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Endocrinologic Diseases in Pediatric Cardiac Intensive Care

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Abstract

Objectives—The objectives of this review are to discuss the pathophysiology, clinical impact and treatment of hyperglycemia and disturbances in thyroid and adrenal function prior to and following cardiac surgery in children.

Data Source—MEDLINE, PubMed

Conclusions—Disturbances in glucose metabolism and thyroid and adrenal function are common in critically ill children with cardiac disease and in particular in children undergoing cardiac surgery for complex congenital heart disease. An understanding of the pathophysiology, clinical impact and treatment of these disturbances is essential for the management of these at risk patients.

Keywords

hyperglycemia; hypoglycemia; tight glycemic control; adrenal insufficiency; thyroid disease; congenital heart disease

Critical Illness Hyperglycemia

Critical illness hyperglycemia refers to transient hyperglycemia during severe physiologic stress, traditionally restricted to patients without previous evidence of diabetes. Hyperglycemia is the result of activation of the hypothalamic-pituitary-adrenal (HPA) axis, sympatho-adrenal system and pro-inflammatory cytokines, in response to a physiologically stressful stimuli. Stress hormones such as cortisol, epinephrine, and norepinephrine are released in high proportions, resulting in metabolic, cardiovascular and immune effects. In particular, there is excessive gluconeogenesis, glycogenolysis and insulin resistance (1, 2). These neurohormonal responses result in increased hepatic output of glucose and inhibition of glucose uptake by peripheral tissues. Inflammatory mediators such as tumor necrosis factor- α (TNF- α), interleukin-1 (IL-1), interleukin-6 (IL-6) and C-reactive protein also increase peripheral insulin resistance (2).

The incidence of critical illness hyperglycemia (blood glucose level >126 mg/dL [7.0 mmol/L]) after cardiac surgery in infants and young children has been reported in some series to be as high as 90% in the immediate postoperative period (3, 4). However, the incidence of hyperglycemia has steadily decreased over time. In one series roughly 50% of glucose measurements at 72 hours remained elevated (4), while in a recent clinical trial children assigned to receive standard care generally maintained a blood glucose level in the range of 106–171, despite the fact that only 2% of them received insulin (5).

Hyperglycemia Associated with Adverse Outcomes

Peri-operative hyperglycemia has been associated with worse outcomes following congenital heart surgery. In a large, retrospective cohort study in children undergoing complex cardiac operations, Polito and colleagues found risk-adjusted associations between average and peak early postoperative glucose levels and a composite morbidity-mortality outcome, as well as an association between duration of hyperglycemia in the first 72 post-operative hours and overall hospital length of stay (6). Of interest, in a study by Yung and colleagues patients with an average early postoperative glucose level less than 109 mg/dL had a 7-fold greater adjusted odds of reaching the morbidity-mortality end point, suggesting a U-shaped relationship between postoperative glucose levels and important clinical outcomes (7). Other studies have found associations between postoperative hyperglycemia and higher mortality (8), as well as significant morbidities such as lactic acidosis, cardiac arrest, vasopressor use, ventilation time, and longer intensive care unit and hospital stays (4, 7). Of note, hyperglycemia has not been shown to worsen neurodevelopmental outcomes (3).

The extent to which hyperglycemia is a marker as opposed to a cause of adverse outcomes remains unclear. Studies that do show an association between hyperglycemia and adverse outcomes suggest that the incremental contribution of hyperglycemia to these adverse outcomes is likely to be mitigated by other factors such as age. For example, Moga and colleagues found that there was no incremental risk attributable to hyperglycemia in neonates until 54 hours of sustained hyperglycemia for glucose levels <180 mg/dl (10mmol/l), although the increase in risk occurred after 12–18 hours of exposure to high glucose levels for those patients with more severe hyperglycemia (4).

Tight Glycemic Control (TGC)

Despite the high prevalence of critical illness hyperglycemia in children undergoing cardiac surgery, and its association with adverse outcomes, the perioperative benefits of TGC achieved in adult cardiac patients have not been replicated in the pediatric cardiac population. Four large randomized controlled trials of TGC in critically ill children have been conducted to date, three of which included children following cardiac surgery (5, 9–11). Vlasselaers conducted a single-center randomized controlled trial of TGC in a pediatric intensive care unit (11). Seventy-five percent of the enrolled patients were recovering from cardiac surgery. The study concluded that TGC was of benefit in the study population, with evidence of reduced inflammation, shorten length of stay, and fewer deaths in the TGC arm; although it is important to note that the study was not sufficiently powered to determine differences in mortality between the trial arms and thus this difference could have occurred by chance.

The Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) Trial was the only randomized controlled trial specifically designed to include only patients that underwent cardiac surgery with cardiopulmonary bypass (CPB) up to 3 years of age (5). The primary outcome was the postoperative health-care associated infection rate. Compared to usual care, patients assigned to receive TGC did not experience a significant difference in the rate of health care–associated infections, or important differences in a number of secondary outcomes including mortality or the length of stay in the cardiac intensive care unit (5). In the Control of Hyperglycaemia in Paediatric Intensive Care (CHiP) trial, critically ill children were randomized to TGC (a level of 72–126 mg/dL) or conventional glycemic control (a level below 216 mg/dL) (10). Sixty percent of the children in the trial had been admitted to the intensive care unit after cardiac surgery. Overall the investigators found that TGC failed to reduce mortality.

Risk of Hypoglycemia and Adverse Outcomes

Hypoglycemia is likely to represent as much risk to the cardiac surgery patient as hyperglycemia. The overall rate of severe hypoglycemia in the CHiP study was 7.3% in the TGC group and 1.5% in the conventional treatment group. In the patients that received insulin, the risk of severe hypoglycemia was similar between patients in the cardiac and non-cardiac surgery subgroups (16.4% and 20.3%, respectively). However, in the subgroup of patients who had undergone cardiac surgery, a significantly higher rate of mortality was reported in the patients who had at least one hypoglycemic episode when compared to those who did not (10). In adults, hypoglycemia has also been associated with increased mortality in the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial (12).

Another major concern is the potential association of hypoglycemia with worse neurodevelopmental outcomes. In the pediatric patients enrolled in the Leuven trial conducted by Vlasselaers and colleagues, 25% developed severe hypoglycemia, yet it did not appear to be associated with worse neurodevelopmental outcome 4 years after critical illness (13). Follow up of subjects from the SPECS trial is underway to explore the impact of

hypoglycemia on neurodevelopmental outcomes. In summary, with the exception of one single-center trial, the evidence suggests that TGC is not beneficial following pediatric cardiac surgery.

Thyroid Hormone Replacement Therapy

The thyroid hormones thyroxine (T4) and tri-iodothyronine (T3) are synthesized and secreted by the thyroid gland by iodination of tyrosine residues into thyroglobulin. Production is stimulated by thyroid stimulating hormone (TSH) secreted from the anterior pituitary, which in turn is secreted in response to hypothalamic thyrotropin releasing hormone (TRH). T4 can be considered as the pro-hormone of T3 and is converted to an active T3 by de-iodination. About 80% of circulating T3 is produced by this conversion in the liver and other tissues; the remaining 20% is secreted directly by the thyroid. T3 and T4 are carried in the circulation bound to thyroxine-binding globulin (TBG), transthyretin, and albumin, and exert a negative feedback on the release of TSH and TRH. T3 and T4 bind to thyroid receptor proteins in the cell nucleus (14). As a nuclear transcription factor, T3 also contributes to the up- and down-regulation of genes (15). Target organ responses to thyroid hormones include basal metabolic rate and oxygen consumption, influences on calcium, phosphorus, carbohydrate, protein and lipid metabolism. The end-organ effects depend both on circulating levels of active T3 and also on the level of thyroid receptor occupancy (16). The heart and vasculature are major target organs for thyroid hormone action (17), and marked changes in cardiovascular function occur when thyroid hormone levels are either low or high. Hyperthyroidism leads to increased inotropy, chronotropy and blood volume, and to decreases in systemic vascular resistance, with the net effect being an increase in cardiac output. Hypothyroidism has the opposite effects on cardiovascular function.

Congenital Hypothyroidism

Untreated congenital hypothyroidism can result in growth retardation, deafness, impaired neurogenesis, and congenital heart malformations. Children with congenital hypothyroidism may have an increased incidence of congenital heart disease. A registry study in Italy identified that of 1,372 infants with congenital hypothyroidism, 5.5% had cardiac anomalies. Among the 23 newborns with 2 or more congenital malformations, 17 had cardiac anomalies (74%), but all presented different patterns. The most frequent cardiac malformation was an atrial septal defect (18). Other groups have reported the incidence of CHD in infants with congenital hypothyroidism to be 8% (19), or up to 10-fold higher than the general population (20). Neonates found to have a high TSH should be examined carefully for congenital malformations (particularly cardiac) and for dysmorphic features and confirmatory venous thyroid function tests should be obtained.

Iodine-induced Hypothyroidism

An important consideration when evaluating infants with abnormal thyroid function in the cardiac intensive care unit is to assess exposure to 'environmental' iodine leading to hypothyroidism by the Wolff-Chiakoff effect (21, 22). A recent report noted that three full-term neonates following surgery for congenital heart disease developed hypothyroidism

following exposure to iodinated contrast during cardiac angiography and topical iodine-containing dressings and antiseptics. Of these, one developed severe primary hypothyroidism requiring treatment, the second resolved after transient treatment, and the third resolved spontaneously (23). Other studies have shown that the use of povidone-iodine irrigation in association with delayed sternal closure did not lead to any significant alteration in thyroid function (24–26). Further studies are needed to assess the need for monitoring thyroid function after cardiac angiography or prolonged exposure to iodine-containing antiseptics.

Non-thyroidal Illness

Non-thyroidal illness (NTI) or sick euthyroid syndrome refers to the range of thyroid abnormalities commonly seen during critical illness. Frequently a decrease in T3 levels is seen in the context of an inappropriately normal TSH. After CPB, children often exhibit an initial surge of free thyroid hormones followed by the characteristic findings of NTI: a low T3 with an inappropriately normal or suppressed TSH (27, 28). Depending on the severity of illness, infants and children may also develop a decreased T4, with both T3 and T4 reaching their nadir in the first 24–48 hours (29–32). Recovery is generally expected within 1–2 weeks, preceded by a rise in TSH, however the sickest patients often have more prolonged depression of the thyroid axis and delayed recovery (29, 33). NTI after cardiac surgery has been associated with greater severity of illness, longer hospital and intensive care unit length of stay, prolonged mechanical ventilation, and higher inotrope scores (28, 34). Nutrient restriction during this process can further aggravate thyroid axis suppression (35).

Marks et al followed prospectively 21 patients, aged 1–11 years after cardiac bypass surgery (34). All of the patients in the cohort developed thyroid function abnormalities consistent with NTI. In this cohort, the decrease in TSH appeared to occur at the same time as the changes in the other hormones instead of preceding them as has been demonstrated in other studies. No relationship was found between CPB and aortic clamp times and the degree of NTI, however hormone levels on the night of the surgery were predictive of clinical outcome.

T3 Supplementation

Thyroid hormone supplementation has been studied during and after cardiac surgery. Portman et al conducted a prospective randomized trial of infants less than 1 year of age undergoing repair of a ventricular septal defect or tetralogy of Fallot (36). Patients were randomized to either T3 (0.4 mcg/kg) or placebo immediately before the start of CPB and again with myocardial reperfusion. Thyroid hormones declined in the control group through the first 72 hours. Both free and total T3 levels were substantially higher in the treated group over the first 24 hours, but were similar to control values by 72 hours. The heart rate was transiently elevated in the treatment group compared with the controls, and peak systolic pressure-rate product increased after 6 hours as well, which may imply an improvement in myocardial oxygen consumption and cardiac functional reserve.

Bettendorf et al conducted a double-blind, randomized, placebo-controlled study in which 40 children were given a daily infusion of T3 or placebo up to 12 days after cardiac surgery (37). These investigators demonstrated that the children in the treatment group had higher T3 plasma levels after infusion that remained higher during the observation period. The children treated with T3 had lower therapeutic intervention scores (less and shorter requirements for intensive-care measures), increased systolic ventricular function and cardiac output. There was no delay in recovery of thyroid function compared with children in the placebo group, and no adverse effects noted with respect to cardiac rhythm or heart rate. Based on these results, the authors recommend T3 supplementation in children with low cardiac output or complicated CPB operations (37).

Chowdhury et al produced similar results to those of Bettendorf and colleagues (38). Chowdhury et al studied 28 patients who were receiving mechanical ventilation and had a serum total T3 level of less than 40 ng/dL (or <60 ng/dL for newborns) on postoperative days 0, 1, or 2. Fourteen patients were randomized to receive a continuous T3 infusion at 0.05 to 0.15 mcg/kg/hr to maintain serum levels within the range of 80–200 ng/dL. The Therapeutic Interventional Scoring System (TISS) score, which indicates postoperative management requirements, was significantly lower for the treatment group by days 1, 2 and 3, T3 treatment resulted in significantly lower inotropic requirement. Also, of eight newborns tested, mixed venous oxygen saturations were 17% higher in the T3-treated group after 18 to 24 hours but only 2% higher in the untreated group. However, the sample size was inadequate to appropriately test the impact of T3 therapy on this outcome. The length of hospital stay and duration of mechanical ventilation were not significantly different between the two groups. There were no adverse effects on blood pressure, heart rate, or cardiac rhythm in those treated with T3.

More recently the TRICC study, a prospective, multicenter, double-blind, randomized, placebo-controlled trial in children younger than 2 years of age undergoing heart surgery with CPB, evaluated the effect of T3 versus placebo on time to extubation (TTE) as the primary outcome (39). T3 boluses (or placebo) were administered intravenously over the course of 10 minutes immediately before CPB, on release of the aortic cross-clamp, and then at 3, 6 and 9 hours after cross-clamp release. For patients younger than 5 months, TTE was 98 hours (95% confidence interval (CI) 71–142) for patients receiving placebo, compared with 55 hours (CI 44–92) in the T3 treated group. For children over 5 months of age, T3 resulted in a significant delay in median TTE. Adverse event rates, including arrhythmia did not differ between groups. There were no significant differences in heart rate or mean arterial blood pressure during the first 24 hours. There was no difference in the inotropic score in patients treated with T3 versus placebo. Although these studies suggest there may be benefit to normalizing T3 levels acutely in newborns after cardiac surgery, additional adequately powered studies are needed before a uniform recommendation can be made.

Adrenal Insufficiency

The adrenal glands are responsible for producing corticosteroids, mineralocorticoids and androgens. Acute adrenal insufficiency is a life-threatening event that usually manifests when the adrenal cortex fails to produce adequate glucocorticoid and mineralocorticoid in

response to metabolic stress such as surgery, sepsis, or critical illness. Adrenal insufficiency may be characterized as primary or secondary. Primary adrenal insufficiency occurs when the adrenal glands fail to produce both glucocorticoids and mineralocorticoids due to an intrinsic defect in the gland. Secondary adrenal insufficiency can occur when there is failure of adrenocorticotrophic hormone (ACTH) release or action, which is the major stimulus for cortisol release. Exogenous administration of glucocorticoids, particularly in patients treated with high doses of corticosteroids for extended periods of time is a common cause of suppression of the pituitary–adrenal axis, an effect that often last well beyond cessation of therapy. Because mineralocorticoids (i.e., aldosterone) are mainly released in response to the renin-angiotensin system, not ACTH, mineralocorticoids are not affected in secondary causes of adrenal insufficiency. Thus, severe hyponatremia and hyperkalemia resulting from aldosterone deficiency are unlikely to be seen in patients with secondary adrenal insufficiency.

Adrenal insufficiency in critically ill cardiac patients should be suspected when there is hypotension unresponsive to vasopressors or inotropes. Cortisol is essential for vascular responsiveness to catecholamines. Cortisol also stimulates gluconeogenesis, therefore cortisol deficiency can also manifest as hypoglycemia during stress or fasting. Findings on physical examination are more likely to be characteristic of the precipitating illness rather than specifically suggestive of adrenal insufficiency.

Critical Illness-related Corticosteroid Insufficiency

The phrase critical illness-related corticosteroid insufficiency (CIRCI), also known as “relative adrenal insufficiency,” has been used to characterize patients who mount an inadequate corticosteroid response in relation to the severity of illness. It is thought to occur as a result of a decrease in adrenal steroid production due to dysfunction at any point in the hypothalamus pituitary adrenal (HPA) axis or due to tissue resistance to glucocorticoids (40).

The incidence of CIRCI is uncertain, principally because the diagnostic criteria are unclear. Some experts advocate for diagnosis of CIRCI only after a failed ACTH-stimulation test, while others argue that CIRCI exists when a normal or high random cortisol level fails to have an appropriate incremental response to a cosyntropin bolus. The response is calculated by determining the difference between the baseline cortisol concentration and the highest concentration measured at 30 or 60 minutes. Many threshold concentrations have been proposed to define what is an “appropriate” response (40, 41). Recent studies have shown that high cortisol levels during critical illness are a consequence of decreased metabolism and clearance of cortisol rather than increased production (42, 43). These findings would argue against empirical corticosteroid treatment for patients who do not fail a cosyntropin stimulation test and who are thought to have normal endogenous production of cortisol.

Steroids for Abnormal Adrenal Function After Cardiac Surgery

Evidence regarding adrenal function and adrenal response to cardiac surgery has been contradictory. Most studies to date have been retrospective and therefore there is wide

variability in terms of definitions and treatment regimens evaluated. In a study by Schiller et al, 119 children undergoing cardiac surgery were characterized by the complexity of their surgery and their cortisol levels (44). Adrenal insufficiency was defined as a postoperative cortisol level of less than 18.1 mcg/dL or a delta cortisol (postoperative cortisol - preoperative cortisol) of less than 9 mcg/dL, similar to commonly used definitions of CIRCI used in adults. These investigators found that 60.5% of the patients met their criteria for adrenal insufficiency. Interestingly, children with low postoperative cortisol levels did not have a more complex postsurgical course in terms of inotropic support, lactate level, or urinary output regardless of the complexity of the surgery. Neither did they require longer mechanical ventilation, more sedation, nor have a longer intensive care unit length of stay than children with “normal” adrenal function. Similarly, Wald and colleagues studied 51 patients who underwent CPB with a median age of 1.6 years (IQR 0.4–6.5) (45). Despite low total cortisol levels post-surgery (median 4.5 mcg/dL; IQR 3.3–7.5), all patients had a normal response to cosyntropin stimulation demonstrating that the capacity to generate cortisol de novo was intact. There was no association between postoperative total cortisol values (baseline or stimulated) and length of stay, duration of mechanical ventilation, inotrope score or first 24-hour fluid requirements. Of note, patients were treated with pre-operative dexamethasone, which may have accounted for suppression of endogenous cortisol production in the immediate postoperative period but allowed for a normal response to a high dose cosyntropin stimulation test. Interestingly, a greater free cortisol response following cosyntropin stimulation and lower corticosteroid binding globulin (CBG) levels postoperatively were associated with worse clinical outcomes (longer length of stay and higher inotrope score). Higher stimulated free cortisol was also associated with increased fluid requirements in the first 24-hours postoperatively. This was the first pediatric study to show an association between CBG and free cortisol levels and worse clinical outcomes.

Adding to the controversy, a recent prospective study evaluated the adrenal response to cardiac surgery by performing ACTH stimulation testing preoperatively (46). The investigators studied 58 neonates and young infants, of whom 31 underwent CPB, 22 CPB with deep hypothermic circulatory arrest, and 5 controls. The investigators found that all tested patients had normal responses to cortrosyn testing confirming normal adrenal function preoperatively. They noted that cortisol peaked within 2 hours of surgery without differences among groups and most patients exhibited synergy between the pituitary and adrenal stress response with ACTH and cortisol levels tracking as expected. However, 15% of their patients did have low cortisol levels despite normal or high ACTH levels and those were the sicker patients with higher inotropic scores, longer durations of mechanical ventilation and length of stay in the intensive care unit, raising concerns for true adrenal insufficiency.

Interventional randomized trials addressing this issue are scarce. Ando et al randomized 20 neonates undergoing cardiac surgery to receive postoperative hydrocortisone for 2 days or placebo after receiving intra-operative methylprednisolone (47). They found that patients in the placebo group met their definition of adrenal insufficiency, cortisol <5 mcg/dl (2.8 ± 3.3 mcg/dL at 24 hours, 2.8 ± 3.9 mcg/dL at 48 hours, and 4.6 ± 4.3 mcg/dL at 72 hours), though it gradually increased to a low-normal level by day 7. Those patients in the placebo group had worse cardiac function, needed more inotropic support, and had higher lactate

levels, while those treated with hydrocortisone had normal cortisol levels, were less edematous, and had a shorter duration of mechanical ventilation.

A study by Roberts and colleagues evaluated 40 neonates undergoing cardiac surgery and CPB by randomizing patients to either a continuous hydrocortisone infusion (50 mg/m²/day) tapered over 5 days or placebo (48). All patients received methylprednisolone pre-operatively. The newborns treated with post-operative hydrocortisone infusion were less likely to develop low cardiac output syndrome (LCOS) (26% vs 57% placebo; $p=0.049$), had more negative net fluid balance at 48 hours, greater urine output at 0–24 hours and were weaned off catecholamines and vasopressin sooner than those in the placebo group. Ventilator-free days and intensive care unit and hospital length of stay were not significantly different between groups. Although 32.5% of subjects were categorized as having adrenal insufficiency post-surgery (defined as an increase in the cortisol level of <9 mcg/dL 30-minutes after a 1 mcg dose of cosyntropin), the incidence of LCOS in these patients was not significantly different from those with normal adrenal function. Nonetheless, the subjects who met the definition of adrenal insufficiency and were randomized to hydrocortisone treatment were less likely to develop LCOS than those who received placebo. Unfortunately larger trials are needed to assess the effect of steroid supplementation particularly in children who have established CIRCI following cardiac surgery.

Conclusions

Disturbances in glucose metabolism and thyroid and adrenal function are common in critically ill children with cardiac disease and in particular in children undergoing cardiac surgery for complex congenital heart disease. An understanding of the pathophysiology, clinical impact and treatment of these disturbances is essential for the management of these at risk patients.

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