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SYMPOSIUM

Critical Illness Hyperglycemia in Pediatric Cardiac Surgery

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Abstract

Critical illness hyperglycemia (CIH) is common in pediatric and adult intensive care units (ICUs). Children undergoing surgical repair or palliation of congenital cardiac defects are particularly at risk for CIH and its occurrence has been associated with increased morbidity and mortality in this population. Strict glycemic control through the use of intensive insulin therapy (IIT) has been shown to improve outcomes in some adult and pediatric studies, yet these findings have sparked controversy. The practice of strict glycemic control has been slow in extending to pediatric ICUs because of the documented increase in the incidence of hypoglycemia in patients treated with IIT. Protocol driven approaches with more liberal glycemic targets have been successfully validated in general and cardiac critical care pediatric patients with low rates of hypoglycemia. It is unknown whether a therapeutic benefit is obtained by keeping patients in this more liberal glycemic control target. Definitive randomized controlled trials of IIT utilizing these targets in critically ill children are ongoing.

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Introduction

Hyperglycemia is common in nondiabetic critically ill patients admitted to adult[1,2] and pediatric intensive care units (ICUs).[3-6] Until 2000, hyperglycemia often went untreated in ICUs around the globe, as it was thought to simply represent a transient alteration of carbohydrate metabolism in response to severe stress.[7] Since then, a strong association between the occurrence of hyperglycemia in critically ill patients and poor outcomes has been widely reported in children[3-5] and adults,[8-11] and the terms hyperglycemia of critical illness and critical illness hyperglycemia (CIH)[12] were born.

Ten years have passed since the 2001 seminal glycemic control trial by Van den Berghe and colleagues[11] caused excitement among the intensive care community worldwide. Following recommendations of various advisory groups and professional societies,[13-15] glycemic control became and continues to be the standard of care in adult ICUs.

Despite broad recognition that hyperglycemia is associated with adverse outcomes in critically ill children, pediatric intensivists have been reluctant to embrace glycemic control and very few centers report the use of a

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Abbreviations: (CIH) critical illness hyperglycemia, (CPB) cardiopulmonary bypass, (ICU) intensive care unit, (IIT) intensive insulin therapy, (NO) nitric oxide, (TGC) tight glycemic control

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consistent strategy to screen and manage CIH.[16] The fear of iatrogenic hypoglycemia and its potential effects on the immature pediatric brain has been identified as a major—if not the primary—barrier to instituting routine glycemic control in many pediatric ICUs.[16] Furthermore, there is a paucity of prospective randomized studies of glycemic control in the pediatric population and the evidence supporting strict glycemic control has been controversial even in adult patients.[17]

Patients undergoing surgery to palliate or repair congenital cardiac defects represent an important, and very unique, segment of those affected by CIH in the pediatric age group. Of the more than 4 million children born each year in the United States, nearly 40,000 have some form of congenital heart defect and approximately half of these will require some form of therapeutic intervention within the first year of life.[18] Children who undergo cardiac surgery enter the procedure relatively healthy and free from systemic infections or stressors, and the insult to the body is, by definition, iatrogenic. These children go through a well-documented regimen of anesthesia, surgical incisions, vascular, and cardiovascular modulation that can include crystalloid, colloid and blood products, vasoactive drug infusions, deep hypothermia and cardiac arrest, and cardiopulmonary bypass (CPB). Although there may be some similarities in the mechanisms and effects of CIH with pediatric counterparts suffering medical and traumatic insults, the specific study of children undergoing cardiac surgery is warranted and is a golden opportunity to understand CIH better and how it affects outcomes.

Hyperglycemia of Critical Illness in Cardiac Surgery

There are multiple explanations for the development of CIH and these were the basis for the belief that hyperglycemia was merely a marker of illness severity. During stress there is increased counterregulatory hormone and catecholamine secretion that lead to increased gluconeogenesis and glycogenolysis that result in elevation of serum glucose levels. From an evolutionary perspective, the counterregulatory response of an acute stressor would result in a surge in blood glucose levels to assure adequate substrate to maintain skeletal muscle and cerebral functions essential for survival during a literal "fight or flight" response. Under normal physiological circumstances, euglycemia would be achieved following resolution of this stressor (i.e., a successful battle or retreat) and via catabolism of this endogenous glucose "infusion" - perhaps with the assistance of pancreatic insulin secretion, which facilitates glucose entry into cells via insulin-sensitive glucose channels. The prolonged stress encountered in our ICUs is not part of normal ("evolutionary") physiology. In addition to acute stress, prolonged stressor and exogenous factors may exacerbate hepatic and peripheral insulin resistance and exacerbate the severity and length of hyperglycemia. Although the mechanisms leading to peripheral insulin resistance in this population are not yet completely defined, increased levels of counterregulatory hormones, inflammatory cytokines, and catecholamines (both endogenous and exogenously administered in the postoperative period) have been linked to the development of insulin resistance.[19,20] There is evidence to suggest that hyperglycemic pediatric patients with cardiovascular failure have beta cell dysfunction and suffer from absolute insulin deficiency.[21] It is still unclear whether hyperglycemia in children undergoing cardiac surgery is due to β-cell dysfunction, an increase in peripheral insulin resistance, or a combination of these factors.[22] In addition, it is unknown if subclinical co-morbid conditions (e.g., hepatic dysfunction) or iatrogenic factors (see next section) also play a role in the development of hyperglycemia in the ICU.

Intraoperative Hyperglycemia

The stress response seen as a result of surgery to palliate or repair congenital cardiac defects is frequently associated with hyperglycemia, particularly when CPB is employed.[23,24] Exposure to the CPB circuit and the resulting pro-inflammatory response, coupled with the fact that most of these patients are also exposed to high doses of corticosteroids during initiation of CPB, and often receive catecholamine-based vasoactive agents, create optimal conditions for the development of CIH.

Hyperglycemia is associated with poor outcome in adult patients with myocardial ischemia, yet the most direct evidence for its role in aggravating ischemia-reperfusion injury stems from extrapolations from experimental data.[25]

Postoperative Hyperglycemia

The occurrence of hyperglycemia after cardiac surgery has been well documented.[23,26,27] All three dimensions of hyperglycemia (intensity, duration and variability)[3,4,27,28] have been associated with poor outcomes in critically ill children in general, including the pediatric postoperative cardiac population. Yates and colleagues[27] found that both the intensity and duration of hyperglycemia were associated with increased morbidity and mortality

in infants undergoing cardiopulmonary bypass for surgical repair or palliation of congenital heart defects. We previously reported that the same was true for a broader pediatric population encompassing all pediatric ages and including patients who did not require cardiopulmonary bypass for their surgical approach.[23] These studies found increased rates of renal failure, liver dysfunction, adverse CNS events (hemorrhage, stroke, seizures), cardiovascular collapse requiring extracorporeal life support, and hospital-acquired infections in patients who were hyperglycemic in the postoperative period.[23,27] Mortality and morbidity were significantly correlated with the duration of postoperative hyperglycemia (**Figure 1**).

Although the etiology of hyperglycemia in children after heart surgery is likely not vastly different than that of hyperglycemia in critical illness in general, there is reason to believe these patients might be particularly sensitive to its pathogenic effects.

Studies have shown that hyperglycemia adversely modulates both endogenous and pharmacologically-induced cardioprotective signal transduction pathways,[29] increases myocardial infarction size, and adversely affects coronary microcirculatory regulation.[30] Hyperglycemia has also been shown to increase systemic vascular resistance, decrease stroke volume and impair cardiac output in rats,[31] and promote cardiomyocyte damage and apoptosis.[32,33] In addition, hyperglycemia has been shown to contribute to renal mesangial cell apoptosis[34] and possibly increase the risk of acute kidney injury and renal failure after cardiac surgery. Of particular concern to children undergoing cardiac surgery is the fact that hyperglycemia worsens cerebral injury by disrupting the blood brain barrier and augmenting ischemic injury.[35,36]

Cellular glucose overload leads to increased peroxynitrite production by increased superoxide production and overwhelms the enzymatic capacity to clear it. A cytokine-induced activation of inducible nitric oxide (NO) synthase provides additional NO. As a result, these two substrates lead to the formation of peroxynitrite, which has been shown to induce apoptosis in rodent cardiomyocytes,[37] thymocytes,[38] renal cells,[39] and neurons.[40] Furthermore, its production in the endothelium rapidly consumes NO and leads to endothelial dysfunction.[41]

Hyperglycemia has also been shown to increase the risk of infection.[42,43] The effect that hyperglycemia has on neutrophil chemotaxis, phagocytosis, and reactive oxygen species generation is controversial.[42] Hyperglycemia may hinder migration of neutrophils and macrophages to an infectious focus[44] and impair complement fixation by immunoglobulin-G and binding to the microbial surface for opsonization.[42]

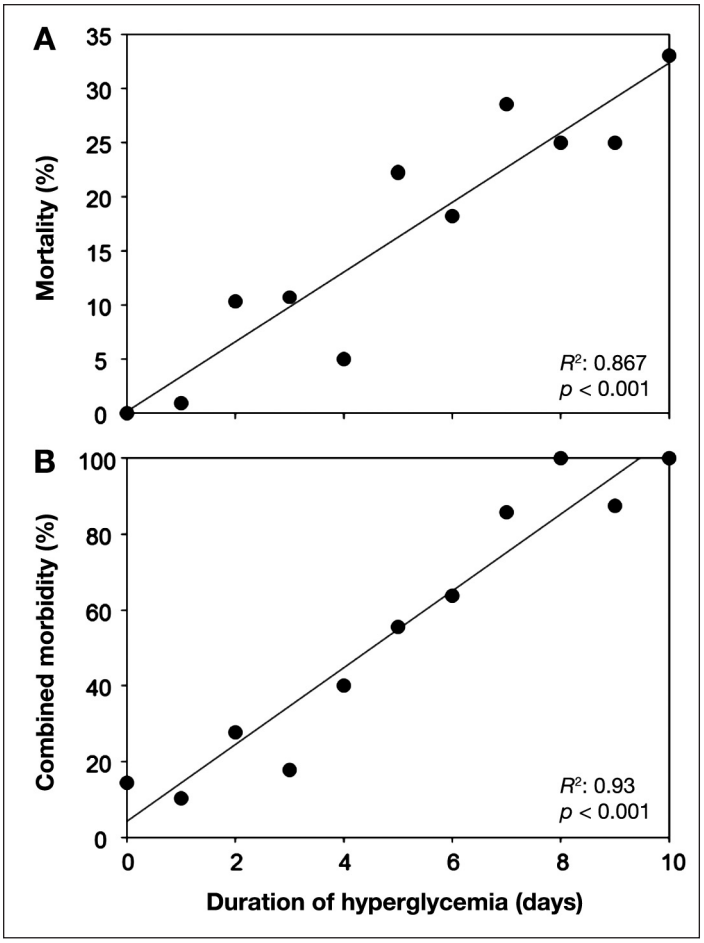

Figure 1. Linear regression between duration of hyperglycemia (>125 mg/dl) after cardiac surgery and mortality **(A)** or morbidity **(B)** showing a strong positive relationship. Modified from Reference 23.

As such, hyperglycemia has the potential to interfere not only with myocardial recovery and vascular integrity after surgery, but also may increase the likelihood of renal, infectious, and central nervous system complications.

Intensive and Conventional Insulin Therapy

Glycemic control through intensive insulin therapy (IIT) has sparked interest and controversy since the landmark trial by Van den Berghe and colleagues reporting a 42% drop in ICU mortality and a 34% drop in overall in-hospital mortality in critically ill adults admitted to a surgical ICU and treated with IIT.[11] Over 60% of participants in this study were status-post cardiac surgery. Many have adopted the vernacular of "intensive" insulin therapy in reference to this study where the

goal blood glucose in the IIT arm was 80 to 110 mg/dl, and outcomes were compared to those who received "conventional" insulin therapy (180 to 215 mg/dl).[11] Neither this nor other studies have compared some form of control (IIT or otherwise) to no control. Subsequent trials have not demonstrated such dramatic benefits from IIT over less strict control, but have repeatedly showed an increased incidence of hypoglycemia in patient groups in whom blood glucose is controlled most strictly.[45-47]

After the results of the initial glycemic control trials[2,11] there was a shift in standard of care practice in ICUs, which in large part was due to recommendations by medical oversight agencies, such as the Institute for Healthcare Improvement and the American Diabetes Association that altered the definition of conventional glucose management for each institution. This resulted in control groups with lower severities of hyperglycemia in subsequent randomized controlled trials of IIT.[17,48] Because the association of morbidity and mortality with hyperglycemia is stronger with higher severities of hyperglycemia,[3,23] studies that compare a euglycemic target with an intermediate target (140 to 180 mg/dl) may not be powered to detect the same absolute risk reduction in mortality observed in the initial Leuven trial by Van den Berghe and colleagues. This makes it challenging to interpret follow up studies that do not show a benefit from intensive insulin therapy.

Two meta-analyses examining the effects of IIT in critically ill adults have not found the practice to be beneficial in medical ICU's.[49,50] However, a meta-analysis that also included data from the Normoglycemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation study,[17] found a survival benefit in adult surgical patients treated with IIT.[50] Both studies found IIT to be associated with a higher incidence of hypoglycemia. More recently, a meta-analysis examining the effects of IIT during and after cardiac surgery in adults found that IIT reduced ICU mortality, ICU length of stay, duration of mechanical ventilation, need for epicardial pacemaker, and incidence of atrial arrhythmias.[51]

Only two randomized controlled trials have examined insulin therapy in critically ill infants or children.[25,52] In a multicenter trial by Beardsall and colleagues,[52] insulin therapy was found to confer minimal clinical benefit and to increase the risk of hypoglycemia significantly in very low birth weight infants. Yet the design of this trial, administering insulin prior to development of hyperglycemia, makes this study difficult to interpret or translate. The most substantive pediatric trial to date was conducted by Vlasselaers and colleagues[53] in Leuven and demonstrated morbidity and mortality benefits to critically ill children from strict glycemic control. However, based on this study, the number needed to treat in order to obtain the benefits of IIT is larger than the number needed to harm due to hypoglycemia.[54] In this study the target blood glucose in the ITT group was 50-79 mg/dl, for children <1 year old, and 70-101 mg/dl for those 1-16 years old.[53] Thus, the high rate of hypoglycemia (approximately 25% of those in the IIT group) was likely due to these controversial targets. These unacceptably high rates of hypoglycemia explain in part why the observed benefits of IIT have not been translated into standard practice by pediatric intensivists. As with the adult surgical study from Leuven, the majority of patients (75%) enrolled in the pediatric trial were those status post cardiac surgery, and thus the finding may have particular relevance to this subpopulation.[53] Because there was no subgroup analysis, it has yet to be determined whether IIT would exert a more beneficial effect on the pediatric postoperative cardiac population and whether results of the Vlasselaers trial[53] were in some way diluted by the inclusion of medical patients and patients with diabetes mellitus. There is a planned neurodevelopmental follow up of this study that may help us understand real versus perceived risks of IIT and hypoglycemia in children.

Intraoperative and Postoperative Intensive Insulin Therapy

In animal models, insulin administration at the time of reperfusion attenuates myocardial injury, at least in part, by reducing cardiomyocyte apoptosis.[55] This protection is mediated by phosphatidylinositol-3-kinase, endothelial nitric oxide synthase, and a resulting local increase in NO production.[25,56] In humans, a solution of glucose, insulin, and potassium administered during ischemia-reperfusion can protect the ischemic myocardium during cardiac surgery.[57] Interestingly, the cardio-protective effect of insulin during ischemia-reperfusion is blunted by hyperglycemia.[58] This is evidence of a direct pathogenic role of prolonged exposure to nonphysiological glucose levels, and the ability of insulin to have a therapeutic effect.

A study[25] involving neonates undergoing repair of d-transposition of the great arteries or truncus arteriosus prospectively randomized patients to receive conventional insulin therapy (n = 7) or tight glycemic control (TGC) (n = 7). The target level in the TGC group was 50 to 80 mg/dl. Insulin therapy was initiated at the start of the operation

and continued throughout the entire procedure. Insulin infusion was administered until discharge from the pediatric ICU or until two-thirds of the caloric intake was administered as bolus feedings. Despite its small sample size, this study demonstrated that intraoperative (and postoperative) TGC attenuated the inflammatory response related to the surgical procedure and protected the myocardium.[25] Specifically, patients treated with TGC had significantly lower blood lactate, cardiac troponin I, heart fatty acid binding protein, C-reactive protein, interleukin-6, and interleukin-8 compared with the conventionally treated subjects.[25] These data strongly suggest that TGC in the intraoperative period protected myocytes from ischemia-reperfusion and preserved function. The longer-term effects of this strategy, such as cardiac, neurodevelopmental, and cognitive cannot be inferred from this small-sized short-term trial, although follow up assessments are ongoing.

A study examining the effect of intraoperative glycemic control on long-term neurological outcomes of 171 patients with d-transposition of the great vessels undergoing surgical repair, demonstrated that intraoperative hyperglycemia was not associated with adverse neurodevelopmental outcomes at 1, 4 and 8 years after surgery.[59] On the converse, patients who developed intraoperative hypoglycemia tended to exhibit electroencephalographic seizure activity and had slower electroencephalogram recovery compared to their euglycemic and hyperglycemic counterparts.[59]

The safety and effectiveness of IIT in the pediatric cardiac surgical population require further study. The ideal glycemic target for these patients is still controversial. It is very likely, however, that the same glycemic control targets used for critically ill adult patients might not be appropriate for the entire pediatric age spectrum. One must take into consideration that TGC trials have been set to maintain patients at normal fasting glucose levels, or as in the most recent pediatric trial, at age-adjusted fasting normoglycemic ranges.[53] However, most patients in the critical care setting are not truly fasting and receive some form of nutrition through intravenous or enteral routes. Therefore, a fasting glucose level may not be the ideal target for these patients, especially when one considers the increased incidence of hypoglycemia seen in the IIT groups of the existing pediatric trials of glycemic control. Hypoglycemia has been associated with increased morbidity and mortality in critically ill children[5] and most intensivists believe that hypoglycemia is more dangerous than hyperglycemia itself.[16,60] However, hypoglycemia naturally occurs in the pediatric ICU with or without insulin therapy and is more prevalent in patients requiring mechanical ventilation and vasoactive infusions[5] or after cardiac surgery with CPB.[61] Observational studies suggest that glycemic ranges not strictly in the euglycemic range may accrue a survival benefit[62] and be associated with a lower incidence of hypoglycemia.[61] In addition to these more permissive glycemic targets, the use of continuous glucose monitors[63] might facilitate safer drug titration during IIT while alleviating some of the fear related to the development of iatrogenic hypoglycemia.

A protocol-driven approach to identify and manage hyperglycemia in critically ill patients has been successfully and safely implemented in the pediatric setting and in pediatric postoperative cardiothoracic surgery patients, where subjects were safely maintained at a glycemic target of 80 to 140 mg/dl.[12,24] The incidence of hypoglycemia in these studies was absent to very low (<5%)[24] when contrasted with the high incidence of hypoglycemia seen in the Vlasselaers trial[53] in which approximately 25% of their patients developed hypoglycemia. However, since this protocol was applied to all patients in those units,[12,24] it is unknown whether any benefit could result from maintaining patients within the desired glycemic range. No pediatric randomized controlled trials have been performed to date examining the potential benefit from a more permissive glycemic target.

Ongoing Clinical Trials of IIT in Children

A randomized controlled trial entitled Safe Pediatric Euglycemia in Cardiac Surgery[64] is underway to evaluate the effect of IIT to maintain blood glucose in children up to 3 years old within the euglycemic range after pediatric cardiac surgery requiring CPB while patients undergo continuous glucose monitoring.

The Control of Hyperglycemia in Pediatric Intensive Care trial,[65] also underway, will study the effect of TGC in a broader critically ill pediatric population and will compare the differences in the effect of IIT among cardiac and noncardiac populations.

Lastly, the Pediatric ICUs at Emory-Children's Center Glycemic Control[66] is a prospective, randomized controlled trial to evaluate the outcome benefit, safety, and resource utilization impact of maintaining strict glucose control in children with life-threatening conditions in the pediatric ICU, with a significant enrollment of children following cardiac surgery. The primary goal of this study is to determine whether normalizing hyperglycemia is a safe

approach to improving multisystem organ function in critically ill children requiring intensive care. This phase III trial will include critically ill patients from 1 month to 21 years randomized to receive strict (80 to 140 mg/dl) or conservative (190 to 220 mg/dl) glycemic control.

The pediatric critical care community eagerly anticipates the results of these studies as they will help provide age-specific guidance regarding glycemic control strategies and their potential benefits in the pediatric population. Regardless of whether the current studies show outcome benefit, findings that regular glycemic control can be safely obtained in this population will be critical, and because of the unique aspects and properties of children undergoing cardiac surgery, this group deserves further special investigation.

While attempting to maintain equipoise and considering the experimental data available on the subject to date, it is our belief that some form of glycemic control should be practiced in children following cardiac surgery. It is our opinion that this would best be accomplished by developing a strictly protocolized approach to manage glycemic control, so that variability caused by individual preferences are significantly reduced. Such approach should include a validated insulin administration protocol that is tailored to the target population, appropriate staffing resources, use of accurate monitoring technologies, the ability to react rapidly to blood glucose measurements below the target range, and a robust data platform to monitor protocol performance and clinical outcome measures.

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