Hyperglycemia during cardiac surgery

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In the 40 years since its introduction into clinical practice, the role of glucose-insulin-potassium (GIK) during cardiac surgery has remained undefined.[1] Although there is growing evidence that hyperglycemia is detrimental and insulin therapy is beneficial to the diabetic patient during cardiac surgery, the significance of hyperglycemia in the nondiabetic cardiac surgical patient and the potential benefits of GIK are still the subject of intense debate.

In a recent issue of the *Journal*, Doenst and coworkers[2] provide evidence that hyperglycemia is an independent predictor of perioperative morbidity and mortality in both diabetic and nondiabetic patients. Their study is unique in that they chose to assess the highest glucose level during cardiopulmonary bypass (CPB) as an independent variable rather than postoperative glucose levels. They hypothesized that this measurement would reflect perioperative insulin resistance and would not be influenced by inotropic agents. Their data corroborate our own work and that of others showing that diabetic patients with increased perioperative glucose levels (>200 mg/dL) have poorer outcomes after cardiac surgery.[3-5] There is no controversy in these findings because all cardiac surgeons now agree that maintaining serum glucose levels at less than 200 mg/dL is the standard of practice for all diabetic patients in the perioperative period. The most optimal serum glucose level, length of treatment, contents of the insulin solution, and mechanisms responsible for these beneficial effects are now the subject of clinical investigations by our own group and other investigators.

Although there is no controversy regarding the detrimental effects of hyperglycemia and the benefits of insulin in the diabetic patient, the effects of hyperglycemia and the need for insulin therapy in the nondiabetic patient undergoing cardiac surgery are still the subject of debate. One of the shortcomings of the study by Doenst and coworkers[2] is that the authors fail to distinguish between nondiabetic patients who exhibit the normal response of insulin resistance on CPB and those patients with either the metabolic syndrome or undiagnosed diabetes. For example, patients without diabetes who exhibit insulin resistance during CPB will have normal glucose levels after CPB in the intensive care unit (ICU). In fact, it has been our experience that hypoglycemia might develop in these patients if they are vigorously treated with insulin during CPB to obtain more normal glucose levels. These patients would be less likely to exhibit an increased incidence of postoperative morbidity and mortality. Patients with persistent hyperglycemia after surgical intervention in the ICU (>200 mg/dL) might represent a different population more prone to postoperative morbidity. Indeed, in the series by Doenst and coworkers,[2] patients with increased glucose levels undergoing CPB were more likely to have reduced ejection fractions, congestive heart failure, cardiogenic shock, and renal failure and require reoperations or more urgent operations. Chronic insulin resistance has been shown to be a risk factor for atherosclerotic disease.[6] Could it be that these patients were diabetic subjects who were not given diagnoses preoperatively? One way to resolve this issue would have been to correlate the peak CPB glucose levels with postoperative ICU glucose levels in the nondiabetic patients. I suspect that nondiabetic patients who did not have persistently increased postoperative glucose levels would be less likely to have experienced increased mortality and morbidity. These additional data would likely determine the significance of hyperglycemia on CPB in the nondiabetic patient. It would also have been important to know how many nondiabetic patients with increased peak glucose levels undergoing CPB went on to be given diagnoses of diabetes in the year after their cardiac surgery. Despite the numerous studies

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showing that lower glucose levels are beneficial to cardiac surgical patients, there are several studies, including our own, demonstrating improved outcomes with systemic GIK infusion, despite the fact that these solutions resulted in systemic hyperglycemia.[7,8] Hence, as noted by Doenst and coworkers,[2] it is still not clear whether hyperglycemia is a risk factor in itself and whether its effect is the same in diabetic and nondiabetic patients.

Another series that shows the beneficial effects of hyperglycemia with GIK infusion in nondiabetic patients appears in this issue of the *Journal* by Quinn and associates.[9] The controversy surrounding GIK has been the result of inadequate studies characterized by lack of randomization, small series of patients, inadequate study design with inconsistencies in inclusion criteria, and differences in composition, volume, and duration of GIK infusions. Furthermore, most studies had perioperative mortality as the primary end point, which might not be attainable in today's practice of cardiac surgery. In their study Quinn and associates have addressed these shortcomings. Their study design was a prospectively randomized, double-blind, placebo-controlled trial consisting of 280 nondiabetic adult patients undergoing primary CABG surgery. Diabetic patients were excluded. The GIK solution consisted of D40W plus 70 U of insulin plus 80 mEq of KCl at 0.75 mL $\cdot$ kg^{-1} $\cdot$ h^{-1} beginning at anesthetic induction and continuing for 6 hours after the operation. The primary end point was postreperfusion cardiac index. GIK-treated patients had higher cardiac indices ($P < .001$), reduced vascular resistance ($P < .001$), and a lower incidence of low cardiac output syndrome (15.9% vs 27.5%, $P = .021$). They required less inotropic support (18.8% vs 40.8%, $P < .001$) and had less evidence of myocardial injury, as defined as a perioperative myocardial infarction and enzyme release (12.3% vs 23.4%, $P = .017$). The beneficial effects were seen in both high-risk patients and in those with low ejection fractions, as well as in low-risk patients and patients with hyperglycemia during the GIK infusion. There was, however, no difference in the incidence of atrial fibrillation or length of hospital stay. These results are almost identical to those of our own series in nondiabetic patients, which showed that GIK not only improved myocardial performance and decreased the need for inotropic support but also decreased the incidence of atrial fibrillation and hospital length of stay.[7] I suspect that the beneficial effect of GIK on lowering the incidence of atrial fibrillation was not observed in this series because the GIK infusion lasted for only 6 hours postoperatively and because β-blockers were not instituted until the fourth postoperative day. This undoubtedly accounted for the high incidence of atrial fibrillation (55%) seen in this series. Similar to our own results, patients receiving GIK had higher postoperative serum glucose levels, but this did not result in any adverse outcomes. These data are also consistent with the meta-analysis by Bothe and colleagues,[8] who found that GIK resulted in a significant improvement of postoperative contractible function and significantly reduced the incidence of postoperative atrial fibrillation.

What can we conclude from these 2 studies regarding the role of hyperglycemia and GIK in the cardiac surgical patient? Hyperglycemia in the diabetic patient is reflective of chronic insulin resistance, is predictive of poor outcomes, and should be aggressively treated. Hyperglycemia in nondiabetic subjects, which occurs only during CPB, is most likely reflective of acute insulin resistance and might not be associated with poor outcomes if glucose levels return to less than 200 mg/dL immediately after surgical intervention. Hyperglycemia (200-240 mg/dL) associated with GIK infusion in nondiabetic patients does not have the same negative prognostic finding seen in diabetic patients because of the protective effects of simultaneous insulin infusion.

Should GIK be given to all patients, both diabetic and nondiabetic, undergoing cardiac surgery? The 2 studies presented in this issue of the *Journal* make a strong point in favor of using GIK in all patients. It is simple to administer, inexpensive, and has virtually no side effects. In diabetic patients we use 500 mL of 5% dextrose in water plus 80 U of insulin plus 40 mEq of KC1 titrated to an algorithm designed to keep serum glucose levels between 120 and 180 mg/dL. The solution is started during anesthetic induction and continued for 18 hours after the operation, at which time the patient's previous diabetic regimen is resumed. For nondiabetic patients, we use 30% dextrose in water plus 50 U of regular insulin plus 80 mEq of KC1 to run at 0.75 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, with supplemental intravenous insulin administered to keep serum glucose levels at 200 mg/dL or less. This solution is also continued for 18 hours after the operation. All patients receiving GIK have their glucose levels checked on an hourly basis and more frequently if adjustments in infusion rates are made. I suspect that the GIK 30% dextrose in water will have its greatest effect in nondiabetic patients undergoing coronary artery bypass grafting (CABG) requiring urgent operations with ejection fractions of less than 50%, those with recent myocardial infarctions, and those with acute coronary syndromes. However, because the incidence of atrial fibrillation is decreased, it could result in a decrease in length of stay of nearly 2 days in all patients.

I believe that there are enough data to recommend the use of GIK in all cardiac surgery patients, both diabetic and nondiabetic. However, to end any controversy, now might be the time to consider a multicenter trial to resolve this issue. Because the detrimental effects of hyperglycemia in diabetic patients is already well established, it would be unethical to randomize these patients to a control group without insulin therapy. The trial would consist of nondiabetic patients undergoing CABG surgery. The type of GIK

solution used and the duration of treatment would be standardized. The primary end point would be the composite end points of death, myocardial infarction, cardiac index, and need and duration of inotropic support. Secondary end points would include weight gain, time to extubation, ICU and hospital length of stay, incidence of wound infections, and atrial fibrillation. There would be a 1-year follow-up to record the incidence of ischemic events, which would include angina, death, strokes, congestive heart failure, and the need for a repeat revascularization procedure. Such a trial would put an end to the GIK controversy and hopefully the need for further editorials.

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