

# Pro: Strict Glycemic Control is Essential in Pediatric Cardiac Surgery

Barry D. Kussman, MBBCh, FFA(SA)

## Introduction

Elevated blood glucose (BG) levels has been identified as a modifiable risk factor for morbidity and mortality in multidisciplinary adult<sup>1-5</sup> and pediatric<sup>6-12</sup> critical care units (CCU). Stress hyperglycemia can be attributed to peripheral and hepatic insulin resistance, increased stress hormone release, drugs (catecholamines, steroids), and excessive dextrose or calorie administration.<sup>13</sup> Although hyperglycemia is an adaptive response to stress, over the short term it causes a negative fluid balance (glycosuria), increased inflammation (increased pro-inflammatory cytokines), impaired immune function (impaired neutrophil and monocyte chemotaxis, phagocytosis and oxidative burst, decreased complement function), endothelial dysfunction (impaired reactive endothelial nitric oxide generation), and a prothrombotic state (platelet aggregation, vasoconstriction), resulting in multi-organ system dysfunction.<sup>4,14</sup> Glucose is specifically toxic to the mitochondria of cells that take up glucose independent of insulin and in proportion to the circulating levels of glucose. In critical illness, overexpression of insulin independent glucose transporters leads to glucose overload in the central and peripheral nervous system, endothelium, liver, immune cells, renal tubules and gastrointestinal tract.<sup>15-17</sup>

The landmark study by Van den Berghe et al. from Leuven, Belgium<sup>18</sup> ushered in the era of intensive insulin therapy (IIT) and tight glycemic control for the critically ill. In the adult cardiac surgery population, hyperglycemia is associated with increased wound infections and mortality.<sup>4</sup> Although a recent meta-analysis of adult studies found that lowering blood glucose with insulin did not affect mortality in all critically ill patients, IIT was effective in lowering the risk of death among postoperative surgical patients<sup>19,20</sup>. Possible explanations for these findings include different patient populations, variability in what constitutes “usual care”, different definitions of tight glucose control, success in achieving target glucose levels, variability in blood glucose level (fluctuation in blood glucose may be worse than constant moderate hyperglycemia),<sup>3,12,21</sup> and accuracy of glucose measurements. In postoperative surgical patients, greater use of central venous and arterial lines allows for greater precision in monitoring and correcting glucose, and the shorter delay between the onset of hyperglycemia and start of glycemic control may be important if there is a time window for prevention of glucose toxicity.

Improved clinical outcomes may not be solely due to control of BG levels. Insulin lowers free fatty acids (excess of which impairs mitochondrial function), normalizes endothelial function, and has anabolic, anti-inflammatory, cardio-protective, and anti-thrombotic effects, all of which may contribute independently to improved outcomes in critical illness.<sup>14,22</sup> It is difficult to distinguish the effects of glycemic control from those of increased insulin levels.

## Pediatric Cardiac Surgery Studies

There is mounting evidence that strict glycemic control may be beneficial for the pediatric patient undergoing cardiac surgery.

Observational (retrospective or prospective) studies in pediatric cardiac surgery (PCS) have found an association between perioperative glycemic derangement and poor early outcome, with the majority of the studies focusing on the postoperative period. In 184 infants undergoing CPB, Yates et al found that duration of hyperglycemia (glucose  $\geq$  126mg/dL) in the first 72 hours postoperatively was associated with increased mortality and morbidity (renal and hepatic insufficiency, infection, CNS event, need for extracorporeal membrane oxygenation (ECMO), and increased duration of mechanical ventilation, intensive care and hospital stay).<sup>23</sup> Although intraoperative glucose levels did not differ between survivors and nonsurvivors, peak postoperative glucose was associated with death. Falcao et al, in a cohort of 213 children, found an independent association between duration of hyperglycemia and morbidity (odds ratio [OR]1.95) and mortality (OR 1.41).<sup>24</sup> After the first postoperative day the durations of mild (126-160 mg/dL), moderate (161-200 mg/dL) and severe ( $>$ 200 mg/dL) hyperglycemia were significantly longer in nonsurvivors. In a study by Ghafoori et al, a peak BG  $>$  130 mg/dL during the first 24 postoperative hours was a significant multivariate predictor of mediastinitis.<sup>25</sup> Patients with glucose levels  $>$ 175 mg/dL during CPB are three times more likely to have postoperative bacteremia.<sup>26</sup>

In contrast, some observational studies have not found an association between glucose metrics and outcome after PCS. Rossano et al reported that following the arterial switch operation, infants who spent  $>$  50% of the time in the first 24 postoperative hours with glucose levels between 80-110 mg/dL were at increased risk of adverse events, while those with levels  $>$ 200 mg/dL were not at increased risk for adverse events.<sup>27</sup> Similarly, DeCampi et al found that in infants  $<$ 10 kg, postbypass and postoperative hyperglycemia were not risk factors for morbidity and mortality, although specific glucose levels used for the analysis were not clearly defined.<sup>28</sup> Three secondary analyses of studies in infant cardiac surgery did not find an association between hyperglycemia and late neurodevelopmental outcome. In infants with D-transposition of the great arteries undergoing an arterial switch operation (Boston Circulatory Arrest Study cohort), de Ferranti et al found no association between intraoperative hyperglycemia (categorical glucose level  $\geq$ 150 mg/dL) and neurodevelopmental outcomes at 1, 4, and 8 years.<sup>29</sup> In infants  $<$  6 months undergoing two-ventricle repairs,<sup>30</sup> or Stage I palliation,<sup>31</sup> hyperglycemia during the first 48 postoperative hours was not associated with adverse neurodevelopmental outcome as assessed by the Bayley scales at one year of age.<sup>30</sup>

Limitations of the aforementioned observational studies include small sample size, limited risk adjustment, high hospital mortality, small number of outcomes for meaningful multivariate analysis, and variability in the definition of hyperglycemia. Polito et al. attempted to overcome some of these limitations and identified associations between perioperative glycemic derangement and poor outcome after complex PCS.<sup>32</sup> In 378 patients (RACHS-1 category  $\geq$ 3<sup>33</sup>, metrics of glucose control (average, peak, minimum, standard deviation, duration of hyperglycemia) were determined intraoperatively and for 72 hours postoperatively. The primary outcome was days of postoperative hospitalization, and the secondary outcome was a composite morbidity-mortality variable ( $\geq$ 1 of the following: death, nosocomial infection, cardiac failure

requiring extracorporeal membrane oxygenation, renal failure requiring dialysis, hepatic injury, new CNS injury). Potential cofounders adjusted for were age, any genetic syndrome, at least one major noncardiac structural anomaly, prematurity, RACHS-1 category, CPB time, multiple procedures during a single operation, need for reoperation or interventional catheterization during the same admission, and inotrope score.

Intraoperatively, only a minimum glucose  $\leq 75$  mg/dL was associated with greater adjusted odds of reaching the composite morbidity-mortality end point (OR, 3.1; 95% CI, 1.49-6.48); intraoperative hyperglycemia was not found to be harmful. Postoperatively, greater duration of hyperglycemia ( $>126$  mg/dL) was associated with longer duration of hospitalization ( $P<0.001$ ). An average glucose  $<110$  mg/dL (OR, 7.3; 95% CI, 1.95-27.25) or  $>143$  mg/dL (OR, 5.21; 95% CI, 1.37-19.89), minimum glucose  $\leq 75$  mg/dL (OR, 2.85; 95% CI, 1.38 to 5.88), and peak glucose  $\geq 250$  mg/dL (OR, 2.55; 95% CI, 1.2-5.43) were all associated with greater adjusted odds of reaching the composite morbidity-mortality end point. As optimal glucose levels in critically ill children are unknown, this study concluded that the optimal postoperative glucose range may be 110 to 126 mg/dL.

The first randomized controlled trial of IIT in pediatric critical care was published in 2009 by the Leuven group.<sup>34</sup> Seven hundred critically ill children were randomized to target BG concentrations of 2.8-4.4 mmol/L (1 mmol/L = 18 mg/dL) in infants (aged  $< 1$  year) and 3.9-5.6 mmol/L in children with insulin infusion throughout CCU stay (intensive group,  $n=349$ ) or insulin infusion only to prevent BG from exceeding 11.9 mmol/L (conventional group,  $n=351$ ). Postoperative cardiac surgical patients (median RACHS-1 score 3) comprised 75% of the cohort. Primary endpoints were duration of CCU stay and inflammation (decrease in C-reactive protein). Mean blood glucose concentrations were lower in the intensive group than in the conventional group (infants: 4.8 [SD 1.2] mmol/L vs. 6.4 [1.2] mmol/L,  $p<0.0001$ ; children: 5.3 [1.1] mmol/L vs. 8.2 [3.3] mmol/L,  $p<0.0001$ ). Hypoglycemia (defined as blood glucose  $\leq 2.2$  mmol/L (40 mg/dL) occurred in 87 (25%) patients in the intensive group ( $p<0.0001$ ) versus five (1%) patients in the conventional group. Duration of ICU stay was shortest in the intensively treated group (5.51 days [95% CI 4.65-6.37] vs. 6.15 days [5.25-7.05],  $p=0.017$ ). The inflammatory response was attenuated at day 5, as indicated by lower C-reactive protein in the intensive group compared with baseline (-9.75 mg/L [95% CI -19.93 to 0.43] vs. 8.97 mg/L [-0.9 to 18.84],  $p=0.007$ ). The number of patients with extended ( $>$ median) stay in PICU was 132 (38%) in the intensive group versus 165 (47%) in the conventional group ( $p=0.013$ ). Nine (3%) patients died in the intensively treated group versus 20 (6%) in the conventional group ( $p=0.038$ ). The authors concluded that targeting of blood glucose concentrations to *age-adjusted* normal fasting concentrations improved short-term outcome of patients in the pediatric ICU, and that the effect on long-term survival, morbidity, and neurocognitive development still needs to be investigated.

Gu et al performed a randomized controlled trial of insulin therapy in PCS, examining the modulating effects of insulin on inflammatory mediators during CPB.<sup>35</sup> Infants undergoing cardiac surgery with bypass were randomly assigned into a routine therapy group ( $n=30$ ) or intensive insulin therapy group ( $n=30$ ). BG levels intraoperatively were 4.4-10 mmol/L (79-180 mg/dL) in the insulin therapy group, with levels 3.1 fold higher in the routine care group by the end of CPB. After the initiation of CPB, the rise in TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 (pro-inflammatory cytokines) was significantly attenuated, while IL-10 levels (anti-inflammatory cytokine) were significantly higher in

the intensive insulin therapy group. Correspondingly, the rise in Nuclear factor- $\kappa$ Bp65 (induces transcription of pro-inflammatory cytokines, adhesion molecules, enzymes generating reactive oxygen species) was significantly attenuated, while the expression of I $\kappa$ B (inhibitor of NF- $\kappa$ B) was significantly higher. This study thus showed that insulin administration during PCS can control blood glucose levels and attenuate the systemic inflammatory response.

Two ongoing pediatric trials are the “Trial of Euglycemia in Cardiac Surgery (TECS)” being performed at Children’s Hospital Boston, and the “Control of Hyperglycemia in Paediatric Intensive Care (CHiP)”, a multicenter study in the UK.

### **Risk of Hypoglycemia**

Hypoglycemia is a frequent complication in critically ill children, even in the absence of insulin therapy, and is associated with mortality and morbidity.<sup>11,12</sup> In children, neural dysfunction (sensory evoked potentials) occurs when the venous plasma glucose concentration decreases below 47mg/dL,<sup>36</sup> suggesting a physiological threshold in the range of 50-60 mg/dL. In neonates, there is no conclusive evidence or consensus in the literature that defines an absolute value or duration of ‘hypoglycemia’ that must occur to produce neurological injury,<sup>37</sup> and little is known of the vulnerability, or lack of it, of the brain of infants at different gestational ages.<sup>38</sup> In the critical care population, early signs of hypoglycemia may be masked by sedatives or muscle relaxants. Adequate glucose intake depends on age and clinical situation, and virtually no extensive studies regarding glucose intake in critically ill children have been performed.<sup>14</sup>

The incidence of hypoglycemia in adult trials of IIT ranged from 5.1-28.6% with a pooled risk ratio of 6.0 (95% CI, 0.78-1.28), and did not differ by CCU setting.<sup>19</sup> In PCS, as described above, a minimum glucose  $\leq$ 75 mg/dL intraoperatively was associated with a greater adjusted odds of reaching a composite morbidity-mortality end point.<sup>39</sup> In the prospective randomized trial by the Leuven group, the incidence of hypoglycemia (defined as blood glucose  $\leq$ 2.2 mmol/L (40 mg/dL) was 25% in the intensive insulin group versus 1% for the conventional group. Thus, as demonstrated in adults studies of IIT, hypoglycemia is a real risk when aiming for strict glycemic control. The risk may be reduced by maintaining higher target levels of plasma glucose concentrations and utilizing continuous rather than intermittent bedside glucose monitoring. In a study of pediatric patients during and after cardiac surgery, the Guardian RT (Medtronic Minimed, Northridge, CA) real-time subcutaneous glucose monitor provided clinically reliable measurements when compared with blood glucose concentrations with the sensor performance remaining reliable under conditions of hypothermia, inotrope use, and body-wall edema.<sup>40</sup> The holy grail for management would be an automated closed-loop glucose control system.

### **Conclusion**

Studies from this decade have shown that a minimalist approach to glucose control in selected perioperative and critically ill patient populations is unwarranted, particularly in those with stress-induced hyperglycemia<sup>41</sup>. In the pediatric cardiac surgical population, intraoperative hypoglycemia and postoperative hyperglycemia and hypoglycemia are associated with adverse outcomes. Unresolved issues are the tightness of the glycemic control needed to improve outcome, whether all patients are at equal risk

for adverse events at a given level of dysglycemia, and whether the benefits of avoiding hyperglycemia justify accepting the known risk of treatment-induced hypoglycemia. A key question is not whether insulin therapy should be given to all critical care patients, but how cellular toxicity caused by glucose levels that are higher than the patient's premorbid levels can be avoided and what the window of opportunity is for doing so<sup>20</sup>.

## References

1. Krinsley JS: Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; 78: 1471-8
2. Krinsley JS: Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Semin Thorac Cardiovasc Surg* 2006; 18: 317-25
3. Krinsley JS: Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; 36: 3008-13
4. Lipshutz AK, Gropper MA: Perioperative glycemic control: an evidence-based review. *Anesthesiology* 2009; 110: 408-21
5. Wass CT, Lanier WL: Glucose modulation of ischemic brain injury: review and clinical recommendations. *Mayo Clin Proc* 1996; 71: 801-12
6. Alaedeen DI, Walsh MC, Chwals WJ: Total parenteral nutrition-associated hyperglycemia correlates with prolonged mechanical ventilation and hospital stay in septic infants. *J Pediatr Surg* 2006; 41: 239-44; discussion 239-44
7. Branco RG, Garcia PC, Piva JP, Casartelli CH, Seibel V, Tasker RC: Glucose level and risk of mortality in pediatric septic shock. *Pediatr Crit Care Med* 2005; 6: 470-2
8. Cochran A, Scaife ER, Hansen KW, Downey EC: Hyperglycemia and outcomes from pediatric traumatic brain injury. *J Trauma* 2003; 55: 1035-8
9. Faustino EV, Apkon M: Persistent hyperglycemia in critically ill children. *J Pediatr* 2005; 146: 30-4
10. Hall NJ, Peters M, Eaton S, Pierro A: Hyperglycemia is associated with increased morbidity and mortality rates in neonates with necrotizing enterocolitis. *J Pediatr Surg* 2004; 39: 898-901; discussion 898-901
11. Srinivasan V, Spinella PC, Drott HR, Roth CL, Helfaer MA, Nadkarni V: Association of timing, duration, and intensity of hyperglycemia with intensive care unit mortality in critically ill children. *Pediatr Crit Care Med* 2004; 5: 329-36
12. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM: Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics* 2006; 118: 173-9
13. Montori VM, Bistrian BR, McMahon MM: Hyperglycemia in acutely ill patients. *Jama* 2002; 288: 2167-9
14. Verbruggen SC, Joosten KF, Castillo L, van Goudoever JB: Insulin therapy in the pediatric intensive care unit. *Clin Nutr* 2007; 26: 677-90
15. Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters PJ, Skogstrand K, Hansen TK, Van den Berghe G: Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest* 2005; 115: 2277-86

16. Van den Berghe G: How does blood glucose control with insulin save lives in intensive care? *J Clin Invest* 2004; 114: 1187-95
17. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G: Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet* 2005; 365: 53-9
18. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. *N Engl J Med* 2001; 345: 1359-67
19. Griesdale DE, de Souza RJ, van Dam RM, Heyland DK, Cook DJ, Malhotra A, Dhaliwal R, Henderson WR, Chittock DR, Finfer S, Talmor D: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *Cmaj* 2009; 180: 821-7
20. Van den Berghe G, Mesotten D, Vanhorebeek I: Intensive insulin therapy in the intensive care unit. *CMAJ* 2009; 180: 799-800
21. Egi M, Bellomo R, Stachowski E, French CJ, Hart G: Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology* 2006; 105: 244-52
22. Macrae D, Pappachan J, Grieve R, Parslow R, Nadel S, Schindler M, Baines P, Fortune PM, Slavik Z, Goldman A, Truesdale A, Betts H, Allen E, Snowdon C, Percy D, Broadhead M, Quick T, Peters M, Morris K, Tasker R, Elbourne D: Control of hyperglycaemia in paediatric intensive care (CHiP): study protocol. *BMC Pediatr* 2010; 10: 5
23. Yates AR, Dyke PC, 2nd, Taeed R, Hoffman TM, Hayes J, Feltes TF, Cua CL: Hyperglycemia is a marker for poor outcome in the postoperative pediatric cardiac patient. *Pediatr Crit Care Med* 2006; 7: 351-5
24. Falcao G, Ulate K, Kouzekanani K, Bielefeld MR, Morales JM, Rotta AT: Impact of postoperative hyperglycemia following surgical repair of congenital cardiac defects. *Pediatr Cardiol* 2008; 29: 628-36
25. Ghafoori AF, Twite MD, Friesen RH: Postoperative hyperglycemia is associated with mediastinitis following pediatric cardiac surgery. *Paediatr Anaesth* 2008; 18: 1202-7
26. O'Brien JE, Jr., Marshall JA, Tarrants ML, Stroup RE, Lofland GK: Intraoperative hyperglycemia and postoperative bacteremia in the pediatric cardiac surgery patient. *Ann Thorac Surg* 2010; 89: 578-83; discussion 583-4
27. Rossano JW, Taylor MD, Smith EO, Fraser CD, Jr., McKenzie ED, Price JF, Dickerson HA, Nelson DP, Mott AR: Glycemic profile in infants who have undergone the arterial switch operation: hyperglycemia is not associated with adverse events. *J Thorac Cardiovasc Surg* 2008; 135: 739-45
28. DeCampli WM, Olsen MC, Munro HM, Felix DE: Perioperative hyperglycemia: effect on outcome after infant congenital heart surgery. *Ann Thorac Surg* 2010; 89: 181-5
29. de Ferranti S, Gauvreau K, Hickey PR, Jonas RA, Wypij D, du Plessis A, Bellinger DC, Kuban K, Newburger JW, Laussen PC: Intraoperative hyperglycemia during infant cardiac surgery is not associated with adverse neurodevelopmental outcomes at 1, 4, and 8 years. *Anesthesiology* 2004; 100: 1345-52

30. Ballweg JA, Wernovsky G, Ittenbach RF, Bernbaum J, Gerdes M, Gallagher PR, Dominguez TE, Zackai E, Clancy RR, Nicolson SC, Spray TL, Gaynor JW: Hyperglycemia after infant cardiac surgery does not adversely impact neurodevelopmental outcome. *Ann Thorac Surg* 2007; 84: 2052-8
31. Ballweg JA, Ittenbach RF, Bernbaum J, Gerdes M, Dominguez TE, Zackai EH, Clancy RR, Gaynor JW: Hyperglycaemia after Stage I palliation does not adversely affect neurodevelopmental outcome at 1 year of age in patients with single-ventricle physiology. *Eur J Cardiothorac Surg* 2009; 36: 688-93
32. Polito A, Thiagarajan RR, Laussen PC, Gauvreau K, Agus MS, Scheurer MA, Pigula FA, Costello JM: Association between intraoperative and early postoperative glucose levels and adverse outcomes after complex congenital heart surgery. *Circulation* 2008; 118: 2235-42
33. Jenkins KJ, Gauvreau K, Newburger JW, Spray TL, Moller JH, Iezzoni LI: Consensus-based method for risk adjustment for surgery for congenital heart disease. *J Thorac Cardiovasc Surg* 2002; 123: 110-8
34. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Cromphaut S, Schetz M, Van den Berghe G: Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009; 373: 547-56
35. Gu CH, Cui Q, Wang YY, Wang J, Dou YW, Zhao R, Liu Y, Wang J, Pei JM, Yi DH: Effects of insulin therapy on inflammatory mediators in infants undergoing cardiac surgery with cardiopulmonary bypass. *Cytokine* 2008; 44: 96-100
36. Koh TH, Aynsley-Green A, Tarbit M, Eyre JA: Neural dysfunction during hypoglycaemia. *Arch Dis Child* 1988; 63: 1353-8
37. Rozance PJ, Hay WW: Hypoglycemia in newborn infants: Features associated with adverse outcomes. *Biol Neonate* 2006; 90: 74-86
38. Cornblath M, Hawdon JM, Williams AF, Aynsley-Green A, Ward-Platt MP, Schwartz R, Kalhan SC: Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. *Pediatrics* 2000; 105: 1141-5
39. Polito A, Ricci Z, Di Chiara L, Giorni C, Iacoella C, Sanders SP, Picardo S: Cerebral blood flow during cardiopulmonary bypass in pediatric cardiac surgery: the role of transcranial Doppler--a systematic review of the literature. *Cardiovasc Ultrasound* 2006; 4: 47
40. Piper HG, Alexander JL, Shukla A, Pigula F, Costello JM, Laussen PC, Jaksic T, Agus MS: Real-time continuous glucose monitoring in pediatric patients during and after cardiac surgery. *Pediatrics* 2006; 118: 1176-84
41. Fahy BG, Sheehy AM, Coursin DB: Perioperative glucose control: what is enough? *Anesthesiology* 2009; 110: 204-6