PRO AND CON

Lee A. Fleisher, MD
Bonnie L. Milas, MD
Section Editors

Pro: Tight Perioperative Glycemic Control

George Carvalho, MD, MSc, and Thomas Schricker, MD, PhD

IN THE AUTHORS' previous article on tight glucose control and outcome in cardiovascular surgery, the following questions that are clinically important for perioperative glycemic control were outlined[1]: (1) What are the clinical hazards of acute perioperative hyperglycemia? (2) What level of glycemia is dangerous for the surgical patient? and (3) When should treatment be initiated, and what should the target blood glucose concentration be?

The authors believe these questions remain relevant because recent investigations have been insufficient to promote a change in clinical practice. In response to studies performed in critically ill patients, most institutions have established protocols for controlling blood glucose levels in the intensive care unit (ICU) and less frequently in the operating room. However, the lack of uniformity of insulin glucose regimens and the diverse populations studied make it difficult for the reader to decipher what glycemic range to aim for and how best to achieve it. The authors think that normoglycemia is the ideal and have shown that it can be accomplished perioperatively by using large doses of insulin in tandem with exogenous glucose.[2] High-dose insulin therapy possesses nonmetabolic effects with potential benefit for surgical patients and in particular for patients with cardiovascular disease. Normoglycemia per se reduces mortality in critical illness and prevents liver, kidney, and endothelial dysfunction, but, in order to fully exploit insulin's anti-inflammatory, cardioprotective, and inotropic effects, both normoglycemia and high-dose insulin are required.[3] In clinical reality, the fear of hypoglycemia has confined insulin therapy to be neither high dose nor to be sufficiently effective to achieve normoglycemia. Current insulin therapy regimens are reactive and permit moderate hyperglycemia before they are initiated. Because hyperglycemia begins preoperatively or in the operating room, treating hyperglycemia and maintaining normoglycemia as early as possible may prove beneficial. The failure to do so leads to an extended period of poor glucose control in the ICU that is harmful but preventable with greater intraoperative vigilance.

This review focuses on evidence from recent investigations involving patients undergoing cardiac surgery. Its purpose is to supplement the previous review and concentrate on intraoperative glycemic control.

That hyperglycemia is hazardous the authors think is now indisputable in the cardiac surgery patient population. Over the last 3 years, observational studies have been published corroborating the association between hyperglycemia and poor outcomes after cardiac surgery. Although links cannot establish causality, the number and consistency of investigations instituting protocols for glycemic control and improving outcome with respect to standard therapy have flourished. In a retrospective study of 8,727 adults undergoing cardiac surgery, the highest blood glucose in the first 60 hours postoperatively was used to classify patients as having "good" (< 200 mg/dL [11.1 mmol/L]), moderate (200-250 mg/dL [11.1-13.9 mmol/L]), or poor (>250 mg/dL [13.9 mmol/L]) blood glucose control.[4] Increasing blood glucose concentration was positively correlated with in-hospital mortality (good, 1.8%; moderate, 4.2%; and poor, 9.6%). Poor blood glucose control was associated with myocardial infarction (odds ratio [OR] = 2.73 [1.74-4.26]), pulmonary (OR = 2.27 [1.65-3.12]), and renal complications (OR = 2.82 [1.54-5.14]). In a study of 200 consecutive patients who underwent coronary artery bypass graft (CABG) surgery, the immediate postoperative blood glucose showed a stronger association with complications (blood glucose ≥ 200 mg/dL [11.1 mmol/L], OR = 3.1; blood glucose ≥ 250 mg/dL [13.9 mmol/L], OR = 12.8) than the presence of diagnosed or suspected diabetes (OR = 2.0).[5] In another observational study of 2,297 consecutive CABG surgery patients,[6] the first blood glucose value obtained immediately after surgery was tested as a predictor of outcome. Patients were stratified into low, <80 mg/dL (4.4 mmol/L); normal, 80 to 110 mg/dL (4.4-6.1 mmol/L); high, 111 to 200 mg/dL (6.2-11.1 mmol/L); and very high, >200 mg/dL (11.1 mmol/L) glycemic strata. Patients with very high glycemia had an increased risk of mortality up to 30 days postoperatively (OR = 7.71; confidence interval [CI], 2.24-26.59) as compared with the normal group. This elevated risk was independent of diabetes status, and those without diabetes had an even worse prognosis. This analysis did not show

From the Department of Anesthesia, McGill University, Montreal, Quebec, Canada.

T.S. is supported by grants from the Canadian Institutes of Health Research (CIHR) and the Fonds de la recherche en sante du Quebec (FRSQ). G.C. is supported by a grant from the McGill University Health Center Research Institute.

Address reprint requests to George Carvalho, MD, MSc, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Room S5.05, Montreal, QC H3A 1A1, Canada. E-mail: george.carvalho@mcgill.ca

1053-0770/09/2306-0025$36.00/0
doi:10.1053/j.jvca.2009.04.015
Key words: glucose, insulin, surgery, diabetes, mortality

significant differences among strata for stroke, deep sternal wound infection (DSWI), or renal failure because of very low incidence rates. However, for all these complications, their incidence was greater in patients who arrived in the ICU with an elevated blood glucose. An important message from these investigations is that early ICU blood glucose impacts outcome. Because early blood glucose is a reflection of glycemic control during surgery, it appears that intraoperative blood glucose control is relevant. Whether it is the blood glucose concentration per se or events that affect glycemia such as the suppression of the stress response by anesthesia, the magnitude of surgical trauma, the use of cardiopulmonary bypass, exogenous glucose administration, blood transfusions, or inotropic support that adversely affect outcome is not certain.

Persuasive evidence to support the importance of glycemic control in the operating room recently has become available. A retrospective observational investigation in 6,280 patients, 25% of whom were diabetic, revealed that glycemia during CPB was an independent risk factor for mortality in both diabetic (OR = 1.20; CI, 1.08-1.32) and nondiabetic patients (OR = 1.12; CI, 1.06-1.19 per mmol/L increase in blood glucose). In addition, poor glycemic control was associated with major adverse events, a composite of death, stroke, DSWI, low-output syndrome, and myocardial infarction (OR = 1.06; CI, 1.03-1.09 per mmol/L increase in blood glucose).[7]

In another report in 525 subjects, an association between intraoperative hyperglycemia defined by the occurrence of at least 1 blood glucose measurement ≥200 mg/dL (11.1 mmol/L) during CPB and neurocognitive dysfunction 6 weeks after on-pump CABG surgery was shown in nondiabetic patients.[8] Similar to the study by Doenst et al,[7] pre-CPB and post-CPB measurements were not included in the analysis because CPB was assumed to be the timeframe with the highest risk of emboli and hemodynamic changes leading to neurocognitive dysfunction. Butterworth et al,[9] in a study examining neurologic or neurobehavioral outcomes in patients without diabetes, did not show any benefit with the attempted control of hyperglycemia during CPB. Not surprisingly, normoglycemia was not attained because glucose-containing cardioplegia was administered. Both groups, those treated with insulin and those not treated, showed similar glucose values on arrival to the ICU (178 ± 57 mg/dL [9.9 ± 3.2 mmol/L] and 179 ± 60 mg/dL [9.9 ± 3.3 mmol/L]) and, as expected, similar neurologic outcomes.

Several investigations in diabetic patients have shown the benefit of improving glucose control in this at-risk population. Historically, from the Society of Thoracic Surgeons national database, diabetics undergoing cardiac surgery for CABG surgery, aortic and mitral valve procedures before 2001 were more likely to have worse 30-day mortality, more DSWI, stroke, and prolonged hospitalization.[10] The Portland Diabetic Project,[11] a prospective observational cohort treated with insulin infusions until the 2nd postoperative day aiming for a blood glucose <150 mg/dL (8.3 mmol/L), improved outcomes in this population, negating any incremental morbidity and mortality that previously had been attributed to the preoperative diagnosis of diabetes. A historic study of ever-improving glucose control with continuous perioperative insulin infusions in diabetics has eliminated this "diabetic disadvantage." Dramatically, mortality was reduced by 65% and with more aggressive glucose control in ensuing years has fallen below that of the nondiabetic population (13/117 [1.1%] *v* 44/2,041 [2.1%]). Furthermore, multivariable analysis determined hyperglycemia to be an independent risk factor for mortality and not just an epiphenomenon reflecting the severity of the stress response to surgery in the presence of diabetes. Blood glucose levels on the day of surgery including the intraoperative period as well as on postoperative days 1 and 2 were all independently associated with in-hospital mortality. Beyond postoperative day 3, glycemia continued to be a significant factor for mortality, confirming results from the Leuven trial that glucose control is important in patients with a prolonged ICU stay. The fact that glycemic control was not achieved until the morning after surgery in the Leuven trial may have precluded the early benefit of perioperative insulin therapy. It may be speculated that because intraoperative glucose control in the early hours in the ICU of the Leuven trial was not significantly different between groups, no disparity in outcome was observed.

The rate of DSWI in the same cohort of diabetic patients in Portland showed similarly impressive results; DSWI decreased by 63% to 0.3% (equivalent to that of the nondiabetic population). The length of hospital stay decreased by an average of 2 days, and the incidence of a composite of complications including transfusion requirement, new-onset atrial fibrillation, infection, low-cardiac-output syndrome, prolonged ventilation, and cerebral vascular accident also was reduced.

Other investigators have reproduced the findings of the Portland Protocol. A prospective study of 761 cardiac surgery patients showed not only that diabetics were at an increased risk for wound infections but also that maintaining blood glucose between 120 and 160 mg/dL (6.7-8.9 mmol/L) reduced the risk of wound infection in diabetics from 7.6% to that of the nondiabetic population, 2.0%.[12]

A prospective observational French study on intraoperative blood glucose in 200 diabetic patients undergoing cardiac surgery revealed that poor intraoperative glycemic control, despite insulin therapy, occurred more frequently in patients who suffered in-hospital morbidity.[13] In this study, the 200 diabetic patients received a preoperative subcutaneous bolus of 0.15 U/kg of intermediary insulin the morning of surgery followed by an intraoperative intravenous sliding scale modeled on the Portland Protocol if blood glucose exceeded 180 mg/dL (10 mmol/L). Intraoperative blood glucose was measured every 30 minutes and considered poor if 4 consecutive blood glucose measurements were greater than 200 mg/dL (11.1 mmol/L). Postoperatively, in the critical care unit, glycemia was treated to maintain blood glucose <140 mg/dL (7.8 mmol/L). Only 36% of patients required supplemental intraoperative insulin. Among these patients, 50% had poor intraoperative blood glucose control and arrived in the ICU with an elevated blood glucose level (208 ± 54 mg/dL [11.6 ± 3.0 mmol/L] *v* 148 ± 41 mg/dL [8.2 ± 2.3 mmol/L]) that was more difficult to normalize. In this group of poorly controlled diabetics, all in-hospital morbidities (including cardiovascular, neurologic, respiratory, and renal morbidities), except for infectious morbidities, were more common. The adjusted OR for postoperative severe morbidity among diabetic patients who had poor intraoperative glycemic control as compared with patients who

were well controlled was 7.2 (95% CI, 2.7-19.0). The in-hospital mortality rate was significantly higher in poorly controlled subjects (11.4% *v* 2.4%), and prolonged ICU duration of stay was more frequently observed (46% *v* 19%). Preoperative and postoperative blood glucose concentrations were similar in patients with and without postoperative morbidity, implying that marginal intraoperative blood glucose control was responsible for the differences in outcome.

In a subsequent study by the same group, the same protocol of perioperative glycemic control in diabetic patients was evaluated for its effect on the expected mortality according to the EuroSCORE risk model.[14] A group of 300 consecutive diabetic patients were administered the protocol and compared with 300 consecutive diabetic patients just before the institution of the new protocol. The mean blood glucose level the day of surgery was 142 ± 45 mg/dL (7.9 ± 2.5 mmol/L) in the protocol group versus 169 ± 70 mg/dL (9.4 ± 3.9 mmol/L) in the nonprotocol group. The observed and expected mortality rate was 1.3% versus 4.3% in the protocol group and 4.0% versus 3.9% in the nonprotocol group. Subgroup analysis for risk severity showed the protocol to reduce mortality for moderate-to-high-risk patients (EuroSCORE >4) (OR = 0.24) but showed no significant improvement in low-to-moderate-risk patients (EuroSCORE <4). These findings clearly show that optimal glucose control reduces EuroSCORE expected mortality in diabetic patients undergoing CABG surgery. The authors speculate that, in addition to the reduced mean blood glucose, the lower standard error of the mean signifies more uniform glycemic control.

Data from 7,049 critically ill patients from 4 hospitals showed that survivors experienced less blood glucose variability than nonsurvivors (142 ± 34 mg/dL [7.9 ± 1.9 mmol/L] *v* 158 ± 52 mg/dL [8.8 ± 2.9 mmol/L]).[15] The standard deviation of blood glucose concentration was an independent predictor of ICU mortality and a stronger predictor of mortality than mean blood glucose concentration. As recently revealed, fluctuations in glucose concentration trigger oxidative stress to a greater degree than sustained hyperglycemia.[16] Given these data, it is possible that blood glucose control positively affects outcome by reducing oxidative stress both by controlling the mean blood glucose and the extreme swings that occur during cardiac surgery. In keeping with this hypothesis, the present authors[17] and others,[18,19] using high-dose insulin, have shown the attenuation of the inflammatory response to cardiac surgery as reflected by decreased levels of interleukin 6, interleukin 8, and tumor necrosis factor α. In the present study, the blood glucose values in the first 24 hours in the ICU were 95 ± 20 mg/dL (5.3 ± 1.1 mmol/L) in the glucose-insulin-normoglycemia (GIN) group and 148 ± 41 mg/dL (8.2 ± 2.3 mmol/L) in patients receiving conventional therapy. It, however, remains unknown which component of therapy led to the anti-inflammatory response, hyperinsulinemia, normoglycemia, or the less variable blood glucose levels in those patients receiving GIN.

A potential benefit of GIN therapy's anti-inflammatory actions is the protection of perioperative renal function. Until recently, data assessing blood glucose control and renal outcomes were only available from the critical care population.[20,21] Briefly, in critically ill surgical patients after cardiac surgery, insulin therapy is renoprotective, reducing oliguria from 5.6% to 2.6% and the need for renal replacement therapy from 7.4% to 4.0%. A recent trial retrospectively analyzed 2 groups of more than 1,000 patients before and after the institution of a glycemia insulin protocol.[22] Postoperative renal impairment was assessed with the RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney failure) score and the incidence of postoperative dialysis. Blood glucose was significantly higher in the control group during and after surgery as compared with the insulin protocol group. Blood glucose in the ICU was 133 ± 29 mg/dL (7.4 ± 1.6 mmol/L) in the control group and 103 ± 15 mg/dL (5.7 ± 0.8 mmol/L) in the insulin group. Improved blood glucose control led to reduced incidences of renal impairment, renal failure, and, impressively, a reduction in the incidence of postoperative dialysis from 3.9% in controls to 0.7% in the tightly controlled insulin group. In addition, the rate of mortality in the insulin-treated group was lower (1.2% *v* 3.6%), and patients treated with the new protocol suffered fewer cardiac (14.5% *v* 25.6%) and infectious (4.3% *v* 9.2%) complications. Unfortunately, there was insufficient power to extend these results to diabetic patients. The authors speculate that the benefits of tight glycemic control in patients staying in the ICU for a relatively short period of time are influenced by strict intraoperative glycemic control as most patients' length of ICU stay was less than 2 days.

In another study, the present authors showed that GIN therapy is cardioprotective[23] and promoted an earlier shift to aerobic metabolism during reperfusion. However, unlike other investigations using glucose-insulin-potassium (GIK), the concept of GIN provides normoglycemia throughout the surgery. In contrast, in another study of cardioprotection,[24] patients undergoing CABG surgery were randomized to GIK therapy or to placebo. GIK was administered at a rate of 3 to 5 IU/h of insulin from sternotomy until 6 hours after release of the aortic cross-clamp. Blood glucose in the GIK group was elevated throughout the infusion as compared with placebo with 94% of patients requiring supplemental insulin for a blood glucose >180 mg/dL (10 mmol/L) versus 20% of patients in the placebo group. The total amount of supplemental insulin used was considerable as follows: GIK group median, 50 IU (interquartile range [IQR], 37-73 IU) and placebo group median, 10 IU (IQR, 7-23 IU). Despite moderate-to-severe hyperglycemia, at 6 hours postoperatively, the mean cardiac troponin I levels were lower in the GIK group when compared with the placebo group (6.0 ng/mL [95% confidence limits, 5.2-6.8] *v* 9.0 ng/mL [95% confidence limits, 7.5-10.6]). Fewer patients had a troponin I value >13.1 ng/mL in the GIK group (8.3%) in contrast to the placebo group (19.0%). In that study, it appears that the high-dose insulin was the component responsible for improved cardioprotection because during the GIK infusion patients were hyperglycemic. Insulin, when administered at higher doses, has shown vasodilatory, anti-inflammatory, antioxidative, thrombolytic, inotropic, and cardioprotective actions. Theoretically, these nonmetabolic effects of insulin can benefit patients undergoing cardiac surgery.[1]

Given these secondary benefits and the observed clinical benefits of intensive insulin therapy that have been observed primarily in critical care patients, a large trial with a well-designed intraoperative protocol is necessary. To date, only one

trial has evaluated intraoperative glucose control in a randomized, controlled fashion for on-pump cardiac surgery. Gandhi et al[25] randomized 400 patients to receive either intensive intraoperative insulin therapy when blood glucose exceeded 100 mg/dL (5.6 mmol/L) or conventional glucose management when blood glucose exceeded 200 mg/dL (11.1 mmol/L). Both groups received the same blood glucose regimen postoperatively. Using an insulin sliding scale hyperglycemia was not prevented during surgery. The mean blood glucose level after separation from cardiopulmonary bypass in the treatment group was 123 ± 24 mg/dL (6.8 ± 1.3 mmol/L) in all patients and 132 ± 29 mg/dL (7.3 ± 1.6 mmol/L) in the subgroup of diabetic patients. In the conventional treatment group, the mean blood glucose was 148 ± 35 mg/dL (8.2 ± 1.9 mmol/L) after cardiopulmonary bypass in all patients and 169 ± 49 mg/dL (9.4 ± 2.7 mmol/L) in diabetics.

The authors concluded that "tight" intraoperative glucose control with the application of an "intensive" insulin sliding scale does not reduce morbidity or mortality in nondiabetic and diabetic patients after a variety of cardiac procedures. Surprisingly, an increased incidence of death and stroke with "tight" intraoperative glucose control motivated the authors to question the routine use of insulin therapy during cardiac surgery. Van den Berghe,[26] in an editorial accompanying the article, postulated that intraoperative glucose control is unlikely to be important and that given the brevity of surgery believes that a relative risk reduction of 10% is optimistic. According to van den Berghe, glycemia is vital in the ICU if the patient requires a prolonged ICU admission that is not predictable beforehand.

This study is flawed for a variety of reasons. Briefly, there are too many intraoperative variables hiding behind the cloak of randomization given the small number of subjects enlisted. The selection of outcomes was poor because they are greatly influenced by surgery or anesthesia (stroke, heart block requiring pacemaker, new-onset atrial fibrillation, and prolonged intubation) and should not have been lumped together in a composite. The study was powered based on a relative risk reduction of 40% in the composite outcome. For the assessment of outcomes that matter after cardiac surgery, namely, severe infections, renal and cardiac failure requiring mechanical support, and death, the study was grossly underpowered. Most of the aforementioned components of the composite outcome are not medically modifiable by improving glucose control, and their incidence is so much greater compared with the outcomes of interest. More importantly, the authors would like to reiterate that these results have to be tempered with the fact that the goal of therapy, to maintain glycemia between 80 and 100 mg/dL (4.4 and 5.6 mmol/L), was not achieved, thereby precluding any possible conclusion about the impact of normoglycemia. What can be concluded from this study is the confirmation of a multitude of studies and hospital recommendations for insulin therapy that reactive insulin protocols cannot prevent hyperglycemia nor maintain normoglycemia.[27,28]

The application of intensive insulin protocols has been extremely problematic for critically ill patients as well. The investigators from Leuven, the site from where the international interest in intensive insulin therapy originated, using their intensive insulin therapy protocol, were unable to adequately prevent severe hypoglycemia (<40 mg/dL [2.2 mmol/L]) in 18.7% of their medical ICU population.[29] The VISEP trial, using the Leuven protocol, fared no better with an incidence of severe hypoglycemia of 17.0%, and, for that reason, the trial was discontinued early.[30] The GLUCONTROL study[31] also was terminated before completion because the set target of 80 to 110 mg/dL (4.4-6.1 mmol/L) was not achieved, and the risk of hypoglycemia was unacceptably high. The authors[32] have embarked on a large randomized controlled trial designed to examine whether strict and successful intraoperative glycemic control by using GIN improves outcome after cardiac surgery.

In summary, hyperglycemia is deleterious to the cardiac surgery patient and the prevention and normalization of glycemia appear to be beneficial for cardiac function, the preservation of renal function, and the prevention of severe infectious complications. The primary statement in this review is that no study to date assessing outcome after cardiac surgery has achieved the necessary goal of maintaining intraoperative and postoperative normoglycemia. The authors think that intensive insulin therapy with the goal of normoglycemia cannot be discounted when it has yet to be administered.

REFERENCES

1. Schricker T, Carvalho G: Pro: Tight perioperative glycemic control. J Cardiothorac Vasc Anesth 19:684-688, 2005

2. Carvalho G, Moore A, Qizilbash B, et al: Maintenance of normoglycemia during cardiac surgery. Anesth Analg 99:319-324, 2004

3. Ellger B, Debaveye Y, Vanhorebeek I, et al: Survival benefits of intensive insulin therapy in critical illness: Impact of maintaining normoglycemia versus glycemia-independent actions of insulin. Diabetes 55:1096-1105, 2006

4. Ascione R, Rogers CA, Rajakaruna C, et al: Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. Circulation 118:113-123, 2008

5. Fish LH, Weaver TW, Moore AL, et al: Value of postoperative blood glucose in predicting complications and length of stay after coronary artery bypass grafting. Am J Cardiol 92:74-76, 2003

6. Jones KW, Cain AS, Mitchell JH, et al: Hyperglycemia predicts mortality after CABG: Postoperative hyperglycemia predicts dramatic increases in mortality after coronary artery bypass graft surgery. J Diabetes Complications 22:365-370, 2008

7. Doenst T, Wijeysundera D, Karkouti K, et al: Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. J Thorac Cardiovasc Surg 130:1144, 2005

8. Puskas F, Grocott HP, White WD, et al: Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg 84:1467-1473, 2007

9. Butterworth J, Wagenknecht LE, Legault C, et al: Attempted control of hyperglycemia during cardiopulmonary bypass fails to improve neurologic or neurobehavioral outcomes in patients without diabetes mellitus undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 130:1319, 2005

10. Brown JR, Edwards FH, O'Connor GT, et al: The diabetic disadvantage: Historical outcomes measures in diabetic patients undergoing cardiac surgery—The pre-intravenous insulin era. Semin Thorac Cardiovasc Surg 18:281-288, 2006

11. Furnary AP, Wu Y: Eliminating the diabetic disadvantage: The Portland Diabetic Project. Semin Thorac Cardiovasc Surg 18:302-308, 2006

12. Hruska LA, Smith JM, Hendy MP, et al: Continuous insulin infusion reduces infectious complications in diabetics following coronary surgery. J Card Surg 20:403-407, 2005

13. Ouattara A, Lecomte P, Le Manach Y, et al: Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology 103:687-694, 2005

14. D'Alessandro C, Leprince P, Golmard JL, et al: Strict glycemic control reduces EuroSCORE expected mortality in diabetic patients undergoing myocardial revascularization. J Thorac Cardiovasc Surg 134:29-37, 2007

15. Egi M, Bellomo R, Stachowski E, et al: Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 105:244-252, 2006

16. Monnier L, Mas E, Ginet C, et al: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 295:1681-1687, 2006

17. Albacker T, Carvalho G, Schricker T, et al: High-dose insulin therapy attenuates systemic inflammatory response in coronary artery bypass grafting patients. Ann Thorac Surg 86:20-27, 2008

18. Koskenkari JK, Kaukoranta PK, Rimpilainen J, et al: Anti-inflammatory effect of high-dose insulin treatment after urgent coronary revascularization surgery. Acta Anaesthesiol Scand 50:962-969, 2006

19. Visser L, Zuurbier CJ, Hoek FJ, et al: Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: Effects on inflammatory response during coronary artery surgery. Br J Anaesth 95:448-457, 2005

20. Schetz M, Vanhorebeek I, Wouters PJ, et al: Tight blood glucose control is renoprotective in critically ill patients. J Am Soc Nephrol 19:571-578, 2008

21. Thomas G, Rojas MC, Epstein SK, et al: Insulin therapy and acute kidney injury in critically ill patients a systematic review. Nephrol Dial Transplant 22:2849-2855, 2007

22. Lecomte P, Van Vlem B, Coddens J, et al: Tight perioperative glucose control is associated with a reduction in renal impairment and renal failure in non-diabetic cardiac surgical patients. Crit Care 12: R154, 2008

23. Albacker TB, Carvalho G, Schricker T, et al: Myocardial protection during elective coronary artery bypass grafting using high-dose insulin therapy. Ann Thorac Surg 84:1920-1927, 2007

24. Quinn DW, Pagano D, Bonser RS, et al: Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial. J Thorac Cardiovasc Surg 131: 34-42, 2006

25. Gandhi GY, Nuttall GA, Abel MD, et al: Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial. Ann Intern Med 146:233-243, 2007

26. Van den Berghe G: Does tight blood glucose control during cardiac surgery improve patient outcome? Ann Intern Med 146:307-308, 2007

27. Clement S, Braithwaite SS, Magee MF, et al: Management of diabetes and hyperglycemia in hospitals. Diabetes Care 27:553-591, 2004

28. Hirsch IB: Sliding scale insulin—Time to stop sliding. JAMA 301:213-214, 2009

29. Van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. N Engl J Med 354:449-461, 2006

30. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125-139, 2008

31. National Institutes of Health: Glucontrol study: comparing the effects of two glucose control regimen by insulin in intensive care unit patients. Available at: http://www.clinicaltrials.gov/ct/show/NCT00107601 and http://www.glucontrol.org/. Accessed April 30, 2009

32. Clinicaltrials.gov: Outcomes study of hyperinsulinemic glucose-control in cardiac surgery. Available at: http://www.clinicaltrials.gov/ct2/show/NCT00524472. Accessed April 30, 2009

Con: Tight Perioperative Glycemic Control

Thomas F. Floyd, MD,*† and Jiri Horak, MD*

SINCE THE Leuven Trial in 2001 in which van den Berghe et al[1] reported a head turning 46% reduction in mortality from the application of an intensive insulin treatment (IIT) regimen in critically ill patients, especially surgical patients, reports of subsequent trials have been inconsistent. Despite the profound inconsistencies, both the American Diabetes Association and the American Association of Clinical Endocrinologists have repeatedly published guidelines encouraging IIT regimens.[2-4] Bellomo and Egi,[5] in a 2005 editorial responding to the runaway express train-like deployment of this therapy, raised the following concerns regarding the Leuvin Trial[1]: (1) it was not blinded; (2) subjects were predominantly cardiac surgery patients; (3) patients were administered the equivalent of 2 to 3 L of 10% glucose per day, which is not a common practice; (4) parenteral and or enteral nutrition was provided to all patients within 24 hours of intensive care unit (ICU) admission, which is another uncommon practice; (5) mortality from cardiac surgery in the control group was twice the national average, raising concerns about whether the control group was truly representative of the population; and (6) the reduction in mortality reported "exceeded that of any other interventional trial in critically ill or diabetic patients, stretching the biological plausibility of the findings." The present authors also found the 46% reduction in septicemia, the 41% reduction in the need for dialysis, the 50% reduction in red blood cell transfusion requirements, and the 44% reduction in polyneuropathy to be real eye openers. Nonetheless, IIT was touted as cutting edge, disseminated and deployed worldwide, including at the present authors' institution. Those big numbers were too hard to ignore! Who would not want to embrace such an intervention?

Given the magnitude of the therapeutic benefit seemingly enjoyed by those patients offered the IIT regimen, it would seem as though the results would be so easily replicated—not so fast! A recent 2008 meta-analysis by Weiner et al[6] could not find evidence of a therapeutic benefit, even in surgical subjects. This review included surgically focused trials reported by van den Berghe et al,[1] He et al,[7] Hoedemakers et al,[8] Stecher et al,[9] and van Wezel et al.[10] The most recent meta-analysis published by Griesdale et al[11] found no benefit to IIT among subjects in either the medical (relative risk [RR] = 0.93) or combined medical-surgical ICU setting (RR = 0.99), but there did appear to be significant and important benefit from therapy in the homogeneous surgical ICU setting (RR = 0.63). This review included surgical trials published by van den Berghe et al,[1] Bilotta et al,[12,13] Grey and Perdrizet,[14] and He et al.[7] However, a closer look shows that the benefits seen in the meta-analysis of the surgical group were largely attributable to the contribution of the large population from the unblinded Leuvin Trial,[1] which dwarfed the populations of other included trials. When the populations of such included trials are badly skewed, errors in trial design from the largest trials will also be overemphasized in the meta-analysis.

There is indeed one trial that can stand on its own merits. In the largest single study published to date, the NICE-SUGAR Trial[15] reported on over 6,000 subjects in a randomized, prospective, and blinded test of IIT versus conventional glucose management. The 90-day mortality was significantly higher in the IIT group versus the conventionally treated group (28 *v* 25%, $p < 0.02$) in both surgical and medical subjects. Mortality from cardiovascular causes was also more common in the IIT group (42% *v* 36%, $p < 0.02$), and, finally, severe hypoglycemia was more common in the IIT group (7% *v* .5%, $p < 0.001$). A detailed organ system by organ system review of the purported benefits of the ITT approach could be discussed, but this is not necessary because, as all would agree, the outcome of death trumps all! Bellomo and Egi[16] followed up their warnings in 2005 with more current and incisive commentary on the remarkable discrepancies between the recently published NICE-SUGAR Trial[17] and the Leuvin Trial.[1] They emphasized the inherent difficulties in expecting single-center trials, caused by a litany of potential reasons, to reflect multicenter reality and "scientific truth." The present authors are left truly puzzled as to why such a large effect as seen in the Leuven Trial would not be seen, at least to some smaller degree, in subsequent trials.

In light of the impending derailment of the IIT express, the present authors have taken a step back to reflect on the hypotheses that originally drove this high-speed train. Insulin resistance may be induced by stress associated with acute illness or surgery[18,19]; this will be referred to as "acute stress-induced insulin resistance." Acute stress-induced insulin resistance may coexist with chronic pathologic insulin resistance (CPIR), as with diabetes mellitus and obesity.[20-22] Recent reports suggest that the degree of insulin resistance is a better predictor of mortality than glucose level.[23-25] Insulin resistance is a sign of the severity of illness and the chronicity, if not the diffusivity of disease. CPIR can be identified at the initial presentation in patients with myocardial infarction[26] or in those presenting for cardiac surgery[27] and predicts outcome in both scenarios. Furnary and Wu[28] and others have shown that the inability to achieve euglycemia correlates with poor survival. Perhaps this is because the demonstrated CPIR is simply a biomarker of the severity and diffusivity of comorbidities already known to impact outcome? So very confusing to the present authors, however, is how van den Berghe et al[29] found no survival benefit to IIT in diabetics, whereas Furnary and Wu[30] support just the opposite.

The present authors are particularly concerned about the potential of the IIT approach to actually cause harm. Hypoglycemia in recent studies has been reported at 25% in a pediatric[31] and 29% in hybrid medical-surgical ICU populations.[32] In 14 of 26 randomized trials in which hypoglycemia was reported, the

*From the Departments of *Anesthesiology and Critical Care and †Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA.*

Address reprint requests to Thomas F. Floyd, MD, Department of Anesthesiology and Critical Care, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. E-mail: floydt@uphs.upenn.edu

1053-0770/09/2306-0026$36.00/0

doi:10.1053/j.jvca.2009.08.008

Key words: insulin, tight, intensive, glycemic, control, glucose, insulin resistance, surgery, critical care, hypoglycemia, outcome, perioperative

relative risk of this event was 6.0-fold with IIT compared with conventional therapy.[11] That is consistency! At least 2 randomized trials have been halted because of concerns over hypoglycemia.[33,34] Certainly, other studies using modestly different regimens have reported much lower frequencies of hypoglycemia, but these disparate frequencies reported are true reflections on the difficulties inherent in applying such a protocol en masse. In the recently published NICE-SUGAR Trial[17] in which IIT management led to higher mortality in both surgical and medical subsets, a blood glucose target of ≤180 mg/dL resulted in lower mortality than did a target of 81 to 108 mg/dL, suggesting that hypoglycemia may have had a role in the increased mortality.

Although most of the readers would struggle to describe the pharmacophysiologic hypotheses that support the IIT schemes, they would have no trouble describing the same for the neurologic consequences of severe hypoglycemia. Hypoglycemia that results from overdosing of exogenous insulin can result in death. This fact is not arguable.[29] How many patients would clinicians need to treat to accept 1 brain death outcome? This is not known, but the following scenario is realistic. Would clinicians be in a position to defend, in court, the hypoglycemia-related brain death of a young individual with no history of diabetes mellitus presenting for an atrial septal defect repair who suffered such sequelae from an IIT scheme, initiated intraoperatively, for a hypothermic glucose of 140 gm/dL? The protocols under review would appear to indeed support such an intervention.

In 2006, van den Berghe et al[35] reported that the mean cost associated with IIT in 1,500 ventilated surgical patients was 144 euros per patient, whereas it was only 72 euros per patient in the conventionally treated group. They did not bother to account for the financial impact of personnel required to deal with the management of the IIT or the 7-fold increase in the incidence of hypoglycemia compared with conventional management. They argued that this 72 euro increase in cost was eventually dwarfed by the financial benefit achieved from better overall outcomes. In light of the more recent and broader datasets suggesting otherwise, the increased direct and indirect costs associated with this practice can be viewed legitimately as a massive financial burden, with no proven benefit and likely worse. All of this, of course, ignores the medical and/or medicolegal financial impacts of cases in which hypoglycemia results in injury or death.

The present authors do agree that perioperative control of hyperglycemia and hypoglycemia is important on some level but argue that the current body of evidence overwhelmingly suggests that moderate glucose control (goal <180 mg/dL) during cardiac surgery and in ICUs is more beneficial to patients than tight (80-110 mg/dL) glucose control. The latest evidence from Gandhi et al,[36] Brunkhorst et al,[34] Devos et al,[33] and Finer and Heritier[15] does not support the practice of tight glucose control perioperatively. Setting aside, for good reasons, the multiple observational or retrospective published studies, the randomized controlled trial of perioperative glucose control published by van den Berghe et al[1] in 2001 stands out in its level of support for tight glucose control. The unprecedented decrease in hospital mortality in their surgical population has not been replicated by any another study, not even in follow-up studies by the same group of investigators.[29,37]

The authors do not think the focus of this "Con" article should be to reanalyze the studies and articles regarding arguments for moderate glucose control. The authors do realize that many complex and difficult questions remain to be answered on this topic. What are the exact mechanisms and direct and indirect effects of insulin administration in the perioperative period? What does perioperative hyperglycemia mean? How harmful is it? Are there other effective alternatives for glycemic control in surgical patients? What is the best way to measure glycemia in ICU patients? How cost-effective is this therapy? What role does nutritional cointervention have in all of this? Should clinicians devote their effort and resources to other potentially less risky and more efficient ICU interventions? The authors do not question that there might be still a subgroup of patients who could benefit from tight glucose control.[38]

The implementation and dissemination of IIT protocols has occurred to such an extent that it has become a "standard of care." The evidence, much to the present authors' surprise, does not actually support this practice. Taking down such practices, once they have been accepted as the "standard of care," can be difficult and can even be characterized as "unethical to withhold." Such was the case for aprotinin. The costs associated with the implementation of an IIT scheme for every single patient who enters the hospital, surgical or otherwise, is mind boggling. Clinicians have a responsibility to hold the line on the layering of wasteful health care initiative unless there is irrefutable evidence of its benefit. Until there is better evidence supporting the practice of IIT management in hospitalized patients, surgical patients, or, better yet, in cardiac surgical patients with CPIR, clinicians need to begin the dismantling of this practice . . . yesterday!

REFERENCES

1. van den Berghe G, Wouters P, Weekers F, et al: Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359-1367, 2001

2. Rodbard HW, Blonde L, Braithwaite SS, et al: American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. Endocr Pract 13:1-68, 2007 (suppl 1)

3. Standards of medical care in diabetes—2009. Diabetes Care 32:S13-S61, 2009 (suppl 1)

4. Moghissi ES, Korytkowski MT, DiNardo M, et al: American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care 32:1119-1131, 2009

5. Bellomo R, Egi M: Glycemic control in the intensive care unit: Why we should wait for NICE-SUGAR. Mayo Clin Proc 80:1546-1548, 2005

6. Wiener RS, Wiener DC, Larson RJ: Benefits and risks of tight glucose control in critically ill adults: A meta-analysis. JAMA 300: 933-944, 2008

7. He W, Zhang TY, Zhou H, et al: [Impact of intensive insulin therapy on surgical critically ill patients]. Zhonghua Wai Ke Za Zhi 45:1052-1054, 2007

8. Hoedemaekers CW, Pickkers P, Netea MG, et al: Intensive insulin therapy does not alter the inflammatory response in patients undergoing coronary artery bypass grafting: A randomized controlled trial [ISRCTN95608630]. Crit Care 9:R790-R797, 2005

9. Stecher A, Steblaj S, Kremzar B, et al: The Influence of Normoglycemia on Ventilator-Associated Pneumonia in Trauma Patients. Ljubljana, Slovenia, European Trauma Congress, 2006

10. van Wezel HB, Zuurbier CJ, de Jonge E, et al: Differential effects of a perioperative hyperinsulinemic normoglycemic clamp on the neurohumoral stress response during coronary artery surgery. J Clin Endocrinol Metab 91:4144-4153, 2006

11. Griesdale DE, de Souza RJ, van Dam RM, et al: Intensive insulin therapy and mortality among critically ill patients: A meta-analysis including NICE-SUGAR study data. CMAJ 180:821-827, 2009

12. Bilotta F, Caramia R, Cernak I, et al: Intensive insulin therapy after severe traumatic brain injury: A randomized clinical trial. Neurocrit Care 9:159-166, 2008

13. Bilotta F, Spinelli A, Giovannini F, et al: The effect of intensive insulin therapy on infection rate, vasospasm, neurologic outcome, and mortality in neurointensive care unit after intracranial aneurysm clipping in patients with acute subarachnoid hemorrhage: A randomized prospective pilot trial. J Neurosurg Anesthesiol 19:156-160, 2007

14. Grey NJ, Perdrizet GA: Reduction of nosocomial infections in the surgical intensive-care unit by strict glycemic control. Endocr Pract 10:46-52, 2004 (suppl 2)

15. Finfer S, Heritier S: The NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) Study: Statistical Analysis Plan. Crit Care Resusc 11:46-57, 2009

16. Bellomo R, Egi M: What is a NICE-SUGAR for patients in the intensive care unit? Mayo Clin Proc 84:400-402, 2009

17. Finfer S, Chittock DR, Su SY, et al: Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360:1283-1297, 2009

18. Thorell A, Nygren J, Ljungqvist O: Insulin resistance: A marker of surgical stress. Curr Opin Clin Nutr Metab Care 2:69-78, 1999

19. Lehrke M, Broedl UC, Biller-Friedmann IM, et al: Serum concentrations of cortisol, interleukin 6, leptin and adiponectin predict stress induced insulin resistance in acute inflammatory reactions. Crit Care 12:R157, 2008

20. Bloch-Damti A, Bashan N: Proposed mechanisms for the induction of insulin resistance by oxidative stress. Antioxid Redox Signal 7:1553-1567, 2005

21. Kaneki M, Shimizu N, Yamada D, et al: Nitrosative stress and pathogenesis of insulin resistance. Antioxid Redox Signal 9:319-329, 2007

22. Meigs JB, Larson MG, Fox CS, et al: Association of oxidative stress, insulin resistance, and diabetes risk phenotypes: The Framingham Offspring Study. Diabetes Care 30:2529-2535, 2007

23. Ascione R, Rogers CA, Rajakaruna C, et al: Inadequate blood glucose control is associated with in-hospital mortality and morbidity in diabetic and nondiabetic patients undergoing cardiac surgery. Circulation 118:113-123, 2008

24. Mowery NT, Dortch MJ, Dossett LA, et al: Review of a large clinical series: Insulin resistance despite tight glucose control is associated with mortality in critically ill surgical patients. J Intensive Care Med 24:242-251, 2009

25. Finney SJ, Zekveld C, Elia A, et al: Glucose control and mortality in critically ill patients. JAMA 290:2041-2047, 2003

26. Malmberg K, Norhammar A, Wedel H, et al: Glycometabolic state at admission: Important risk marker of mortality in conventionally treated patients with diabetes mellitus and acute myocardial infarction: Long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation 99:2626-2632, 1999

27. Zindrou D, Taylor KM, Bagger JP: Admission plasma glucose: An independent risk factor in nondiabetic women after coronary artery bypass grafting. Diabetes Care 24:1634-1639, 2001

28. Furnary AP, Wu Y: Clinical effects of hyperglycemia in the cardiac surgery population: The Portland Diabetic Project. Endocr Pract 12:22-26, 2006 (suppl 3)

29. van den Berghe G, Wilmer A, Milants I, et al: Intensive insulin therapy in mixed medical/surgical intensive care units: Benefit versus harm. Diabetes 55:3151-3159, 2006

30. Furnary AP, Wu Y: Eliminating the diabetic disadvantage: The Portland Diabetic Project. Semin Thorac Cardiovasc Surg 18:302-308, 2006

31. Vlasselaers D, Milants I, Desmet L, et al: Intensive insulin therapy for patients in paediatric intensive care: A prospective, randomised controlled study. Lancet 373:547-556, 2009

32. Arabi YM, Dabbagh OC, Tamim HM, et al: Intensive versus conventional insulin therapy: A randomized controlled trial in medical and surgical critically ill patients. Crit Care Med 36:3190-3197, 2008

33. Devos P, Preiser JC, Mélot C: Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: Final results of the glucontrol study. Intensive Care Med 33:S189, 2007

34. Brunkhorst FM, Engel C, Bloos F, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358:125-139, 2008

35. van den Berghe G, Wouters PJ, Kesteloot K, et al: Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. Crit Care Med 34:612-616, 2006

36. Gandhi GY, Nuttall GA, Abel MD, et al: Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: A randomized trial. Ann Intern Med 146:233-243, 2007

37. van den Berghe G, Wilmer A, Hermans G, et al: Intensive insulin therapy in the medical ICU. N Engl J Med 354:449-461, 2006

38. Malmberg K: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ 314:1512-1515, 1997