The Insulin Cardioplegia Trial: Myocardial protection for urgent coronary artery bypass grafting

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Background: Small, nonrandomized clinical trials have demonstrated a beneficial effect of solutions containing insulin and glucose on the recovery of myocardial metabolism and ventricular function after cardioplegic arrest and reperfusion. However, no large, blinded, randomized study has yet determined the effects of insulin-enhanced cardioplegia on clinical outcomes after coronary artery bypass grafting.

Methods: The Insulin Cardioplegia Trial was designed to evaluate the clinical impact of insulin-enhanced cardioplegia on patients at high risk undergoing isolated coronary artery bypass grafting for unstable angina. A total of 1127 patients were randomly assigned at operation to receive cardioplegic solution supplemented with 10 IU/L insulin ($n = 557$) or placebo ($n = 570$). All personnel with direct patient contact were blinded to randomization group.

Results: Overall operative mortality was 2.2%, with no significant differences between groups. The prevalences of postoperative low output syndrome (insulin 10.4%, placebo 9.7%, $P = .7$) and enzymatic myocardial infarction (insulin 21.0%, placebo 18.8%, $P = .3$) were not different between groups. The primary composite outcome of low output syndrome and/or enzymatic myocardial infarction revealed no difference between groups (insulin 30.0%, placebo 26.3%, $P = .2$).

Conclusions: Despite encouraging results from smaller, nonrandomized studies, the Insulin Cardioplegia Trial failed to demonstrate a clinical benefit of insulin-enhanced cardioplegic solution for patients undergoing high-risk isolated coronary artery bypass grafting.

Several reports from large database registries have documented the improved clinical results after isolated coronary artery bypass grafting (CABG).^{1,2} However, certain groups of patients continue to face increased risk of morbidity and mortality after this operation. These include patients with left ventricular dysfunction, elderly patients, and patients who undergo urgent operations because of unstable angina or critical coronary anatomy.³⁻⁵

Improved methods of myocardial protection may improve the results of surgery

in these high-risk populations. Demonstration of incremental benefits for conventional clinical outcomes such as mortality and Q-wave myocardial infarction (MI), however, would require prohibitively high numbers of patients to achieve clinical and statistical significance. We have previously demonstrated that postoperative low cardiac output syndrome (LOS) is an alternative objective outcome that may be used to evaluate alternate methods of myocardial protection.⁶ In addition, determining the area under the curve of creatine kinase MB isoenzyme fraction (CKMB) over time provides a more sensitive measure of enzymatic myocardial injury.^{7,8} In the Warm Heart Trial,⁷ the largest prospective evaluation of myocardial protection to date, the incidence of postoperative LOS and enzymatic MI was more than 20% among patients undergoing urgent operations. Any clinical evaluation of a new cardioplegic intervention should therefore be targeted toward the reduction of LOS and enzymatic MI in those patients with unstable angina who require urgent, isolated CABG.

In 1965, Sodi-Pollares and colleagues⁹ first described the beneficial effects of a glucose-insulin-potassium infusion on the electrocardiographic changes during acute MI. The use of glucose-insulin solutions during heart operations has produced conflicting results.^{10,11} One potential confounding factor in the early studies of glucose-insulin-potassium solutions was the routine use of moderately hypothermic (25°C–28°C) cardiopulmonary bypass. In retrospect, metabolic stimulation of the heart may not have been effective at temperatures that inhibit normal enzyme function. The advent of normothermic or warm heart surgery has prompted a renewed interest in myocardial protection.⁷ We believe that a reassessment of myocardial metabolic stimulation is required at systemic and myocardial temperatures that more closely reflect current standards of practice and in patients who may receive the most potential benefit. The Insulin Cardioplegia Trial was designed as a large, double-blinded, prospective randomized trial to evaluate the impact of insulin-enhanced cardioplegia on objective clinical outcomes after isolated, urgent CABG for unstable angina or critical coronary anatomy.

Methods

Patient Population

A total of 3301 patients underwent urgent isolated CABG at Toronto General Hospital (n = 2382) or Sunnybrook and Women's College Health Science Centre (n = 919) between June 1996 and July 1999. There were 1271 patients screened for possible entry into this study, 1127 (34%) of whom were eventually randomly assigned to receive either insulin-enhanced cardioplegic solution (n = 557) or placebo (n = 570). Exclusion criteria for the study included any potential for concomitant surgery (eg, left ventricular aneurysmectomy or mitral valve repair), failure to obtain consent, refusal to participate, or inclusion in a competing clinical trial. A demographic comparison between study partici-

pants and nonparticipants has demonstrated no differences in postoperative LOS or perioperative MI.

The requirement for urgent surgery at the University of Toronto is determined by a combination of symptoms and coronary anatomy. Patients with angina refractory to intravenous medical therapy or those with critical left main coronary artery stenosis are recommended to undergo surgery within 72 hours of cardiac catheterization on an urgent basis. All patients enrolled in the study signed a written consent form approved by the respective institution's investigational review board.

Surgical Technique

A computer-generated randomization schedule was created and stratified by institution and surgeon to allow participants to conduct the surgical procedure according to individual preference. All patients received uniform perioperative anesthetic care, which has been described in detail previously elsewhere.^{12,13} Before anesthetic induction, a perfusionist not involved in the study case would open a sealed randomization envelope and proceed to prepare the study cardioplegic solution. Patients randomly assigned to the insulin group received a final concentration of 10 IU/L of Humulin R (Eli Lilly Canada; Mississauga, Ontario, Canada), whereas the placebo group received an equal volume of the inactive vehicle solution (courtesy of Eli Lilly Canada). All personnel with direct patient contact both during and after surgery remained blinded to the randomization group. The final cardioplegic solution has been described previously and represented an 8:1 mixture of oxygenated blood to crystalloid solution to achieve the following final concentrations: 6 mEq/L magnesium sulfate, 50 mmol/L glucose, and either a low (8 mEq/L) or a high (30 mEq/L) concentration of potassium chloride.¹⁴ All patients received an initial infusion of the high-potassium solution followed by maintenance with the low-potassium formulation.

Surgeons were permitted to use antegrade delivery of cardioplegic solution, retrograde delivery, or a combination of antegrade and retrograde delivery. Similarly, the cardioplegic temperature and the degree of systemic hypothermia were left up to surgeon preference. All proximal and distal anastomoses were completed during a single crossclamp period in most cases. Measurements of arterial blood gases, hematocrit, serum glucose, and serum potassium were performed every 20 minutes during the crossclamp period. Treatment of perioperative hypoglycemia or hyperglycemia is described in detail here and was standardized, as was the treatment of hyperkalemia.

Treatment of Hypoglycemia, Hyperglycemia, and Hyperkalemia

A strict protocol was developed for the treatment of abnormal serum glucose levels because of possible neurologic concerns related to hyperglycemia or hypoglycemia. Normal values in our laboratory range from 3 to 7 mmol/L. Because of the increased concern about hypoglycemia versus hyperglycemia, patients were given intravenous dextrose (25-g boluses) for any blood sugar value less than 5 mmol/L in the first four hours after the operation. In a pilot study, we observed that those patients with a blood sugar less than 10 mmol/L before leaving the operating room were at risk for development of hypoglycemia in the early postoperative period.¹⁴ Patients were therefore given a 25-g intravenous bolus of

dextrose if their last intraoperative blood sugar was less than 10 mmol/L. Because of the neurologic concerns of severe hyperglycemia, all patients with a blood sugar greater than 20 mmol/L in the first 4 postoperative hours were given a 5- to 10-IU intravenous bolus of Humulin R. In cases of insulin-dependent diabetes or persistent hyperglycemia, an intravenous insulin drip was administered until the patient reverted to the usual preoperative insulin regimen.

Patients with hyperkalemia during the crossclamp period were treated with furosemide or intravenous insulin. If the serum potassium level rose above 5.5 mmol/L, a 20-mg intravenous bolus of furosemide was administered. If the serum potassium climbed above 6.0 mmol/L, a 10-IU bolus of insulin was given intravenously.

Study Outcomes

The composite primary end point of the trial was the development of enzymatic MI, postoperative LOS, or both. Enzymatic MI was determined after obtaining serial measurements of CKMB. Measurements of CKMB were performed at 0, 2, 4, 8, 24, and 48 hours after arrival into the intensive care unit. Integration of the CKMB release over time curve was performed in all patients with at least 4 samples ($n = 962$, 85%). An integrated value greater than 1000 IU · h was used as a binary cutoff for the determination of enzymatic MI.⁸ To account for survivors with fewer than 4 samples, an analysis was repeated with two different end points for enzymatic MI: peak CKMB greater than 20 and peak CKMB/creatinine kinase ratio greater than 5%.

Clinical records of all patients who received intra-aortic balloon pump or postoperative inotropic support were flagged and reviewed by an independent outcomes committee blinded to treatment group. Each record was reviewed by at least three individuals (see Appendix 1 for outcomes committee members), and a determination of LOS was made by majority opinion.

All other clinical outcomes were recorded by the respective institution's clinical database manager. Stroke was defined as any new gross neurologic deficit or abnormal computed tomographic scan result. A description of the primary study end points is provided in Appendix 2.

Statistical Analysis

All data were collected prospectively and entered into a trial database. The SAS statistical software package (version 6.0 for Windows; SAS Institute, Inc, Cary, NC) was used for all statistical analyses. Categorical variables were analyzed with the χ^2 test or Fisher exact test as appropriate and are expressed as absolute or percentage frequencies. Continuous data were analyzed with the Student t test and are expressed as mean $\pm$ SD. Stepwise logistic regression analyses were performed to determine the independent predictors of LOS, MI, and the primary composite endpoint. Exact probability values are reported to enable the reader to discern clinical and statistical significance.

Results

Patient Demographic Characteristics

Table 1 compares the preoperative demographic characteristics in the insulin and placebo groups. Despite the ran-

domized nature of the trial, patients in the insulin group were more likely to have depressed ventricular function ($P = .02$) and left main coronary artery stenosis ($P < .001$). In addition, patients in the insulin group were more likely to have symptoms of congestive heart failure ($P < .001$).

Intraoperative Data

Table 2 compares the intraoperative data between the two groups. There were no significant differences in any of the operative variables apart from total cardioplegic volume. Patients in the insulin group received more cardioplegia than did those in the placebo group, although the difference is probably not clinically significant. The total volume of crystalloid delivered in the insulin group translates into a mean insulin dose of 44 IU per patient given directly to the heart during a mean crossclamp period of 66 minutes.

Exogenous Insulin and Glucose Treatment

Figure 1 compares the needs for exogenous insulin or glucose between the groups. According to protocol, insulin was given intravenously to treat severe hyperglycemia or hyperkalemia in 190 patients (32%) in the placebo group and 70 (12%) in the insulin group ($P < .001$). Patients who required insulin received a mean intravenous dose of 17 ± 14 IU in the insulin group and 16 ± 12 IU in the placebo group ($P = .5$). Intravenous administration of dextrose was required to treat hypoglycemia in 32 patients (5%) in the insulin group and 19 patients (3%) in the placebo group ($P = .05$). No patient with perioperative hypoglycemia had any neurologic complications. Among patients who required exogenous dextrose therapy, a mean dose of 36 ± 45 g was administered in the insulin group, compared with 22 ± 9 g in the placebo group ($P = .09$).

Primary End Points

The prevalences of the primary and secondary end-points in each group are displayed in Figure 2. There were no differences in either LOS, enzymatic MI, or the composite end point of LOS and/or MI. The mean area under the CKMB $\times$ time curve in the insulin group was 972 ± 759 IU · h (range 246-9352 IU · h) and in the placebo group was 883 IU · h (range 122-14,039 IU · h, $P = .5$). Separate analyses for the alternate definitions of enzymatic MI revealed no group differences (data not shown).

Subgroup and Multivariable Analyses

Because of baseline differences in demographic characteristics between groups, both subgroup and multivariable analyses were performed. Figure 3 demonstrates the effect of preoperative disposition (coronary care unit vs regular floor), left ventricular function, and congestive heart failure on the prevalence of LOS with or without MI in each of the groups. Patients proceeding to surgery from the coronary care unit had a higher prevalence of LOS, MI, or both than

TABLE 1. Preoperative patient characteristics in the Insulin Cardioplegia Trial

	Insulin (n = 557)	Placebo (n = 570)	P value
Age (y, mean $\pm$ SD)	64 $\pm$ 11	63 $\pm$ 10	.5
Body surface area (m ² , mean $\pm$ SD)	2.0 $\pm$ 0.2	2.0 $\pm$ 0.2	.8
Female gender	26%	26%	.9
New York Heart Association functional class			.2
I	1%	0%	
II	2%	3%	
III	8%	6%	
IV	89%	91%	
Preoperative disposition			.3
Floor	81%	78%	
Coronary care unit	19%	22%	
Congestive heart failure	13%	6%	<.001
Previous surgery	4%	4%	.9
Diabetes mellitus			.8
Type 1	22%	21%	
Type 2	7%	6%	
Hypertension	58%	57%	.9
Peripheral vascular disease	17%	13%	.09
Chronic obstructive pulmonary disease	2%	2%	.9
Hypercholesterolemia	65%	66%	.9
Renal insufficiency	5%	4%	.3
Preoperative MI			.2
Unspecified	8%	7%	
Non-Q wave	19%	15%	
Q wave	10%	8%	
Left ventricular ejection fraction			.02
>60%	31%	33%	
40%-59%	42%	49%	
20%-39%	24%	16%	
<20%	3%	2%	
Extent of coronary artery disease			.6
Single vessel	26%	25%	
Double vessel	16%	17%	
Triple vessel	58%	58%	
Left main coronary artery disease			
>10%	35%	26%	<.001
>50%	10%	7%	.04

did those housed on the regular floor (37% vs 28%, $P = .01$). There was no effect of either left ventricular function or congestive heart failure, nor were there any significant differences between groups after stratification for each of these risk factors. Figure 4 demonstrates the effect of cardioplegic temperature on the primary outcome. Again, there were no differences between groups at any cardioplegic temperature. Similarly, cardioplegic direction did not affect the development of LOS or enzymatic MI.

A stepwise logistic regression model was developed for the primary outcome of LOS and/or MI. Reoperation (odds ratio 3.92, 95% confidence interval 2.06-7.46), preoperative status (cardiac care unit vs floor odds ratio 1.44, 95% confidence interval 1.05-1.98), and age (odds ratio 1.02, 95% confidence interval 1.00-1.03) were the independent predictors of LOS and/or MI.

Discussion

Despite the well-documented improvements in surgical outcomes after CABG, certain subgroups continue to be at high risk for perioperative morbidity and mortality.¹⁻⁶ Improvements in myocardial protection may improve the results of surgery in these high-risk subgroups, but documentation of a clinically significant effect has become increasingly difficult. The current mortality rate associated with isolated CABG (2%) necessitates the recruitment of thousands of patients to demonstrate even a 50% reduction in death. We have previously shown that postoperative LOS is a more sensitive measure of ischemic injury that correlates with mortality, MI, and other objective clinical outcomes.⁶ The Insulin Cardioplegia Trial was therefore designed to prospectively evaluate the ability of preischemic metabolic enhancement to improve the results of surgery in high-risk

Figure 1. Requirement for exogenous insulin to treat hyperkalemia or hyperglycemia was higher in placebo group (white bars). Requirement for intravenous glucose to treat hypoglycemia was higher in insulin cardioplegia group (black bars). Asterisk indicates $P < .05$; double asterisk indicates $P < .001$.

Figure 2. Prevalences of LOS, enzymatic MI, and primary composite end point of LOS and/or MI (LOS/MI) in the Insulin Cardioplegia Trial. There were no statistically significant differences in any objective clinical outcomes between placebo group (white bars) and insulin cardioplegia group (black bars).

TABLE 2. Perioperative patient characteristics in the Insulin Cardioplegia Trial

	Insulin (n = 557)	Placebo (n = 570)	P value
Cardiopulmonary bypass time (min, mean $\pm$ SD)	83 $\pm$ 27	82 $\pm$ 24	.3
Crossclamp time (min, mean $\pm$ SD)	66 $\pm$ 21	64 $\pm$ 20	.3
No. of grafts			.8
1	1%	1%	
2	9%	11%	
3	33%	32%	
4	41%	41%	
5	14%	14%	
6	1%	1%	
Conduit used			
Left internal thoracic artery	93%	95%	.3
Right internal thoracic artery	4%	3%	.2
Cardioplegic temperature			.9
Warm ($>32^{\circ}\text{C}$)	10%	9%	
Tepid (25°C - 32°C)	37%	39%	
Cold ($<10^{\circ}\text{C}$)	53%	51%	
Cardioplegic direction			.7
Antegrade	68%	69%	
Retrograde	7%	5%	
Antegrade and retrograde	24%	25%	
Cardioplegic volume (L)	4.4 $\pm$ 5.0	4.0 $\pm$ 2.7	.04
Inotropic support			
Renal dose dopamine	24%	24%	.6
Norepinephrine for low systemic vascular resistance	7%	5%	.5
High dose	10%	10%	.7
Intra-aortic balloon pump	5.0%	3.9%	.3
LOS	10%	10%	.7
MI	21%	19%	.3
Postoperative stroke	2.7%	2.7%	.3
Ventilation (h, mean $\pm$ SD)	18 $\pm$ 51	11 $\pm$ 7	.1
Hospital stay (d, mean $\pm$ SD)	12 $\pm$ 13	11 $\pm$ 6	.2
Operative mortality	2.1%	2.2%	.4

patients undergoing urgent, isolated CABG for unstable angina.

Previous, smaller studies have documented metabolic,

functional and clinical benefits of glucose-insulin-containing solutions. Lazar and colleagues^{15,16} completed two prospective randomized trials in patients with diabetes and in

Figure 3. Subgroup analysis for Insulin Cardioplegia Trial. Prevalence of primary composite end point (LOS and/or MI) is shown in each cardioplegic group. Patients proceeding to surgery from intensive care unit (ICU) had higher rate of primary composite end point than did those housed on regular floor (37% vs 28%, $P = .01$). There was no effect of either left ventricular ejection fraction (LVEF) or congestive heart failure (CHF) on rate of LOS and/or MI. There were no differences between groups when stratified for preoperative status (intensive care unit vs floor), left ventricular function (left ventricular ejection fraction <40% or >40%), or presence of congestive heart failure.

patients undergoing urgent surgery for unstable angina. In contrast to our results, they reported improvements in clinical outcomes, including a reduction in postoperative atrial fibrillation and shorter ventilation, intensive care unit stay, and hospital stay. Unfortunately, these studies were not blinded and only included a small number of patients ($n = 30$). Another important distinction is the use of intravenous insulin therapy for 24 hours after the operation. In the Insulin Cardioplegia Trial, insulin was given only in the cardioplegic solution and was not continued into the postoperative period. Our previous blinded study of patients undergoing elective CABG demonstrated a metabolic and functional benefit of insulin cardioplegia that lasted for 4 hours after crossclamp removal.¹⁴ It is therefore conceivable that a combination approach in which insulin cardioplegia is supplemented with postoperative intravenous therapy might afford substantial clinical benefit.

There were several controversial details in the design of this trial. First, contamination with insulin in the placebo group may have confounded the overall results. Almost a third of the patients in the placebo group received insulin to treat hyperglycemia or hyperkalemia. Extrapolation of the

Figure 4. Prevalences of LOS, MI, and primary composite end point (LOS, MI, or both, LOS/MI), are shown for each cardioplegic study group and temperature range. There were no differences between groups even when stratified by cardioplegic temperature. Incidence of enzymatic MI was lower in placebo group in those patients who received cold cardioplegia. Asterisk indicates $P < .05$.

data of Lazar and coworkers implicates this contamination as a possible cause for the relatively low rate of LOS in the placebo group. We repeated our analysis and eliminated the 190 patients in the placebo group who received intravenous insulin, but we still failed to demonstrate any beneficial effect of insulin therapy. In the Warm Heart Trial,⁷ normothermic cardioplegia resulted in a 33% reduction in the incidence of LOS, from 9% to 6% ($P < .05$). Despite restriction of the trial to high-risk patients with unstable angina, the overall LOS rate of 10% in the Insulin Cardioplegia Trial approached that of the Warm Heart Trial. The combined rate of LOS and/or MI in the Warm Heart Trial was 20%, compared with 28% in Insulin Cardioplegia Trial, which is reflective of the higher risk patient population. The study was sufficiently powered to detect a 50% reduction in LOS (94% power) and a 25% reduction in either enzymatic MI (82% power) or the composite primary outcome (89% power).

Table 1 illustrates that roughly 30% of patients in both groups received postoperative inotropic support. However, only 5% of patients required intra-aortic balloon pump support, and the total rate of LOS (as determined by committee) was only 10%. Thus two thirds of the patients who received inotropic support received either low-dose dopamine for renal perfusion or transient levophed for low systemic vascular resistance in the setting of high cardiac output.

Another possible confounding effect was related to the differences in cardioplegic technique among the participating surgeons. We deliberately stratified the study by surgeon to assess the effect of insulin enhancement in a wide

variety of cardioplegic strategies. We believe that this decision improved the generalizability of this study to all cardiac surgeons, irrespective of their individual cardioplegic technique. A subgroup analysis failed to demonstrate any effect of either cardioplegic temperature or direction on the development of LOS, although the prevalence of enzymatic MI was higher among the patients who received normothermic blood cardioplegia. In an analysis by cardioplegic temperature or direction, there was no group effect on the prevalence of the primary composite outcome. Finally, the use of alternate end points might have demonstrated differences between groups. The study of Lazar and colleagues¹⁵ used an inotrope score that revealed a reduction in inotropic support in those patients who received intravenous insulin.

Summary of Study Limitations

The following are limitations of the study: high use of intravenous insulin in the placebo group, short-term (intraoperative) administration of study drug, variability in cardioplegic temperature and delivery, and relatively low rate of adverse events. The evaluation of metabolic enhancement before anticipated ischemia required reexamination in the contemporary era of blood cardioplegia and relative normothermia. This prospective, randomized, double-blind trial failed to demonstrate any meaningful clinical benefit to those patients who received insulin-enhanced cardioplegia. The results of CABG are affected by intraoperative technical factors, such as the quality of the coronary arteries and conduits. That is not to say that intraoperative myocardial protection is no longer important to the outcome of CABG. Rather, a novel intervention concentrated during a short period of cardioplegic arrest no longer has a meaningful impact on clinical outcomes when one uses contemporary methods of myocardial protection. However, perioperative support with glucose-insulin-containing solutions may yet prove useful when used both in the operating room and in the intensive care unit. In addition, other high-risk subgroups, such as those with poor left ventricular function or diabetic cardiomyopathy, may derive benefit from this form of metabolic therapy. The results of several studies now in progress should further define the role of metabolic enhancement during CABG.

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Appendix 1

Insulin Cardioplegia Trial (ICT) Investigators

Steering Committee: George T. Christakis, MD, Joan Ivanov, PhD, C. David Naylor, MD, DPhil, Vivek Rao, MD, PhD, and Richard D. Weisel, MD. Trial Coordinators: Michael A. Borger, MD, Gideon Cohen, MD, PhD, Vania DeSouza, MD, and Barbara Weller, RN. Safety, Monitoring, and Outcomes Committee: Davey Cheng, MD, Jacek Karski, MD, Keyvan Karkouti, MD, C. David Mazer, MD, Terry M. Smith, MD, Bill I. Wong, MD, and Terrence M. Yau, MD. Biochemical Support: Frank Merante, PhD, Donald A.G. Mickle, MD, Molly K. Mohabeer, and Laura C. Tumiat. Participating Surgeons: Gopal Bhatnagar, MD, George T. Christakis, MD, Stephen E. Fremes, MD, and Bernard S. Goldman, MD, Sunnybrook and Women's College Health Science Centre; and Robert J. Cusimano, MD, Tirone E. David, MD, Christopher M. Feindel, MD, Lynda L. Mickleborough, MD, Charles M. Peniston, MD, Anthony C. Ralph-Edwards, MD, Hugh E. Scully, MD, Glen

S. Van Arsdel, MD, Richard D. Weisel, MD, and Terrence M. Yau, MD, Toronto General Hospital.

Appendix 2

Primary Study End Points

LOS has been previously defined by our group as the need for intra-aortic balloon pump support or prolonged inotropic stimulation (>30 minutes after admission to the intensive care unit) after operation. Patients requiring low-dose dopamine ($<5 \mu\text{g}/[\text{kg} \cdot \text{min}]$) for renal perfusion or those requiring vasopressors for low systemic vascular resistance in the setting of high cardiac outputs were not considered to have LOS. A clinical database manager prospectively recorded the prevalence of LOS among all cardiac surgical patients at each institution according to these objective criteria. In the Insulin Cardioplegia Trial, the records of all patients who received intra-aortic balloon pump or postoperative inotropic support were flagged and reviewed by an independent outcomes committee blinded to treatment group. Each record was reviewed by a minimum of three individuals (see Appendix 1 for outcomes committee members), and a determination of LOS was made by majority opinion.

Enzymatic MI was determined from serial measurements of CKMB. Measurements of CKMB were performed at 0, 2, 4, 8, 24,

and 48 hours after arrival at the intensive care unit. Integration of the CKMB release over time curve was performed in all patients with at least 4 samples ($n = 962$, 85%). We previously reported that integrated time values of $645 \text{ IU} \cdot \text{h}$ are correlated with MI, as assessed by technetium Tc 99m pyrophosphate imaging. An integrated value greater than $1000 \text{ IU} \cdot \text{h}$ was used as a binary cutoff for the determination of enzymatic MI. To account for survivors with fewer than 4 samples, an analysis was repeated with two different end points for enzymatic MI: peak CKMB greater than 20 and peak CKMB/creatinine kinase ratio greater than 5%.

Discussion

Dr Edward D. Verrier (*Seattle, Wash*). How do you reconcile the differences in all the experimental literature that show enhanced protection with the lack of efficacy in this clinical trial?

Dr Rao. That is a good question. I think that all the experimental literature and even our previous studies in low-risk patients, where we looked for very subtle differences, have demonstrated benefit. The purpose of this trial was to see whether the subtle differences that are obtained under highly controlled circumstances would translate into objective clinical benefit in the usual population undergoing high-risk CABG. This study failed to demonstrate that these improvements translated into meaningful clinical benefit for these patients.

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