timing in more recent years.² Despite the increase in risk profile, however, morbidity and mortality remained constant or decreased throughout the study.

Redo-CABG surgery may be required as a result of graft disease, progression of native coronary atherosclerosis, or a combination of these factors.^{3,4,19} Of these three indications, vein graft disease is by far the most common.^{3,4,19} Approximately 40% of saphenous vein grafts are occluded 10 years after CABG surgery and a further 30% are stenotic, predominantly because of vein graft atherosclerosis.⁴

Several previous studies have noted an increased risk of mortality in redo-CABG patients with patent or diseased grafts.⁴⁻⁷ The increased risk is primarily due to atheroembolism from saphenous vein grafts, a widely recognized complication.^{5,10,20} Patent LITA grafts may also increase risk due to graft injury during dissection.²¹

Retrograde cardioplegia may decrease the risk of atheroembolism during redo-CABG. Retrograde delivery has been hypothesized to result in less embolization than antegrade delivery,²² and anecdotal evidence sug-

gests that retrograde delivery of cardioplegic solution can dislodge atheroemboli that have already occurred.²¹ Previous studies, with relatively small numbers of patients undergoing reoperations, have suggested that retrograde cardioplegia decreases the use of intra-aortic balloon pumping⁸ and mortality.^{9,10} We therefore analyzed a large cohort of redo-CABG patients to determine whether patent or stenotic grafts increase the risk of mortality and whether retrograde cardioplegia mitigates this risk.

We were unable to demonstrate a statistically significant effect of previous graft status, to any coronary territory, on mortality (Table I). We were surprised to find that patients with the highest risk of mortality were not those with stenosed grafts to the LAD, but rather patients without a previous LAD graft. However, this may simply be a reflection of marginal coronary anatomy in these patients. Stenosed grafts to the RCA or circumflex territory did not result in a significantly increased risk of mortality.

As expected, we found a higher incidence of stenosis in saphenous vein grafts to the LAD when compared with LITAs. Although injury to the LITA occurred in 12.5% of patients at risk in this study, only one death occurred in this group. We therefore concur with previous investigators that a functioning LITA graft is not a contraindication to redo-CABG.²¹

Our use of retrograde cardioplegia in redo-CABG patients increased over time (see Fig 1) as the benefits of this technique became more apparent in the literature. We were more likely to use retrograde delivery in patients with one or more stenosed grafts (see Fig 2). Retrograde cardioplegia, alone or in combination with antegrade cardioplegia, resulted in a significant reduction in mortality (see Fig 3). In addition, multivariable analysis revealed that retrograde cardioplegia was the most significant independent predictor of survival (Fig 4). Although surgeons differed with regard to which cardioplegia delivery technique was used, individual surgeon was not an independent predictor of mortality. In addition, the surgeon with the second lowest mortality in our series (2.8%) used antegrade cardioplegia almost exclusively. Therefore, we do not believe that the benefit of retrograde cardioplegia is simply a surgeon-specific finding.

We were unable to demonstrate a beneficial effect of retrograde cardioplegia on the incidence of myocardial infarction or low cardiac output syndrome. However, this lack of effect may be due to the higher risk profile of the retrograde cardioplegia group, that is, more patients with stenotic vein grafts.

Fig 3 reveals that the lowest risk of mortality occurred in patients receiving retrograde cardioplegia

alone. However, previous studies by our group have revealed that isolated retrograde cardioplegia may result in inadequate myocardial perfusion. In a randomized trial of 107 patients undergoing CABG,²³ we found that retrograde cardioplegia resulted in increased myocardial lactate production, increased creatine kinase MB release, and decreased adenosine triphosphate levels when compared with antegrade cardioplegia. In addition, we used intraoperative contrast echocardiography to demonstrate that retrograde cardioplegia resulted in poor perfusion of the right ventricle.²⁴ Antegrade perfusion of the saphenous vein graft to the RCA resulted in a marked improvement in right ventricular perfusion.²⁴ Therefore, the optimal myocardial protection strategy for redo-CABG may be retrograde cardioplegia supplemented by antegrade perfusion of new vein grafts, in particular to the RCA.

Conclusions

In this large retrospective study, we were unable to detect a significantly increased risk of in-hospital mortality for patients with patent or stenosed grafts. The lack of association may be due to our increased use of retrograde cardioplegia in patients with stenosed grafts. Retrograde cardioplegia, alone or in combination with antegrade cardioplegia, resulted in a significant reduction in mortality. We therefore recommend the use of retrograde cardioplegia in all patients undergoing redo-CABG.

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Appendix

Variables assessed in predictive models

Year of redo-CABG operation

Time since previous CABG operation

Number of previous CABG operations

Sex

Age

Left ventricular grade: Left ventricular ejection fraction, as assessed by angiography or 2-dimensional echocardiography, where grade I $\geq 60\%$, grade II = 40% to 59%, grade III = 20% to 39%, and grade IV < 20%

Recent (<30 days) myocardial infarction

Timing: Elective, semi-urgent (operation during same hospitalization for cardiac event), urgent (operation < 72 hours of cardiac event), and emergency (operation < 12 hours of cardiac event)

Canadian Cardiovascular Society angina class

New York Heart Association heart failure class

Congestive heart failure: History of hospital admission for congestive heart failure

Renal failure: Serum creatinine > 200 $\mu\text{mol/L}$ or history of renal failure

Diabetes mellitus

Hypertension

Hypercholesterolemia

Chronic obstructive pulmonary disease

Peripheral vascular disease: History of peripheral or carotid vascular disease

Previous stroke or transient ischemic attack

CPB temperature: Normothermia (minimum systemic temperature > 35°C) or mild (30°-35°C), moderate (20°-29°C) or profound (<20°C) hypothermia

Cardioplegia temperature: Cold (<20°C), tepid (20°C-35°C), or warm (>35°C) blood cardioplegic solution

Cardioplegia delivery: (1) Antegrade, retrograde, or combined (antegrade and retrograde) cardioplegia; (2) intermittent or near continuous

CPB time

Crossclamp time

Previous graft status: None, occluded, stenosed, or patent grafts to the LAD, circumflex, and RCA territories

Number of diseased vessels

Number of new grafts

Use of LITA at reoperation

Surgeon

Discussion

Dr Hendrick B. Barner (*St Louis, Mo*). Others have touted the benefits of retrograde cardioplegia for redo-CABG, but this is the first report demonstrating a reduction in operative mortality with its use. I have used antegrade-retrograde cardioplegia for coronary reoperations during the same time frame but in about 80% of cases from the beginning. Your use of retrograde cardioplegia was only 55% in 1997. Since it is clearly helpful, it is surprising to me that its use has not been greater. Has its use increased since then? If not, why?

I assume these data were generated by 6 or 7 operating surgeons. This poses questions regarding the distribution of cases among those individuals and whether you entered the surgeon into the analysis of risk factors for hospital mortality.

You initiated this analysis to also determine the effect of graft status on the risk of hospital death and found that it was not a risk factor, which is contrary to some reports of more than a decade ago. You also ligated or divided all diseased vein grafts after the initial dose of antegrade cardioplegia, which I practiced some years ago but abandoned because of my increasing use of all arterial conduits at reoperation and concern over perioperative hypoperfusion. Did you not divide diseased vein grafts if they were replaced with an arterial conduit?

Contrary to the experience from the Cleveland Clinic and the Massachusetts General Hospital, you did not find that emergency timing was a risk factor for hospital death, whereas it was a most important one at these institutions. This may well be related to your definition of "emergency," which commonly means transport to the operating theater directly from the catheterization laboratory or the intensive care unit, as opposed to your definition of "within 12 hours of the cardiac event." I would also wonder whether there were too few patients in this category to provide meaningful data?

Finally, I am curious about the use of tepid cardioplegic solution, which was introduced by 2 of your coauthors. I adopted this modality in 1995 with the modification of having both the patient and cardioplegic solution at 33°C. I use it in all operations on the heart and was surprised to see that its usage remains uncommon at the Toronto General Hospital. Would you care to comment on this?

Dr Borger. Thank you very much, Dr Barner, for your comments. I will try to answer your questions in sequence.

The use of retrograde cardioplegia did increase over the 8 years of this study, and it continues to increase in redo-CABG at our institution.

The number of surgeons that were analyzed for this study was 10. We did look at surgeon-specific operative mortality, and there were some differences. However, there were no significant outliers, that is, each one of the surgeons fell within the 95% confidence intervals of the group mean. Also, an interesting point is that the surgeon with the lowest operative mortality in this group of patients used predominantly retrograde cardioplegia, but the surgeon with the second lowest operative mortality used almost exclusively antegrade cardioplegia. Therefore, it was not simply that the surgeons with the lowest mortality used retrograde cardioplegia. In other words, this is not a surgeon-specific result. I honestly believe that retrograde cardioplegia is of benefit in redo-CABG surgery.

Regarding your question whether or not we ligated all saphenous vein grafts, there was one group of patients in whom we did not use this technique because of a very important article published by the Cleveland Clinic. According to this article, in patients with a large noncritically stenosed LAD vein graft that is going to be bypassed with a LITA, it is

better not to divide the vein grafts because of possible poor perfusion of the LAD territory. Therefore, in these patients we often left the saphenous vein graft in place.

With regard to the definition of operative timing, our definition is always a bit different from that of American studies. We defined *urgent timing* as operations performed during the same hospitalization stay as the initial admission for the cardiac event and *emergency timing* as those operations performed within 12 hours of a cardiac event. The risk of mortality in patients undergoing urgent and emergency operations was increased in our univariate analysis. However, it fell out during the multivariable analysis.

Finally, with regard to tepid cardioplegia use, the majority of our surgeons at our institution do use cold antegrade blood cardioplegia plus or minus retrograde cardioplegia. Of course, we performed the Warm Heart Trial several years ago, which showed some benefit with warm cardioplegia, but there is always the worry about increased neurologic threat. Tepid cardioplegia has been demonstrated by Dr Weisel and his colleagues to possibly be superior temperature to cold or warm cardioplegia. However, we think that cold cardioplegia still gives us the best safety margin, which is often necessary in these complicated redo-CABG operations. Therefore, I do not believe that the number of patients receiving tepid cardioplegia will be increasing in the near future at our institution. Ideally, the number of patients who receive retrograde cardioplegia during redo-CABG surgery will increase at our institution.

Dr D. Craig Miller (*Stanford, Calif*). I have a quick question,

Dr Borger. What is happening to your redo-CABG patients? You have long waiting lists in Canada, and I believe your unit has gone from 1000 to 2000 or maybe nearly 3000 pump cases a year. Yet, your incidence of redo-CABG stayed about the same, 100 or so a year. Are the patients requiring redo-CABG going to other centers in Ontario or perhaps across the lake?

Dr Borger. Before 1990, the number of total CABGs at our institution did increase at a linear rate. However, the number has been fairly constant over the 8 years of this study, from 1990 to 1997. When we looked at the number of redo-CABGs as a percentage of all of the CABG procedures done, once again, it remained relatively constant over this time period.

This is in contrast to previous studies, in particular from the Cleveland Clinic, that suggest that redo surgery may be increasing in prevalence over time. I am not exactly sure why our prevalence did not increase over these 8 years. Presumably, it is related to improvements in medical management, particularly aggressive cholesterol-lowering management, and it may also be related to our increasing use of additional arterial grafts, but that is only speculative at this point. One other hospital in the Toronto area did perform progressively more redo-CABG operations over the 8-year time period, so that may have affected our trends as well.