



Tight Perioperative Glucose Management Should Start in the Operating Room

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The treatment of hyperglycemia was originally explored in the management of acute coronary syndromes. Over the last decade, the focus has shifted to both diabetic and nondiabetic patient populations after cardiac surgery, as well as critically ill ICU patients where improved morbidity and mortality was seen in those for whom tight glycemic control was employed (1). Intraoperative hyperglycemia is an independent risk factor for postoperative morbidity and mortality after cardiac surgery (2, 3). Recent studies have suggested that tight intraoperative glycemic control significantly decreases in-hospital morbidity (2, 3). Furthermore, there is a 29.6% incidence of undiagnosed diabetes in this patient population (4). This observation, along with the fact that diabetic patients have a higher rate of complications after coronary artery bypass grafting (CABG), supports tight intraoperative glycemic control (4). Lazar et al. suggest that using a modified glucose-insulin-potassium (GIK) solution in diabetic patients decreases morbidity, enhances survival, and diminishes recurrent ischemic events (5). In a nonrandomized study over 15 years involving 3554 patients, Furnary et al. found that controlling perioperative glucose levels in diabetic patients decreased absolute mortality by 57% (3). In a retrospective observational study of 409 patients undergoing cardiac surgery, Gandhi et al. found that a 20mg/dL increase in the mean intraoperative glucose level was associated with increased postoperative mortality and morbidity (2). Ouattara et al. demonstrated that events after CABG was 7.2% more likely in those patients with poorly controlled intraoperative blood glucose levels (6).

The rationale for tight intraoperative glycemic control can be likened to the routine approach of diabetic patients to administer insulin prior to high glucose meals. Hypothermia, the stress response to surgery, and the impact of extra-corporeal circulation, as well as intrinsic mechanisms of insulin resistance lead to glucose-insulin mismatch in the OR (7-11). This observation combined with the preponderance of data supporting the benefits of insulin treatment irrespective of its hypoglycemic effects forms the rationale for intraoperative initiation of therapy (12).

Turina et al. summarized the negative effects of hyperglycemia on the early phase of the immune response, the cytokine network, and the phagocytic phase of the immune response (13). Hyperglycemia impairs endothelial function and increases levels of proinflammatory cytokines such as IL-6. It is believed that these effects on the immune system lead to the increased susceptibility and severity



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of infections in both diabetic and nondiabetic patients with acute hyperglycemia (13).

Insulin administration may be beneficial by both glucose lowering and non-glucose lowering mechanisms (12). In both experimental animal data and human studies, insulin infusions appear to have beneficial anti-inflammatory effects by reducing C-reactive protein (CRP) and serum amyloid A (SAA). In a study of CABG patients, the increase in plasma CRP 16 hours postoperatively was 30 times greater than those seen in patients with ST segment elevation myocardial infarctions (STEMI) (14). Insulin also appears to have favorable effects as a vasodilator primarily via a nitric oxide (NO) effect. Rodent studies have demonstrated that insulin exerts myocardial protection by enhancing NO synthetase through P13-kinase-Akt pathways (15).

Thus initiate insulin administration in the OR. As stated earlier, pre-emptive treatment rather than reactive hyperglycemic treatment has strong theoretical, scientific and practical benefits. One can make the argument that the conditions of the operating room warrant treatment – it is the time when glucose-insulin mismatch occurs. The mechanisms leading to the disturbances in the glucose-insulin relationship are multifactorial, including inadequate insulin secretion, decreased total body glucose uptake, increased absorption of glucose by the kidneys, hypothermia, rewarming as well as cardiopulmonary bypass (7-11).

Hyperglycemia and insulin-depleted states can lead to an overabundance of free fatty acids and a relative lack of glycolysis-derived ATP which is essential to myocardial cell membrane stabilization. It has thus been suggested that glucose metabolism be maintained during these situations to inhibit further fluid accumulation, stabilize membranes and attenuate cellular edema. Other data reveal that insulin treatment mitigates posts ischemic tissue necrosis, infarct size, metabolic acidosis and also prevents myocardial stunning (16-17).

Inadvertent hypoglycemia as a consequence of tight glycemic control has also been described. Chaney et al. reported that 40% of patients in the “tight control” group required treatment for postoperative hypoglycemia (18-19). Other data suggest that despite insulin treatment, intraoperative hyperglycemia could not be adequately controlled. Several studies using a modified insulin clamp technique, the Vellore regimen, the hyperinsulinemic normoglycemic clamp technique, and various modifications of insulin infusion regimens reveal the safe and effective use of this treatment in cardiac surgical patients (20-23).

Although the precise details of the timing of insulin therapy, the desired target serum glucose level, and the duration of therapy remains controversial, the beneficial effects of tight glycemic control and insulin administration appear to be firmly established in patients undergoing cardiac surgery. Therefore, initiation of glycemic control in the operating room makes intuitive sense. Although some say “better late than never”, that should not apply to the aggressive treatment of intraoperative hyperglycemia during cardiac surgery.

References:

1. Van Den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; 345:1359-67.
2. Gandhi GY, Nuttal GA, Abel MD, et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. *Mayo Clin Proc* 2005; 80(7):862-66.
3. Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2003; 125:1007-21.
4. Lauruschkat AH, Arnrich B, Albert AA, et al. Prevalence and risks of undiagnosed diabetes mellitus in patients undergoing coronary artery bypass grafting. *Circulation* 2005; 112:2397-2402.
5. Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* 2004; 109:1497-1502.
6. 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* 2005; 103:677-8.
7. Lehot JJ, Piriz H, Villard J, et al. Glucose homeostasis: comparison between hypothermic and normothermic cardiopulmonary bypass. *Chest* 1992; 102:106-11.
8. Braden H, Cheema-Dhadli S, Mazer D, et al. Hyperglycemia during normothermic cardiopulmonary bypass: the role of the kidney. *Ann Thorac Surg* 1998; 65:1588-93.
9. Kuntschen FR, Galletti PM, Hahn C, et al. Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. *J Thorac Cardiovasc Surg* 1985; 89:97-106.
10. Kuntschen FR, Galletti PM, Hahn C, et al. Glucose-insulin interactions during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1986; 91:451-9.
11. Svensson S, Svedjeholm R, Ekroth R, et al. Trauma metabolism and the heart: Uptake of substrates and effects of insulin early after cardiac operations. *J Thorac Cardiovasc Surg* 1990; 99:1063-73.
12. Dandona R, Chaudhuri A, Ghanim H, et al. Anti-inflammatory effects of insulin and the pro-inflammatory effects of glucose. *Semin Thorac Cardiovasc Surg* 2006; 18:293-301.
13. Turina M, Fry DE, Polk HC, et al. Acute hyperglycemia and the innate immune system: Clinical, cellular, and molecular aspects. *Crit Care Med* 2005; 33:1624-1633.
14. Visser L, Zuurbier CJ, Hock FJ, et al. Glucose, insulin and potassium applied as perioperative hyperinsulinaemic normoglycaemic clamp: effects on inflammatory response during coronary artery surgery. *Br J Anaesth* 2005; 95(4): 448-457.
15. Gao F, Gao E, Yue T-L, et al. Nitric oxide mediates the antiapoptotic effect of insulin in myocardial ischemia-reperfusion: the roles of P13 – kinase, AKT, and the endothelial nitric-oxide synthetase phosphorylation. *Circulation* 2002; 105:1497-1502.
16. Lazar HL. Enhanced preservation of acutely ischemic myocardium using glucose-insulin-potassium solutions. *J Card Surg* 1994; 9 Suppl: 474-8.
17. Lazar HL, Zhang X, Rivers S, et al. Limiting ischemic myocardial damage using glucose-insulin-potassium solutions. *Ann Thorac Surg*. 1995; 60:411-6.
18. Chaney MA, Nikolov MP, Blakeman BP, et al. Attempting to maintain normoglycemia during cardiopulmonary bypass with insulin may initiate postoperative hypoglycemia. *Anesth Analg* 1999; 89:1091-5.
19. Bhatia A, Cadman B, Mackenzie I. Hypoglycemia and cardiac arrest in a critically ill patient on strict glycemic control. *Anesth Analg* 2006; 102:549-51.
20. Carvalho G, Moore A, Qizilbash B. Maintenance of normoglycemia during cardiac surgery. *Anesth Analg* 2004; 99:319-24.
21. Miriam A, Korula G. A simple glucose insulin regimen for perioperative blood glucose control: the Vellore regimen. *Anesth Analg* 2004; 99:598-602.
22. Furnary AP, Cheek DB, Holmes SC, et al. Achieving tight glycemic control in the operating room: Lessons learned from 12 years in the trenches of a paradigm shift in anesthetic care. *Semin Thorac Cardiovasc Surg* 2006; 18:339-45.
23. Smith CE, Styn NR, Kalhan S, et al. Intraoperative glucose control in diabetic and nondiabetic patients during cardiac surgery. *J Cardiovasc Vasc Anesth* 2005; 19:201-8.