Does size matter? What is your infarct rate after coronary artery bypass grafting?

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There is compelling evidence that the 30-day mortality rate after coronary artery bypass grafting (CABG) has been on the decrease over the past 10 years. This conclusion is based, in part, on data from 1991 to 2000 derived and analyzed from both a multisite national voluntary database and a Veterans Administration mandatory database.^{1,2} In the voluntary database, changes in the patient risk profile and outcomes of more than 1 million patients undergoing isolated CABG procedures were analyzed. The results indicated that, over the past decade, patients undergoing CABG were increasingly older and had more comorbidities. This was associated with a 30% increase in the predicted relative risk for mortality, from 2.6% to 3.4%. Despite this increase in risk, however, there was a decrease in the risk-adjusted mortality rate, from 4.8% to 2.9%. A subset analysis of the Medicare-aged population revealed an even greater increase in the predicted mortality for this group of patients, from 3.3% to 4.4%. The observed operative mortality rates in patients 65 years and older, however, declined from 5.4% to 4.1%, a relative risk reduction of 24.1%. These findings suggest that we are providing superb care to patients with coronary artery disease amenable to surgical intervention.

Possible explanations for the decrease in the observed mortality rate despite an increase in the expected mortality rate over the past decade include the introduction of critical care pathways, surgical service lines, formation of cardiac surgical teams, technical improvements in cardiopulmonary bypass, introduction of new myocardial protection strategies and methodologies, "fast-track" management, and changes in selection criteria.² As a consequence, one might be inclined to believe that the mortality rate after CABG has finally reached an acceptable level. Obviously, this is not the case, for the only acceptable mortality after CABG is 0.0%. Moreover, these types of studies do not take into account that the complication rates of death, myocardial infarction (MI), severe ventricular dysfunction, and heart failure after CABG might exceed 10% to 15% in selected patient populations, that nearly two thirds of in-hospital deaths after CABG surgery are related to cardiovascular events, and that the cost to the US health care system could exceed \$2 billion.³ There is also increasing evidence that the incidence of myocardial necrosis after CABG, as measured on the basis of measurement of serum creatine kinase (CK) and its MB isoenzyme (CK-MB), occurs more frequently than previously appreciated and is associated with a significant decrease in medium-term and long-term survival.

In 2001, Costa and colleagues⁴ reported that only 38.1% of 496 patients who underwent CABG had normal postoperative CK-MB levels. When the CK-MB levels were stratified into cohorts of enzyme increases of normal, 1 to 3 times the upper limits of normal (ULN), 3 to 5 or more times the ULN, and more than 5 times the ULN, the incidence of death at 30 days after CABG was 0.0%, 0.5%, 5.4%, and 7.0%, respectively ($P = .001$ among the 4 groups). Late mortality rates (1 year) for these groups were 1.1%, 0.5%, 5.4%, and 10.5%, respectively. The peak postoperative cardiac enzyme level also strongly correlated with worse clinical outcome ($P = .009$). Steuer and associates⁵ reported similar findings in 2002. These investigators examined postoperative serum aspartate aminotransferase and CK-MB levels and their relationship to early cardiac-related death and late survival in 4911 patients who underwent CABG consecutively during a 6-year period. They found that elevated enzyme levels on the first postoperative day greatly increased the risk of

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early cardiac death (aspartate aminotransferase, ≥ 2.35 $\mu\text{kat/L}$ [odds ratio, 9.2]; CK-MB, ≥ 61 $\mu\text{g/L}$ [odds ratio, 6.0]) and were associated with a 40% to 50% risk increase in late mortality at 7 years. This increased risk of death was constant over time. Thus it is becoming increasingly clear that biomarkers of myocardial necrosis are frequently increased after CABG, and this is associated with a decrease in short-term, medium-term, and long-term survival.

The pathophysiology of CABG-related mortality has been under intense investigation for many years. Considerable evidence now exists that ischemia-reperfusion injury plays a major role and that one of the underlying mechanisms is the excess accumulation of intracellular calcium concentrations (calcium overload). This can result in the activation of various enzyme systems and signaling pathways that can lead to cell contracture, membrane rupture, gap junction dysfunction, cell death, and cardiac enzyme release. One process that leads to calcium overload is the activation of the sodium-hydrogen exchanger (NHE), which occurs during ischemia and reperfusion. NHEs are a family of membrane proteins that are ubiquitously distributed. Seven isoforms have been identified and are designated as NHE-1 through NHE-7. In the heart NHE-1 is localized primarily in the sarcolemmal membrane and is involved in the transport of hydrogen ions in exchange for sodium ions. During ischemia and reperfusion, activation of the exchanger can lead to increased intracellular sodium concentrations. As a consequence of increased sodium concentrations, the sodium-calcium exchanger operates in the reverse direction, and the result is calcium overload. Thus a novel approach to attenuating or preventing myocyte injury caused by intracellular calcium overload would be to inhibit the activation of the NHE.

In this issue of the *Journal*, Boyce and colleagues⁶ present both a strong rationale for using such an agent (cariporide) and compelling clinical evidence that this agent might be beneficial in patients undergoing CABG. The findings are quite impressive.

The primary end point of all-cause mortality or MI was significantly reduced in the group receiving 120 mg of cariporide (high dose) compared with the group receiving placebo. Specifically, the event rate in the high-dose cariporide group was 12.2%, whereas it was 16.2% in the placebo group ($P = .027$). A significant reduction in the event rate was apparent within the first 24 hours and was maintained throughout the 6-month follow-up period. Although the mortality rates were similar across treatment groups, a pronounced reduction in the risk of non-fatal Q-wave and non-Q-wave MIs was observed. Treatment with 120 mg of cariporide was associated with a 32% relative risk reduction in nonfatal MIs when compared with placebo. Other interesting findings include the observations that high-dose cariporide was associated with (1) a reduc-

tion in left ventricular dysfunction-associated events compared with placebo at 6 months (9.4% vs 13.5%, respectively); (2) a reduction in the extent of infarction, as indicated by peak CK-MB values; and (3) a reduction in the event rate that was independent of whether the patients received blood cardioplegia or crystalloid cardioplegia.

On the basis of the results of this study, one might conclude that the myocardial necrosis that occurs during CABG is due, in part, to inadequate myocardial protection, that the underlying mechanism is related to activation of the sodium-hydrogen exchanger, and that cariporide is a promising new therapy for reducing complications or death after CABG. These are not unreasonable conclusions given that the population studied was a large prospectively defined cohort of the randomized, multicenter clinical trial known as GUARDIAN.⁷ In the GUARDIAN trial the patients enrolled were at risk of myocardial necrosis caused by different clinical settings (acute coronary syndromes, percutaneous transluminal coronary angioplasty, or CABG). This study had a well-defined, clinically important, composite end point of death or nonfatal MI. A central electrocardiographic core laboratory classified all investigator-reported ischemic events and screened serial CK-MB values and electrocardiograms for all patients for the presence of previously unreported database-identified MI. The committee was blinded to treatment assignments throughout the study. All primary and secondary end points were validated by an independent, blinded, end point validation committee. The cardiac enzyme values were prospectively collected as part of the study design, and the 6-month follow-up was excellent, with less than 1% of the patients unavailable for assessment. Finally, the large number of patients undergoing CABG permitted a robust statistical analysis. For a variety of reasons, however, the results of this subgroup analysis do not conclusively demonstrate that the NHE inhibitor cariporide is a cardioprotective agent in human subjects.

First, these positive findings were observed in a subset of patients, whereas in the overall GUARDIAN population, a treatment benefit could not be demonstrated. This might well be due to the heterogeneity of the population of patients studied, but the goal of the GUARDIAN trial was not achieved (ie, to show a superiority of at least one of the doses versus placebo in patients at risk of myocardial necrosis).

Second, because there was no discernable dose-response relationship in the CABG cohort, the observed benefit could still be due to chance.

Third, the duration of drug treatment was quite variable. Although all the patients undergoing CABG received placebo or a dose of 20 mg, 80 mg, or 120 mg of cariporide 15 minutes to 2 hours before the operation, the postoperative treatment was variable and ranged from 1 to 7 days, with a

median duration of 2.4 days. The investigator determined the treatment duration on the basis of the clinical status of the patient. This inconsistency of dosing complicates the determination of an optimal duration of treatment. On the other hand, pharmacokinetic modeling to establish a minimum effective concentration for cariporide during surgical intervention yielded a threshold concentration of approximately 500 ng/mL, the level reached in the majority of patients in the 120-mg treatment arm but in few of those in the 80-mg arm and none of those in the 20-mg arm.⁸

Fourth, the mortality rate was similar between the placebo group and all treatment groups. This observation, however, should not be used to detract from the finding that high-dose cariporide reduced the composite end point of all-cause mortality or MI. Given the sample size per treatment arm, the study did not have sufficient statistical power to detect a treatment effect in the mortality component of the end point alone. Another explanation for not observing an improvement in survival with treatment after CABG in this study might be that it could take longer than 6 months to discern a beneficial effect on medium-term and long-term mortality, this also raises the issue of the appropriateness of using composite end points. Although mortality is ultimately the most important end point when evaluating the efficacy of a medical intervention, the use of this end point alone requires the enrollment of thousands of patients because of a much smaller event rate. If the sample size is not increased to accommodate mortality as the sole primary event, single end point studies will be underpowered, and a potentially effective therapeutic intervention could go unrecognized. In this study, because a reduction in the incidence of an MI or a reduction in infarct size (nonfatal end points) have been clearly linked to increased survival, the use of the composite end point of all-cause mortality or MI as a primary end point is appropriate. Furthermore, because infarction might result in immediate death without preceding electrocardiographic or enzymatic evidence of myocardial injury, exclusion of mortality from an end point focusing on myocardial injury would underestimate the event rate and possibly exclude the most severe events from analysis.

Although not conclusive, the results of this study are very encouraging. The findings support the concept that

NHE inhibition is a promising novel therapeutic approach for reducing complications and death after CABG. A definitive answer will most likely have to await the results of the EXPEDITION trial, a multicenter clinical trial that is examining the efficacy of a continuous infusion of cariporide on short-term and medium-term outcomes after CABG. Should this study demonstrate a salutary effect of the agent on the composite end points of death or nonfatal MI, this would be the first therapy to do so and would represent significant progress toward improving the clinical outcome of patients after CABG.

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