GLUCOSE CONTROL IN CRITICALLY ILL CHILDREN
Search for Optimal Strategies

Jennifer Verhoeven

Cover

The outstretched branches of the sugar maple trees
Basking in the autumn sun
The breeze embracing the trees in a dance
I never thought of trees as having fun

(modified from The Sugar Maple Tree by Diann Sheldon)

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GLUCOSE CONTROL IN CRITICALLY ILL CHILDREN
Search for Optimal Strategies

Glucose controle bij ernstig zieke kinderen
zoektocht naar optimale strategieën

Proefschrift

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Do not be afraid to go out on a limb…
That's where the fruit is.

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Chapter 1
Introduction

…Severe acute malnutrition affects 20 million children under 5 years of age each year and contributes to 1 million deaths per year…

INTRODUCTION

Approximately 5000 children, aged 0 to 18 years, with a variety of medical and surgical conditions are admitted to the 8 Dutch Pediatric Intensive Care Units (PICU's) each year. A distinct subgroup of these children has critical illness, defined as any condition in which a patient requires mechanical aid or pharmacological agents to support failing vital organ functions. A variety of metabolic disturbances characterize the condition of critical illness, including hyperglycemia, dyslipidemia and increased protein turnover. This hypercatabolic state is characterized by excessive breakdown of proteins to mobilize amino acids for tissue healing and synthesis of acute phase proteins and glucose in the liver. It may lead to profound breakdown of lean body mass and consequently put children at risk for protein-energy malnutrition.[1] Malnourished children have a higher risk of complications, such as hospital acquired infections due to poor immune defense, poor wound healing, decreased muscle function (heart, skeletal and respiratory muscle), impaired gut function and longer dependency on mechanical ventilation. All this results in longer length of hospital stay and increased mortality.[2] Poor nutritional status has also been associated with adverse consequences on growth and development in children after discharge. Furthermore, the occurrence of "stress hyperglycemia" has been identified as an independent risk factor for adverse outcome in critically ill children with various diagnoses.[3]

The landmark study of the Leuven group in 2001[4] reported reduced mortality in adult surgical intensive care patients treated with strict insulin therapy aimed at normalizing blood glucose levels. The efficacy of glycemic control[5] has been much debated since then and concerns were raised about extrapolating this therapy to children. Only one randomized controlled trial of glycemic control in pediatric intensive care patients has been published so far, again by the Leuven group.[6] The authors reported shorter duration of PICU stay and mortality with the use of strict glycemic control. This study was criticized,[7] however, notably for the 25% incidence of hypoglycemic events in the intervention group. Hypoglycemia is a serious complication of insulin therapy. It is thought that neonates and young children do have an increased risk for developing hypoglycemia and are very vulnerable to complications caused by hypoglycemia, as their brains are still developing.[3]

Despite increased awareness for adequate nutritional support during critical illness, even today, malnutrition in PICU patients commonly occurs. Twenty percent of children admitted to a PICU are acutely or chronically malnourished at the time of admission, and their nutritional status deteriorates during hospitalization.[8] Adequate feeding is essential for complete recovery and normal functioning of the growing child. Clinicians working in the pediatric intensive care unit are challenged to provide adequate nutrition for optimal tissue synthesis and immune function while avoiding complications of under- or overfeeding. Therefore, nutritional therapy should aim to:[9] 1) provide adequate amounts of energy, especially when energy stores are depleted; 2) manipulate insulin secretion via glucose; and 3) conserve or restore the body protein mass.

The focus of this thesis is on energy requirements in critically ill children in the acute phase of disease in relation with the hyperglycemic response to stress. Furthermore we elaborate on the causes and consequences of hyperglycemia.

ENERGY REQUIREMENTS

Energy expenditure

Predicting resting energy expenditure

Generally used equations to estimate resting energy expenditure (REE) are based on characteristics, such as weight, height and sex.[10] However, these equations have been shown to be inaccurate in critical illness and may underestimate or overestimate the true energy requirements in the individual.[8] Nutritional intake based on estimated requirements often result in inadequate prescriptions. The cumulative effect of inaccurate estimations and suboptimal delivery of nutrition may result in significant caloric imbalances over time.

Measuring energy expenditure

Measuring energy expenditure allows for a more accurate monitoring of the child's varying needs in the course of critical illness. Two basic approaches have been developed; direct and indirect calorimetry. Direct calorimetry measures heat liberated from the body.[11] It can be performed in specialized insulated chambers but is not applicable in a clinical setting.

The doubly labeled water method is the golden standard method of indirectly estimating total daily energy expenditure (TDEE), which includes energy expended in physical activity.[12] It is suitable for free-living subjects and measures TDEE over a period of days, but it is costly and requires specialized laboratory equipment. As the results are not readily available, its use in clinical practice is of limited value and restricted to the research setting.[13]

Indirect calorimetry, using a metabolic monitor, can be performed at the bedside to measure the volume of oxygen consumed (VO_2) and the volume of carbon dioxide produced (VCO_2). The principle to calculate energy expenditure from gas exchange is calculated according to the modified Weir formula[14] : Energy Expenditure (kJ/day) = 4184 (5.5 VO_2 + 1.76 VCO_2); VO_2 and VCO_2 in l/min. The second parameter obtained from indirect calorimetry, the respiratory quotient (RQ), defined by the VCO_2 to VO_2 ratio, is partially determined by the substrate use in the child (carbohydrate: 1.00, protein: 0.83, and fat: 0.70). Underfeeding, which promotes use of endogenous fat stores, lowers the RQ, whereas overfeeding, which results in lipogenesis, raises the RQ.

Although indirect calorimetry is a well-validated and accurate method for measuring energy expenditure in critically ill, mechanically ventilated children[15], it is not infallible. It is less accurate if there is no steady hemodynamic, respiratory and/or metabolic state to ensure

that respiratory gas exchange is equivalent to tissue gas exchange, if there is an air leak of more than 10%, and if the level of inspired oxygen is high (FiO_2 of >60%). As it takes 24 hours before most critically ill patient have been stabilized, it is difficult to accurately measure energy expenditure in the sickest children in the acute phase of intensive care admission. In addition, nursing care (e.g. endotracheal aspiration and daily toiletry), pain, anxiety, fever and medication (e.g. sedatives, analgesics, beta blockers) can also reduce the accuracy of indirect calorimetry when it is performed during a short period of time.[16] Lastly, the initial purchase and the maintenance of metabolic carts are expensive and training is needed to perform the measurements and interpret the results. For all these reasons the method is not used routinely. Many health professionals therefore still rely on predictive equations and tables to assess the energy requirements for individual patients.[17]

Energy intake

Several studies among critically ill children and adults have shown that nutritional needs are frequently not fulfilled by the actual nutritional intake.[2, 18] This may be due to the lack of routine nutritional assessment, the poor estimation of energy and protein needs, and inadequate substrate delivery. A major problem in clinical practice is to define general nutritional requirements for critically ill children, as demands range widely between individual patients.[2] Many PICUs use predictive equations with additional correction factors for type of illness (e.g. ARDS, sepsis, trauma or surgery), activity and intestinal absorption. However, these equations may incorrectly estimate individual energy needs. It has been suggested, therefore, that energy expenditure measurements are better than estimations.[19] In the clinical setting, the measured energy expenditure reflects the resting energy expenditure and this should be considered the minimum value for energy intake. However, the optimal energy intakes during the acute and recovery phases of critical illness remain unclear.

Regarding substrate delivery, studies have shown that 75-90% of the prescribed caloric intake was actually delivered.[2] Fluid volume restriction, procedural interruptions, interruption due to gastrointestinal intolerance and mechanical problems, such as gastric tube occlusion or displacement and absence of venous access for parenteral feeding were the main reasons for inadequate delivery.[2]

In conclusion, many factors can contribute to inadequate nutrition supply and under- or overfeeding of children admitted to the PICU. Standard nutritional assessment and standard evaluation of nutritional supply should be an integrated part of daily practice, for which a team consisting of dieticians, intensivists and specialized intensive care nurses can be made responsible.

HYPERGLYCEMIA

Pathophysiological aspects

Critically ill children, who are exposed to acute and chronic stress, often develop hyperglycemia through multiple proposed mechanisms (Figure 1).[20]

Many studies over the past 10 years in adults and children, challenge the assumption that hyperglycemia is a normal physiologic response to stress. The cause of hyperglycemia in critically ill children is multifactorial and presumed to be due to a combination of insulin resistance, absolute insulin deficiency, glycogenolysis and increased hepatic gluconeogenesis resulting from release of catecholamines, cortisol, glucagon, inflammatory mediators and cytokines. The relative contributions of these factors are unknown, but the effect of increased catecholamines, counter-regulatory hormones, and proinflammatory mediators is thought to impair insulin signaling in target cells, leading to peripheral insulin resistance and high blood glucose.

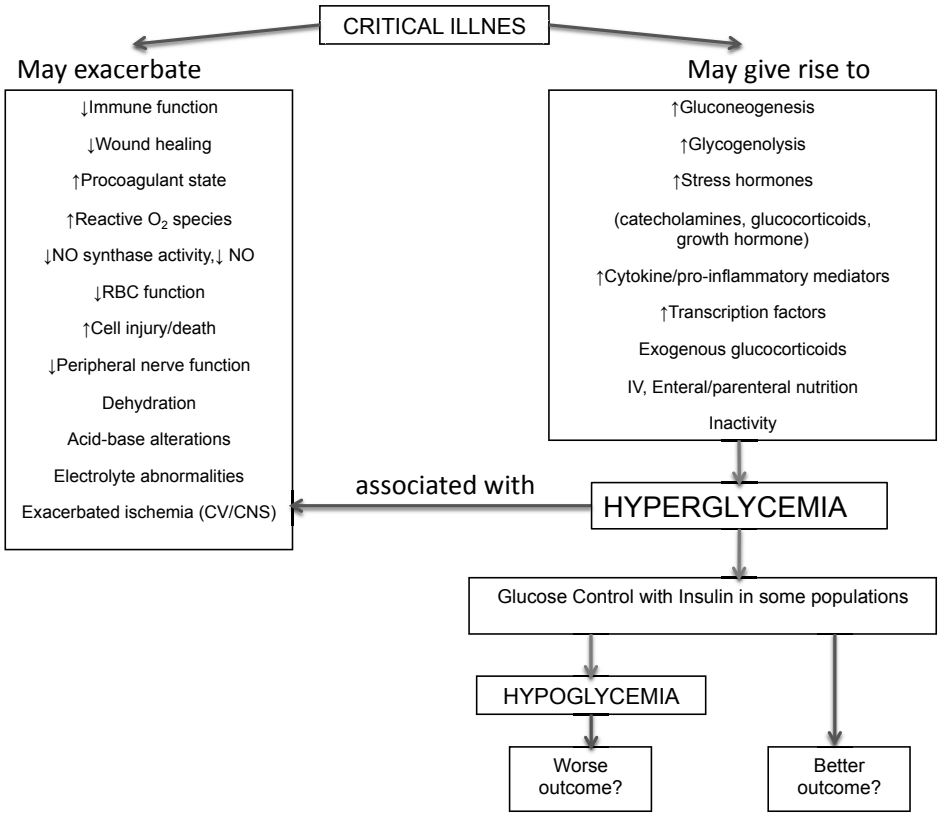

Figure 1 Summary of the presumed causes and consequences of hyperglycemia in critical illness.
Factors that predispose critically ill children to develop hyperglycemia.
CV, cardiovascular; CNS, central nervous system; NO, nitric oxide; IV, intravenous. Reproduced from Fahy et al. (5)

Concurrently, the release of catecholamines, somatostatin, FFAs, and proinflammatory cytokines, such as tumor necrosis factor alpha, directly and adversely effects pancreatic beta-cell function, such that insulin production is inhibited. This, will lead to relative hypoinsulinemia with high blood glucose levels. Moreover, in response to stress, glucagon synthesis is up-regulated, likely because of stimulation of pancreatic cells by cortisol and epinephrine. Taken together, this leads to increased glucagon/insulin ratios and favours gluconeogenesis, resulting in central insulin resistance with increased hepatic glucose production. The combination of increased glucagon, suppression of insulin secretion, and insulin resistance results in hyperglycemia and inability of the organism to use substrate at the tissue level.[21] Also exogenous factors, such as glucose or drug (e.g. glucocorticoids, catecholamines) administration contribute to the development of hyperglycemia during critical illness.[22]

Clinical assessment of insulin sensitivity and β-cell function

Insulin sensitivity quantifies the ability of insulin to lower blood glucose concentration by stimulating glucose uptake and suppressing its production. Thus insulin sensitivity has multiple aspects and, in principle, cannot be reduced to a single index. However, it has become customary to define insulin sensitivity as the ability of insulin to stimulate glucose uptake and to consider the hyperinsulinemic euglycemic clamp as the gold standard method for its assessment.[23] The clamping technique is a difficult method to apply in clinical practice, because of its complicated implementation. The hyperinsulinemic euglycemic clamp technique requires a steady IV infusion of insulin to be administered in one arm, while serum glucose level is "clamped" at a normal fasting concentration by administering a variable glucose infusion in the other arm. Numerous blood samples are taken for monitoring glucose so that a steady "fasting" level can be maintained. The degree of insulin resistance should be inversely proportional to the glucose uptake by target tissues during the procedure. In other words, the less glucose is taken up by tissues during the procedure, the more insulin resistant a patient is.[24]

The assessment of β-cell function is difficult because of the complexity of the β-cell response to secretory stimuli. A gold standard for β-cell function assessment does not exist. The available methods are based on measurements of insulin concentration or on modeling analysis of C-peptide to calculate pre-hepatic insulin secretion in relation with blood glucose levels. The latter method or measuring both, could be more accurate because insulin undergoes some first-pass hepatic extraction and peripheral insulin levels may not reflect true insulin secretion.[23]

Insulin sensitivity and β-cell function may be analyzed indirectly with the use of "minimal" models which require IV or oral administration of glucose. Examples are the frequently sampled IV glucose tolerance test (FSIGT), and the oral glucose tolerance test (OGTT).[23] Though simpler than the glucose clamp, these methods still remain quite complicated and laborious.

The search for easy-to-use and inexpensive quantitative tools has led to the development of homeostatic assessments of insulin sensitivity. These tests are based on paired fasting glucose and insulin levels, and use mathematical calculations to assess insulin sensitivity and β-cell function. Examples are the fasting insulin level, glucose/insulin and insulin/glucose ratio, homeostatic model assessment (HOMA), and quantitative insulin sensitivity check index (QUICKI). The HOMA model has been most widely employed in clinical research and practice to assess insulin sensitivity. The original HOMA model is described by the following equation: HOMA-IR=(FPIxFPG)/22.5, where IR is insulin resistance, FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L). The formula for the estimation of β-cell function is: HOMA-B=(20*FPI)/(FPG-3.5).[23] The updated HOMA model (i.e., the computer model) is available from www.OCDEM.ox.ac.uk[25] and can be used to determine insulin sensitivity (HOMA-%S) and β-cell function (HOMA-%B) from paired fasting plasma glucose and insulin or C-peptide concentrations. Although the described tests were originally developed for application in diabetes mellitus and metabolic diseases, some of the techniques have also been used to evaluate insulin response to hyperglycemia in critically ill patients. The hyperinsulinemic euglycemic clamp technique revealed severe insulin resistance in critically ill medical patients on the day after ICU admission and this was associated with severity of illness, BMI and measured energy expenditure by indirect calorimetry.[26] HOMA in non-fasting critically ill adults with acute renal failure, showed an association between mortality and insulin resistance.[27] HOMA was also used to differentiate between patients with over insulin resistance (hyperglycemia), non-overt insulin resistance (normal glucose but elevated HOMA) and those who were insulin sensitive.[28]

There are only few reports on the evaluation of insulin sensitivity or β-cell function in critically ill children. C-peptide/glucose ratios were elevated in children with respiratory failure only, suggesting insulin resistance, whereas decreased ratios were seen in children with respiratory and cardiovascular failure, indicative for β-cell dysfunction.[29] β-cell dysfunction was also suggested in children with meningococcal septic shock, as they showed lower insulin/glucose ratios than children with sepsis only.[30]

Relation with outcome

Table 1 provides details of the main studies that have evaluated the association between glycemic level and outcome such as length of stay, duration of mechanical ventilation, neurological outcome and mortality. All studies but one report an association between hyperglycemia and adverse outcome. The overall conclusion may be that hyperglycemia in critically ill children is associated with increased morbidity and mortality. However, some important limitations of these studies should be pointed out. Most importantly, all except one were retrospectively designed and could not demonstrate causality between the glucose levels and outcome measures; they demonstrated associations only. Furthermore, various

hyperglycemic thresholds were reported. A glucose level of 8.3 mmol/L (150 mg/dL) had the strongest association between hyperglycemia and increased morbidity and mortality.[3]

The reasons why hyperglycemia may be injurious in critically ill children are unclear. Under physiological circumstances, glucose uptake in the liver is directly proportional to blood glucose concentration, while peripheral uptake is insulin dependent. In physiological conditions, hyperglycemia down regulates insulin-independent glucose transporters (GLUT-1, GLUT-2 and GLUT-3), thus protecting cells against glucose overload. However, in critical illness this mechanism fails, resulting in glucose overload in organ systems that express these transporters (e.g. central and peripheral nervous system, erythrocytes, hepatic, immune and endothelial cells, renal tubules and gastrointestinal mucosa). Glucose overload causes free-radical formation, promotes injury to hepatic mitochondria and other cellular structures, leads to apoptosis and cell death in certain organs, and can impair the innate and humoral immune response to infection. In contrast, skeletal muscle and the myocardium, which normally take up glucose predominantly via the insulin-dependent GLUT-4 transporter, may be relatively protected against toxic effects of circulating glucose.[22, 31]

GLYCEMIC CONTROL

Insulin action

Insulin is the most potent anabolic hormone in the body. It has profound effects on both carbohydrate and lipid metabolism, and significantly influences protein and mineral metabolism. Insulin treatment may give protective effects by inhibiting some of the pathologic processes caused by high blood glucose levels. Furthermore it exerts anabolic effects on lipid and protein metabolism, on modulation of counter-regulatory hormones and catecholamines commonly increased during stress, and it has direct anti-inflammatory properties. It has been suggested that hepatic insulin resistance remains refractory to intensive insulin therapy. In critical illness, the expression of PhosphoEnolPyruvate Carboxy Kinase (PEPCK), which is the rate-limiting enzyme of gluconeogenesis, is increased due to elevated levels of cortisol and catecholamines. Under normal conditions, insulin is a potent inhibitor of PEPCK. However, in critically ill patients both the expressions of PEPCK and hepatic glucokinase, which controls glucose uptake and glycogen synthesis, remain unaltered by insulin therapy. As a result, insulin lowers glucose predominantly through increased skeletal muscle glucose uptake by increasing the expressions of GLUT-4 and hexokinase-II.[3] In Figure 2 the mechanism of stress-induced hyperglycemia and influence of insulin therapy is shown.[32]

Table 1 Summary of reports on glucose level and outcome in pediatric critical care

Author (year) [Design]	Population (n, diagnosis)	Median age yr (range)	Glucose Threshold (mmol/L)	Outcome Associations	Mortality (%)	Worst Outcome
Gore et al (2001)[38] [retrospective]	58 Burn ≥60% BSA	6.5 (range unknown)	7.8	Persistent hyperglycemia (≥40% of glucose measurements)	17%	Nonsurvivors had more often persistent hyperglycemia
Cochran et al (2003)[39] [retrospective]	170 Head trauma	4.0 (0.1-17)	7.5 vs 14.8	Admission glucose	9%	Nonsurvivors had higher admission glucose levels (14.8) than survivors (7.5) and admission glucose levels of 11 associated with worse neurological outcome
Srinivasan et al (2004)[40] [retrospective]	152 MV or Vasoactive support	6.0 (1-12)	7.0	Peak glucose level at 24h and 48h	15%	Peak glucose in nonsurvivors was higher and lasted longer
Branco et al (2005)[41] [prospective]	57 Septic shock	2.8 (0-7.1)	9.9	Peak glucose level during all PICU stay	49%	Peak glucose was associated with 2.59-fold increase in risk of death
Faustino et al (2005)[42] [retrospective]	942 All PICU admissions	3.2 (0.3-10.8)	6.7	Peak glucose at 24h and within 10 days	4%	Peak glucose increased relative risk for dying with 2.5 (within 24 hrs >8.3) and 5.68 (within 10 days>6.7)
Wintergerst et al (2006)[43] [retrospective]	1094 All PICU admissions	2.8 (0-21)	*6.7*	Peak glucose, hypoglycemia and glucose variability	5%	Length of stay was associated with hyper-and hypoglycemia (<3.6). Increased glucose variability had the strongest association with increased mortality and length of stay.
Yates et al (2006)[44] [retrospective]	184 Post cardiac surgery	0.3 (0.1-0.6)	7.0	Peak glucose and glucose variability	11%	Nonsurvivors had higher peak glucose levels and longer duration of hyperglycemia. Duration of hyperglycemia was associated with longer ventilator use and length of stay
Branco et al (2007)[45] [retrospective]	50 bronchiolits with MV	0.2 (0.1-0.4)	8.3	Peak glucose and sustained hyperglycemia during 6 hours	0%	Hyperglycemia was not independently associated with morbidity (eg duration of MV or PICU stay)
Rossano (2007)[46] [retrospective]	93 Post cardiac surgery (Arterial switch)	2.5 weeks (range unknown)	11.0	Peak glucose during the first 24 hours postoperatively	1%	Patients with majority of time spend in blood glucose range 4.4-5.5 mmol/L had highest number of adverse events (infection, renal insufficiency, thrombus, seizure/stroke, postoperative arrhythmia, ventricular dysfunction, cardiac arrest, pericardial effusion, pulmonary hypertensive crisis)

Falcao (2008)[47] [retrospective]	213 Post cardiac surgery	0.3 (0.06-2.3)	15.9 vs 21.2 (peak glucose) 6.1 vs 8.1 (mean glucose)	Peak and mean glucose levels and duration of hyperglycemia during 10 days	7%	Nonsurvivors had higher peak and mean glucose levels and longer duration of hyperglycemia
Day (2008)[48] [retrospective]	97 Meningo-coccal sepsis	2.1 (range unknown)	7.0	Peak glucose	4%	Hyperglycemia was inversely correlated with ventilator free days at 30 days
Hirshberg (2008)[49] [retrospective]	All PICU patients	2.0 (range unknown)	8.3 Hypoglycemia<3.3	Glucose variability	3%	Hyperglycemia and glucose variability were associated with mortality
Polito (2008)[50] [retrospective]	378 Post cardiac surgery (RACHS ≥3)	0.6 (0.01-14.4)	6.9	Duration of hyperglycemia	4%	Longer duration of hyperglycemia during 72 hours was associated with longer duration of hospital stay
Tude Melo (2010)[51] [retrospective]	286 Severe traumatic brain injury	7.0 (0.1-17.0)	11.1	Peak glucose within first 48 hrs	33%	Peak glucose level was associated with mortality

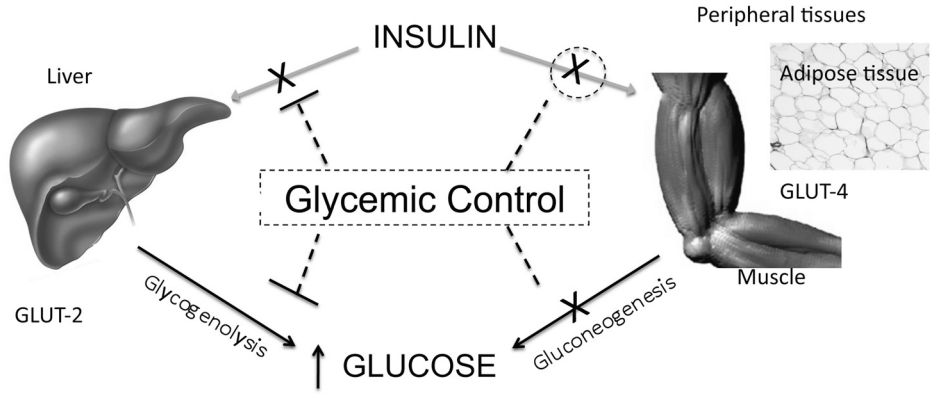

Figure 2 Mechanism of stress-induced hyperglycemia. Changes occurring during stress (dark solid lines) cause insulin resistance (X) in the liver (stimulating glycogenolysis) and in peripheral tissues (reducing glucose uptake and stimulating gluconeogenesis). Insulin therapy (dashed lines) reverses peripheral but not hepatic insulin resistance. Reproduced from Branco et al. (32)

What is the evidence?

Glycemic control in critically ill adults

In 2001 van den Berghe et al. described the use of insulin to treat hyperglycemia and normalize blood glucose level (4.4-6.1 mmol/L) in adult patients admitted to the surgical intensive care unit.[4] This trial, known as the Leuven study, showed that strict insulin therapy reduced overall in-hospital mortality, and also reduced bacteremia, acute renal failure, the need for red-cell transfusions and critical-illness polyneuropathy. In 2006 van den Berghe et al. reported a second large randomized controlled trial of glycemic control, this time in medical adult patients.[33] Mortality had gone down in a subgroup of patients who stayed in ICU longer than 3 days and overall morbidity had improved with the use of strict glycemic control. Since then, only a few studies have been able to reproduce the findings of the Leuven studies. Alarmingly, two studies planned as large randomized controlled trials evaluating the effect of glycemic control in adults (Glucocontrol and VISEP, efficacy of Volume substitution and Insulin therapy in severe SEPsis) were stopped prematurely mainly because of concerns about increased incidence of hypoglycemia.[34-35] Another large trial in adult critical care, the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation) trial did not show additional survival benefit by controlling blood glucose at the 4.4-6.1 mmol/L range compared to 8.0-10.0 mmol/L.[36]

Despite the seemingly contradictory outcomes, professional organizations such as the American Association of Clinical Endocrinologists, the American Diabetes Association, Surviving Sepsis Campaign and other authorities suggested that stress hyperglycemia should be considered in any critically ill patient with a blood glucose level in excess of 6.1 mmol/L. They recommended intensive insulin therapy for the management of hyperglycemia in adult critically ill patients.[37]

Glycemic control in critically ill children

Two large randomized controlled trials of glycemic control in critically ill children have been published so far.[6, 38] The first trial, by the Leuven group, included 317 infants <1 year and 383 children ≥1 year, mainly admitted after cardiothoracic surgery. They reported decrease of mortality; 3% for those treated with intensive insulin therapy versus 6% for controls.[6] The second trial included 239 severely burned children and showed that intensive insulin therapy improved post-burn mortality, as indicated by decreased incidence of infections and sepsis.[38] However, in both studies severe hypoglycemic events occurred in a quarter of the children in the intervention group.[7] A follow-up study has been initiated by the Leuven group to study the long-term consequences of hypoglycemia and of hyperglycemia on neurocognitive development.

In summary, nutritional support of critically ill children is of major importance. Indirect calorimetry can be used to measure resting energy expenditure and to tailor individual nutritional support for critically ill children with various clinical conditions. Hyperglycemia frequently occurs and is associated with adverse outcome. Glycemic control for critically ill children is controversial; there is no evidence for aiming at very strictly regulated blood glucose levels.

Research on pathogenesis of hyperglycemia in critically ill children can guide the development of preventive and therapeutic strategies. The HOMA model can be used to assess insulin sensitivity and pancreatic β-cell function associated with hyperglycemia.

AIM OF THE THESIS

The studies presented in this thesis focused on energy requirements in critically ill children in the acute phase of disease in relation with the hyperglycemic response to stress.

The overall aims of this thesis are:

- To determine the actual energy needs of critically ill, mechanically ventilated children.
- To study the value of prediction equations for energy expenditure in relation to energy expenditure measurements.
- To explore the mechanisms that lead to hyperglycemia in critically ill children.
- To evaluate the use of a glucose control protocol for prevention and treatment of hyperglycemia with insulin in critically ill children.

OUTLINE OF THE THESIS

Chapter 1 provides a general introduction and the aims of the studies. Current methods to determine energy requirements are presented, as well as notions about assessment of insulin sensitivity in critically ill children.

PART I

Energy requirements

The daily energy expenditure of mechanically ventilated children is measured by indirect calorimetry. Results are compared with prediction equations in **chapter 2** and with actual caloric intake in **chapter 3** to identify under-and overfeeding. In **chapter 4** we evaluate whether "new" equations derived from actual energy expenditure measurements of ventilated critically ill children correctly predict energy expenditure in a larger group of patients and whether they were adequately fed.

PART II

Hyperglycemia

Two studies on pathophysiological aspects of hyperglycemia in homogenous groups of critically ill children are discussed in chapters 5 and 6. **Chapter 5** concerns a homogenous group of children with meningococcal sepsis and septic shock; we studied the occurrence of hyperglycemia in relation with the insulin response and exogenous factors, such as glucose intake and drug use. **Chapter 6** concerns children undergoing cardiac surgery for congenital heart disease; we evaluated peri-operative blood glucose levels and related these to endogenous stress hormone production, inflammatory mediators and exogenous factors such as caloric intake and glucocorticoid use.

PART III

Glycemic control

Chapter 7 concerns a heterogeneous group of critically ill children with hyperglycemia just before start of insulin therapy. As it would be useful to predict which children could benefit from insulin therapy, the relationship between the endogenous insulin response to hyperglycemia and clinical outcome is explored.

The implementation of a stepwise nurse-driven glucose control protocol for the treatment of hyperglycemia in critically ill children is evaluated in **chapter 8.** The results of a randomized controlled trial on intensive insulin therapy in critically ill children with high incidence of hypoglycemic events is discussed in **chapter 9**.

A synthesis and general discussion of the results are given in **chapter 10.** Summary and conclusions are presented in **chapter 11**.

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PART I

ENERGY REQUIREMENTS

I can accept failure, but I can't accept not trying (***Michael Jordan***)

Chapter 2

Comparison of measured and predicted energy expenditure in mechanically ventilated children

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ABSTRACT

Objective

To determine the energy requirements in mechanically ventilated pediatric patients using indirect calorimetry and to compare the results with the predicted metabolic rate.

Design

In 50 mechanically ventilated children with a moderate severity of illness, energy expenditure was measured by indirect calorimetry. Daily caloric intake was recorded for all patients. Total urinary nitrogen excretion was determined in 31 patients.

Results

Although there was a close correlation between the measured total energy expenditure (mTEE) and the predicted basal metabolic rate (pBMR)($r=0.93$; $p<0.001$), Bland-Altman analysis showed lack of agreement between individual mTEE and pBMR values. The ratio of caloric intake /mTEE was significantly higher in the patients with a positive nitrogen balance (1.4 ± 0.07) compared with those with a negative nitrogen balance (0.8 ± 0.1; $p<0.001$).

Conclusions

Standard prediction equations are not appropriate to calculate the energy needs of critically ill, mechanically ventilated children. Individual measurements of energy expenditure and respiratory quotient by means of indirect calorimetry in combination with nitrogen balance are necessary for matching adequate nutritional support.

INTRODUCTION

Nutritional support is an essential management aspect of pediatric intensive care patients. Energy requirements of critically ill children were determined by calculation of basal metabolic rate with adjustment for degree of stress (1, 2). Daily energy expenditure determination in the critical care setting can be performed by indirect calorimetry (3). Indirect calorimetry is the method by which the metabolic rate is calculated from measurements of oxygen consumption and carbon dioxide production. Use of indirect calorimetry enables the clinician to assess more accurately the patient's caloric energy needs and the patient's ability to utilize nutrient substrates (4). In this way appropriate feeding regimens for critically ill children can be designed.

Studies of nonventilated children have shown a wide variation of measured resting energy expenditure. It was recommended in these studies that measurement of resting energy expenditure (mREE) should be performed in individual patients instead of using a prediction equation for ensuring adequate nutrition (5, 6). In only six studies with small numbers of mechanically ventilated children were results of energy expenditure using indirect calorimetry presented (Table 1) (2, 7-11). In five of these six studies resting energy expenditure was measured, and in one study prolonged measurements of energy expenditure were performed. These studies all showed a wide variation in individual actual energy requirements in different diseases and a wide range in the ratio of measured total energy expenditure (mTEE) or mREE to predicted basal metabolic rate (pBMR).

Table 1 Study population characteristics

[Reference]	Age group	n	Diagnosis	MEE/pBMR	MEE (range)
[7]	5-17 years	9	Head injury	1.19 ± 0.07[(a)]	-
[8]	5 days-46 months	20	Wide range	1.02 ± 0.07 [(b)]	100-343[(b)]
[2]	2-18 years	18	13 trauma; 5 other	1.48 ± 0.09[(a)]	130-336[(a)]
[9]	2 days-120 months	12	Wide range	-	125-236[(a)]
[10]	2 months-12 years	26	Open heart surgery	0.96 ± 0.03[(a)]	126-289[(a)]
[11]	3 months-10 years	18	Wide range	0.97 ± ?[(a)]	-
Present study	2 days-13 years	50	Wide range	1.04 ± 0.03[(b)]	85-270[(b)]

MEE, Measured Energy Expenditure; pBMR, predicted Basal Metabolic Rate; mTEE, measured Total Energy Expenditure; mREE, measured Resting Energy Expenditure

[(a)] mREE (kJ/kg per day)
[(b)] mTEE (kJ/kg per day)

The purpose of this study was to perform measurements of energy expenditure, which represent total daily energy expenditure in mechanically ventilated children, in order to get a better insight into actual energy requirements and to compare these measurements with the pBMR, energy intake, and nitrogen balance.

MATERIALS AND METHODS

Patient selection

Patients were eligible for the study when they met the following criteria:

1 Mechanical ventilation with a Servo Ventilator 300 (Siemens-Elema, Solna, Sweden) either with pressure regulated volume control mode or with volume support mode.

2 A fractional inspired oxygen (FiO_2) of less than 0.60.

3 A tube leakage of less than 10% (considered not to influence the measurement significantly (12)). Tube leakage was determined by comparison of inspired and expired tidal volumes measured by the ventilator, assuming that there were no other leaks in the patient-ventilator circuit.

4 A haemodynamic stable condition indicated by a normal, stable bloodpressure according to age within 2 SD (13), and normal renal function expressed by a normal serum creatinine concentration (14).

Severity of illness on the day of measurement was assessed by the Pediatric Risk of Mortality score (PRISM) (15) and Therapeutic Intervention Scoring System (TISS) (16).

The local Ethical Committee approved the study and informed consent was obtained from the parents.

Energy expenditure

Oxygen consumption (VO_2), carbon dioxide production (VCO_2) and respiratory quotient (RQ) were measured with a previously validated metabolic monitor (Deltatrac I MBM-100 and Deltatrac II MBM-200, Datex Division Instrumentarium, Finland) (17). All gas measurements were standardized for temperature, barometric pressure, and humidity (STPD). The Deltatrac is an open system indirect calorimetry device. The difference between the inspired and expired oxygen fractions is measured with a fast-response, paramagnetic differential oxygen sensor (OM-101, Datex Instrumentation). The expired CO_2 fraction is measured with an infrared CO_2 sensor. Before each test, the calorimeter was calibrated with a reference gas mixture (95% O_2, 5% CO_2). The accuracy of the Deltatrac was assessed with a butane burner. The mean error of VO_2 and VCO_2 obtained in repeated tests was 2.7 ± 0.5 and 3.7 ± 0.6% respectively. The mean RQ was 0.62 ± 0.01 (RQ of butane 0.615), with a mean error of 2.2 ± 0.4%. Studies were carried out for a period of at least 4 h with a maximum of 24 h. The mean coefficient of variation for measured energy expenditure was 4.6 ± 0.4%.

Measurement results of at least 4 h were considered to represent the total daily energy expenditure (18, 19). Mean mTEE was calculated using the modified Weir formula [20]: mTEE = 4184(5.5 VO_2 + 1.76 VCO_2); mTEE in kJ/day; VO_2 in l/min; VCO_2 in l/min. The respiratory quotient was calculated by dividing VCO_2 /VO_2. The nonprotein RQ was calculated with the formula: (VCO_2 - 4.84N)/(VO_2 - 6.04N). N is urinary urea nitrogen excretion in g/min. pBMR was calculated from each patient's weight, age and sex using the appropriate Schofield equations (21).

Caloric intake

The patients were fed enterally and/or parenterally. Enteral feeding was given continuously via a nasoduodenal drip with standard soja-based formula (Nutrilon soja for children £ 6 months, Nutrilon soja plus for children 6-12 months, 75% Nutrison soja and 25% water and 4% Fantomalt added for children 1-4 years, 90% Nutrison soja and 10% water and 4% Fantomalt added for children 4-10 years, and Nutrison soja for children > 10 years of age Nutricia, Zoetermeer, The Netherlands). Parenteral feeding was given either by peripheral infusion or by a central venous line (Intralipid 20%, Pharmacia Upjohn Holland and Aminovenös N-paed 10%, Fresenius, The Netherlands). Fluid and electrolyte intakes were adjusted to individual requirements. Daily caloric intake (subdivided into carbohydrate, protein and fat) was recorded for all patients. Caloric intake was corrected for extra protein calories from plasma infusions and/or albumin infusions on the day of measurement.

Urinary nitrogen excretion

In 31 patients, urine was collected on the day of measurement and analyzed for urinary urea nitrogen. In the remaining 19 patients, urine was not collected because of logistical problems. In 18/31 patients a urinary bladder catheter was in place and urine was collected over a 24-h period. In 13/31 patients, however, a pediatric urine collector was used and urine was collected over a shorter period but over 1of at least 6 h. This can be used to estimate a 24 hour period, but the inconsistency has to be taken into account when interpreting the results.

Total urinary nitrogen excretion (TUN) was defined as 1.25 x urinary urea nitrogen, in order to adjust for the 20% of urinary nitrogen loss as ammonia, creatinine, and uric and amino acids (22). No correction was made for nitrogen losses through stools, skin, wound, nasogastric suction, or blood sampling. Nitrogen balance was calculated with the following formula:

Nitrogen balance (mg/kg per day) = (protein intake/6.25) - (urinary urea nitrogen x 1.25).

Statistical analysis

Statistical analyses were performed with a software program (SPSS 7.0 for Windows 95, SPSS Software, Chicago, IL, USA). Results are expressed as mean ± SEM, unless otherwise indicated. For comparisons between groups the independent samples t-test was used. A p-value of 0.05 or less was defined as statistically significant. Pearson's correlation coefficient (r) and a Bland-Altman plot were used to evaluate the relationship between mTEE and pBMR (23).

RESULTS

From among the 80 patients who were admitted consecutively from September 1995 to May 1996 to our pediatric intensive care unit (PICU) 30 patients were excluded because they did not fulfill the inclusion criteria. The study group consisted of 50 patients, 28 boys and 22 girls, with a wide range of clinical characteristics (Table 2). The median age was 7 months (2 days-13 years). Median PRISM score was 6 (0-13) and median TISS score was 17 (10-32) (Table 3). All patients were sedated with midazolam and/or morphine and 4 patients with pharmacological muscle paralysis. Five patients received inotropic drugs. There were no known pathological gastrointestinal absorption disturbances. The mean day of measurement after intubation was 5 ± 4 days. Ventilatory characteristics were as follows: mean FiO_2 was 0.35 ± 0.018 and mean tube leakage was 6 ± 1%; 24 patients were on pressure regulated volume control, 25 on volume support, and 1 was on continuous positive airway pressure. The results of the energy expenditure measurements are shown in Table 3. The correlation coefficient between mTEE and pBMR was r= 0.93 ($p<0.001$). A Bland-Altman plot for mTEE and pBMR shows a wide scatter around the mean (difference from the mean: -2120 to + 1970 kJ/day) (Fig 1)

Thirty-five patients received enteral nutrition (EN), 7 received only glucose infusion, 6 received total parenteral nutrition (TPN) and 2 received a mixture of EN and TPN. Mean caloric intake was 243 ± 17 kJ/kg per day.

TUN was determined in 31 patients (Table 3). Mean TUN was 249 ± 22 mg/kg per day. The nitrogen balance was positive in 19 patients and negative in 12 patients. The ratio of caloric intake/mTEE was significantly higher in the patients with a positive nitrogen balance (1.4 ± 0.1 mg/kg per day) compared with those with a negative nitrogen balance (0.8 ± 0.1 mg/

Table 2 Clinical Diagnosis of study patients

Diagnosis	Number of patients
Congenital heartdefect	15
Sepsis	9
Pneumonia	6
(RS) Bronchiolitis	5
Resection subglottic stenosis	4
Upper airway obstruction	3
Near drowning	2
Leigh's Syndrome	1
Pediatric AIDS	1
Cardiomyopathy	1
Status asthmaticus	1
Post pylorotomy	1
Status epilepticus	1
Total	50

Table 3 Patient characteristics and measurements results

Patients (n=50)	Mean ± SEM	Range
Age	25 ± 6 months	2 days – 13 years
PRISM	6 ± 1	0-13
TISS	18 ± 1	10–32
Intake (kJ/kg per day)	243 ± 17	22–520
mTEE (kJ/day)	1987 ± 238	640-8678
mTEE (kJ/kg per day)	212 ± 5	85-270
pBMR (kJ/day)	2029 ± 212	590-6903
pBMR (kJ/kg per day)	213 ± 6	98-298
RQ	0.89 ± 0.01	0.77-1.02
TUN (n=31) (mg/kg per day)	249 ± 22	68-493
N-balance (n=31) (mg/kg per day)	-4 ± 38	-471-335

PRISM, Pediatric RISk of Mortality score; TISS, Therapeutic Intervention Scoring System; mTEE, measured Total Energy Expenditure; pBMR, predicted Basal Metabolic Rate; RQ, Respiratory Quotient; TUN, Total Urinary Nitrogen excretion; N-balance, Nitrogen balance

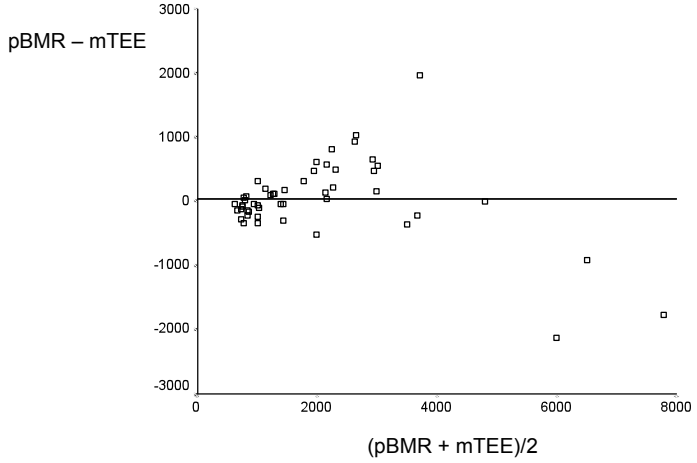

Figure 1. Bland-Altman plot for mTEE and pBMR

kg per day; p<0.001) (Table 4). The actual caloric intake in patients with a positive nitrogen balance was 318 ± 21 versus 163 ± 29 kJ/kg per day for patients with a negative nitrogen balance (p<0.001). There was no significant difference in nonprotein RQ between patients with a positive or negative nitrogen balance. In 6 patients the nonprotein RQ was > 1.0. The carbohydrate intake in 4 of them was 9-10 mg/kg per min, and in the other 2 patients, 4.2 and 7.5 mg/kg per min, respectively.

Table 4 Nitrogen balance in relation to ratio of intake/mTDEE and nonprotein RQ

	N-balance > 0	N-balance < 0	P-value
Patients	19	12	
Intake/mTEE	1.4 ± 0.1	0.8 ± 0.1	<0.001
Nonprotein RQ	0.90 ± 0.02	0.87 ± 0.02	0.3

N-balance, Nitrogen balance; mTEE, measured Total Energy Expenditure; RQ, Respiratory Quotient

DISCUSSION

We determined the metabolic and nutritional state of a heterogeneous group of mechanically ventilated PICU patients with different clinical diagnoses. Because of methodological problems (tube leakage, FiO_2 above 0.60, unstable haemodynamics), we were only able to perform energy expenditure measurements on 50 of the 80 mechanically ventilated patients admitted to our PICU in the study period.

As a consequence of these limitations only patients with a moderate severity of illness in the beginning of disease or patients recovering from a severe illness could be included for indirect calorimetric studies, as is indicated by the low PRISM and TISS scores of our patient population.

Total energy expenditure consists mainly of basal metabolic rate, growth, heat loss, and mechanical work. Growth can account for a substantial proportion of the energy expenditure in children (30- 35%), especially in the first year of life (24). However, in critically ill, mechanically ventilated children, counter-regulatory hormones could diminish and even stop growth, and mechanical ventilation will reduce the work of breathing (8). As a result the total energy, which is needed, will be lower and resemble basal metabolic rate. So far, there have been only six previous studies on mechanically ventilated children in which TEE or REE was measured by means of indirect calorimetry (2,7-11). In five of these studies, there was a correlation between mTEE or mREE and pBMR. These correlations are misleading because of the wide variation in individual measurements. In our study, we also found a wide range of individual measurements. From the wide scatter of the Bland-Altman plot, it becomes obvious that the use of predicted energy expenditure is inappropriate for clinical purposes. Our study showed that the mean coefficient of variation for measured energy expenditure was 4.6 ± 0.4% compared with a coefficient of variation of 19.4% for prediction of mREE for an individual as stated by Schofield. This also advocates the use of measured energy expenditure instead of using prediction equations.

Prolonged measurements of energy expenditure, like we did in our study, give a better reflection of total daily energy expenditure. The calorie intake should be based on these measurements rather than on the basal or resting energy expenditure. These prolonged measurements are only possible in clinically stable, sedated patients. To determine resting energy expenditure a shorter period can be used (20-30 min with a steady state of 5 min

during which average VO_2 and VCO_2 change by less than 10% and average RQ changes by less than 5%)(25).

In order to provide an appropriate number of calories, caloric intake should be individualized using mTEE and RQ. In our study, we showed that feeding according to the mTEE could be a guideline because the ratio of caloric intake/mTEE was significantly higher in patients with a positive nitrogen balance (1.4 ± 0.07) compared to those with a negative nitrogen balance (0.8 ± 0.1) ($p<0.001$). Feeding higher than mTEE is necessary for growth and tissue repair. In our patients with a positive nitrogen balance, the caloric intake exceeded the mTEE by 40%. However, in the case of enteral feeding, not all of the administered calories will be absorbed; the loss of energy in stools can account for 10-20% of the total caloric intake (26).

The RQ is the ratio of VCO_2 to VO_2 and reflects the percent substrate utilization of fat and carbohydrate in the body. By excluding protein, the nonprotein RQ provides a range of substrate utilization from 0.70 (100% fat utilization) to 1.0 (100% glucose utilization). Alcohol or ketone metabolism may reduce the nonprotein RQ below this range to 0.67. Overfeeding with lipogenesis may increase it above this range to 1.3. In our study, 4 patients with a carbohydrate intake of 9-10 mg/kg per min showed an RQ > 1.0, suggesting excessive carbohydrate intake resulting in lipogenesis. A lower carbohydrate intake, however, can also lead to an RQ > 1.0, as was shown in 2 of our patients with a carbohydrate intake of 4.2 and 7.5 mg/kg/min, respectively. There seems to be a maximum carbohydrate oxidation rate and thus a maximal capacity to use carbohydrate as a source of calories in the stressed patient. Beyond this oxidation maximum carbohydrate administration will lead to hyperglycemia, excess of CO_2 (RQ > 1.0) and hepatic steatosis (27,28). An excessive amount of carbohydrate will not always lead to an RQ > 1.0, because in the hypermetabolic patient there is still ongoing oxidation of fat for energy, resulting in an RQ < 1.0 (29). This was the case in 2 of our patients with a carbohydrate intake of 9.8 and 11.4 mg/kg per min and an RQ which was < 1.0 (0.78 and 0.95, respectively). Thus, the RQ can be used to detect overfeeding, but one should be cautious in using it as such.

In summary, this study shows that in critically ill, mechanically ventilated pediatric patients, although mTEE seemed to resemble pBMR, there was a wide range in the ratio of mTEE to pBMR and lack of agreement. Therefore, it seems not to be appropriate to use a standard prediction equation but to perform individual measurements of energy expenditure and RQ with indirect calorimetry in combination with nitrogen balance for matching adequate nutritional support. Outcome-based studies could give more insight into how optimal nutritional support could be given to mechanically ventilated children in the intensive care setting.

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Chapter 3

Energy expenditure and substrate utilization in mechanically ventilated children

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ABSTRACT

Objective

To determine the value of indirect calorimetry and nitrogen balance (N-balance) in order to evaluate the current feeding protocols of mechanically ventilated children.

Study design

A cross-sectional prospective study. In 36 mechanically ventilated children energy expenditure was measured by indirect calorimetry and total urinary nitrogen excretion (TUN) was determined. Substrate utilization and respiratory quotient (RQ) were calculated from the measured values of oxygen consumption (VO_2), carbondioxide production (VCO_2) and TUN. The RQ was compared with RQ of the macronutrients administered (RQmacr) according to the modified criteria of Lusk.

Results

The total measured energy expenditure (TMEE) showed a wide variation (range 155 to 272 kJ/kg/day). The N-balance was positive in 20 and negative in 16 patients. The ratio of caloric intake/TMEE was significantly higher in patients with a positive N-balance (1.5 ± 0.06) as compared with those with a negative N-balance (0.8 ± 0.1; $p<0.001$). There was a significant relation between the difference of RQ minus RQmacr versus the ratio caloric intake/TMEE ($r=0.72$, $p<0.001$). Carbohydrate and fat utilization were not significant different in patients with a positive or negative N-balance. Protein utilization was significantly higher in those patients with a negative N-balance.

Conclusions

Measurement of TMEE with indirect calorimetry results in accurate determination of energy needs in critically ill mechanically ventilated children. Feeding according to or in excess the TMEE is correlated with a positive N-balance. A combination of the RQ and the RQmacr can be helpful in differentiating under- or overfeeding.

INTRODUCTION

Protein-energy malnutrition is an important consequence of pediatric critical illness and is associated with increased physiologic instability and increased quantity of care (1,2). In critically ill patients there is a substantial interpatient variability in energy expenditure. The supply of calories based on prediction equations can be misleading and result in under- and overfeeding (3,4). Underfeeding will alter the immune function, the cardiorespiratory system and the gastro-intestinal tract (1). Overfeeding can affect respiratory and hepatic function and increases the risk of mortality (4).

Indirect calorimetry makes it possible to accurately determine energy expenditure and respiratory quotient. This can be used to monitor the adequacy and appropriateness of current nutritional support. Furthermore when urinary nitrogen values are measured it allows the determination of substrate utilization.

Until now only a small number of studies on mechanically ventilated children were presented with results of energy expenditure and substrate utilization using indirect calorimetry (5-11).

The purpose of this study is to determine the value of indirect calorimetry combined with nitrogen balance in order to evaluate the current feeding protocols of mechanically ventilated children and to obtain guidelines for improvement for individual patient groups or disease states.

MATERIALS AND METHODS

Patient Selection

Patients were consecutively included in this study after admission to level III Pediatric Intensive Care Unit, when they fulfilled the following criteria:

- mechanical ventilation with a Servo Ventilator 300 (Siemens-Elema, Solna, Sweden) either with pressure regulated volume control or volume support mode.
- FiO_2 of less than 0.60.
- tube leakage of less than 10% (considered not to influence the measurement significantly (12)). Tube leakage was determined by comparison of inspired and expired tidal volumes measured by the ventilator assuming that there were no other leaks in the patient-ventilator circuit.
- haemodynamically stable condition as indicated by a normal, stable blood pressure within 2 SD of the age-related mean normal value (13) and a normal renal function expressed by a normal serum creatinine concentration (14).

Severity of illness on the day of measurement was assessed by the Pediatric Risk of Mortality score (PRISM) (15).

The study was approved by the local Ethical Committee and informed consent was obtained from the parents or caregivers before entering into the study.

Energy Expenditure

Oxygen consumption (VO_2), carbon dioxide production ($VCO_{2)}$) and respiratory quotient (RQ), standardized for temperature, barometric pressure and humidity (STPD) were measured with a previously validated metabolic monitor (Deltatrac I MBM-100 and Deltatrac II MBM-200, Datex Division Instrumentarium Corp. Finland) (16). The Deltatrac is an open system indirect calorimetry device. The difference between the inspired and expired oxygen fractions is measured with a fast-response, paramagnetic differential oxygen sensor (OM-101, Datex Instrumentation). The expired CO_2 fraction is measured with an infrared CO_2 sensor. The accuracy of the Deltatrac was assessed with a butane burning set. Butane used for experiments was weighed before and after each experiment on a precise scale. The value obtained by the metabolic monitor for the total CO_2 was compared to the predicted value of CO_2 based on the weight of butane. The accuracy of the Deltatrac was assessed with a butane burning set every 3 months. Before each study, the calorimeter was calibrated with a reference gas mixture (95% O_2, 5% CO_2). The coefficient of variation of O_2 consumption, CO_2 production, and RQ did not exceed ± 4%. Studies were carried out during different measurement periods from 4-24 hours. A measurement period more than 4 hours resembled a 24 hour measurement with a coefficient of variation within 10% (17). Total measured energy expenditure (TMEE) was calculated using the modified Weir formula (18): TMEE = 4184(5.5 VO_2 + 1.76 VCO_2); TMEE in kJ/day; VO_2 in L/min; VCO_2 in L/min).

Caloric intake

The patients were enterally and/or parenterally fed according to the current feeding protocol. The first 12-24 hours only a glucose infusion is given. After 24 hours nasoduodenal feeding is started. The amount of feeding is 25-50% of the needs for healthy children and is increased to 100% in 2-4 days. Parenteral feeding is given if enteral feeding is not possible to give and increased in 2-4 days. Fluid and electrolyte intakes are adjusted to individual requirements. The caloric intake at the day of measurement was recorded. The amount of caloric intake was corrected for extra protein calories of plasma infusions and/or albumin infusions on the day of measurement. Retrospectively the results of energy expenditure measurements were combined with the amount of calories given. Enteral feeding was given continuously with a nasoduodenal drip with standard soja-based formula (Nutrilon soja for children < 6 months, Nutrilon soja plus for children 6-12 months, 75% Nutrison soja and 25% water and 4% Fantomalt added for children 1-4 years, 90% Nutrison soja and 10% water and 4% Fantomalt added for children 4-10 years and Nutrison soja for children > 10 years of age Nutricia, Zoetermeer, The Netherlands). Parenteral feeding was given either by peripheral infusion or by a central venous line (Intralipid 20%, Pharmacia Upjohn Holland and Aminovenös N-paed 10%, Fresenius the Netherlands).

A RQ of the macronutrients administered (RQmacr) was obtained from the modified Lusk table after determining the carbohydrate to fat ratio for the total nonprotein calories of the infused regimen (20). The RQ was compared with the RQmacr. The RQ was assumed to approximate the RQmacr if RQ = RQmacr ± 0.05 (21). No correction was made for loss of carbohydrates and fat when enteral nutrition was given. This has to be taken into account when interpreting the results.

Urinary nitrogen excretion

Urine was collected on the day of measurement and analyzed for urinary urea nitrogen. In 23 patients a urinary bladder catheter was in place and urine was collected over a 24-hour period. In 13 patients a pediatric urine collector was used and urine was collected over a shorter period of at least 6 hours which value can be used to estimate a 24 hour period. This inconsistency has to be taken into account when interpreting the results. Total urinary nitrogen excretion (TUN) was defined as 1.25 x urinary urea nitrogen, in order to adjust for the 20% of urinary nitrogen loss as ammonia, creatinine, and uric and amino acids (22). No correction was made for nitrogen losses through stools, skin, wound, nasogastric suction, or blood sampling. Nitrogen balance (N-balance) was calculated with the following formula:
N-balance (mg/kg/day) = (protein intake/6.25) - (urinary urea nitrogen x 1.25).

Substrate utilization

Net substrate utilization was calculated from the measured values of VO_2, VCO_2 and nitrogen excretion according to previously published methods (23). The following formulas were used: protein utilization (g/min) = 6.25 x urinary urea nitrogen (N); fat utilization (g/min) = $1.67(VO_2 - VCO_2) - 1.92$ N; fat synthesis (g/min) = $1.67(VCO_2 - VO_2) + 1.92$ N; glucose utilization (g/min) in case of net fat utilization = $4.55VCO_2 - 3.21VO_2 - 2.87$ N; glucose utilization in case of net fat synthesis = $1.34(VCO_2 - 4.88$ N), where VO_2 is oxygen consumption in litres per minute (L/min), VCO_2 is carbon dioxide production in L/min and N is urinary urea nitrogen excretion in g/min. The RQ was calculated by the formula: VCO_2/VO_2

Statistical Analysis

Statistical analysis was performed with a statistical analysis software program (SPSS 7.0 for Windows 95, SPSS Software, Chicago, IL). Results are expressed as mean ± SEM, unless otherwise indicated. For comparisons between groups the independent-samples t-test was used. Pearson's correlation coefficient (r) was used to evaluate the relationship between RQ and the ratio caloric intake/TMEE, between RQ-RQmacr and the ratio caloric intake/TMEE, between TMEE and N-balance and between PRISM and TMEE.
A p-value of 0.05 or less was defined as statistically significant.

RESULTS

A total of 36 patients, 21 boys and 15 girls, with a wide range of clinical diagnoses fulfilled the entry criteria (Table 1). Their median age was 10 months (1 week -13 years). Median PRISM score was 7 (0-17). All patients were sedated with midazolam (0.05 - 0.3 mg/kg/hr) and/or morphine and muscle paralysis was present in 6 patients. Seven patients received inotropic drugs. There were no known gastro-intestinal absorption disturbances. The median day of

Table 1 Clinical Characteristics of Study Patients

Diagnosis	Age	Sex	Intake	VO_2	VCO_2	TMEE	RQ	TUN
Congenital heartdefect	0.25	M	177	6.8	6.2	202	0.92	137
Congenital heartdefect	0.25	M	332	6.9	5.7	201	0.82	76
Congenital heartdefect	0.5	M	404	7.9	6.6	230	0.84	248
RS bronchiolitis	0.75	M	247	8.1	6.9	237	0.85	68
Congenital heartdefect	1.0	F	385	7.6	7.7	231	1.02	150
Congenital heartdefect	1.0	F	353	7.7	6.8	228	0.88	184
Congenital heartdefect	1.25	F	260	7.7	7.2	232	0.93	344
RS bronchiolitis	1.5	M	203	6.5	5.6	193	0.86	147
Sepsis	1.75	M	272	8.2	6.3	237	0.77	196
Congenital heartdefect	2.0	F	412	8.5	7.6	252	0.90	126
Congenital heartdefect	2.5	F	222	7.2	6.4	214	0.89	130
Congenital heartdefect	3.0	F	472	8.8	8.6	266	0.98	244
Meningitis	3.0	M	235	6.6	5.5	192	0.84	144
RS bronchiolitis	5.5	M	193	7.9	7.0	233	0.89	202
Congenital heartdefect	7.0	M	283	7.1	6.0	208	0.85	229
RS bronchiolitis	8.0	M	450	8.7	8.9	266	1.02	334
RS bronchiolitis	9.5	M	237	6.0	5.9	183	0.98	219
Status asthmaticus	10.0	M	298	7.6	7.0	228	0.92	232
Subglottic stenosis	10.0	M	368	7.0	6.7	212	0.95	255
Sepsis	11.0	M	242	6.4	5.4	188	0.85	493
Subglottic stenosis	11.0	M	465	9.2	7.4	252	0.81	116
Subglottic stenosis	13.0	F	387	9.6	8.7	273	0.91	486
Pneumonia	14.5	M	227	9.0	8.2	267	0.92	443
Cardiomyopathy	18.0	F	68	7.6	5.9	218	0.77	198
Sepsis	18.0	M	220	8.9	7.2	253	0.81	323
Pneumonia	19.0	F	65	6.3	5.7	189	0.90	471
Sepsis	22.0	M	118	6.8	5.2	197	0.76	201
Subglottic stenosis	28.0	F	166	6.1	5.3	180	0.86	96
Upper airway obstruction	32.0	M	413	8.2	6.4	236	0.78	298
Upper airway obstruction	33.0	M	61	7.1	5.9	209	0.83	387
Sepsis	36.0	F	289	8.2	7.8	246	0.96	421
Subglottic stenosis	38.5	F	278	5.5	5.2	166	0.95	300
Pneumonia	46.0	F	90	5.7	4.5	165	0.79	160
Sepsis	53.0	F	209	8.3	6.4	233	0.77	310
Sepsis	54.0	F	262	6.1	5.6	183	0.92	429
Sepsis	162.0	M	22	5.4	4.2	156	0.78	346

Age, months; Intake, kJ/kg/day; VO_2, ml/kg/min; VCO_2, ml/kg/min; TMEE, kJ/kg/day; TUN, mg/kg/day

measurement after intubation was 3 days (range 0-15 days). Ventilatory characteristics were: mean FiO_2 0.32 ± 0.02, mean tubeleakage 7% ± 1%; 18 patients were on pressure regulated volume control, 17 on volume support and 1 patient on continuous positive airway pressure. Twenty-eight patients received enteral nutrition, 3 patients received only glucose infusion, 2 patients received total parenteral nutrition and 3 patients received a mixture of enteral and parenteral nutrition.

The TMEE per kg body weight showed a wide variation with a minimum value of 155 kJ/kg/day and a maximum of 272 kJ/kg/day. There was no correlation between the PRISM score and the TMEE (r=0.12, p=0.48).

The median TUN was 230 mg/kg/day (range 68 to 493 mg/kg/day). The N-balance was positive in 20 patients and negative in 16 patients (Table 2).

There was a significant relationship between the ratio caloric intake/TMEE and nitrogen balance (r=0.69, p<0.0001). There was no significant difference in TMEE in patients with a positive or with a negative N-balance (211 ± 8 vs 223 ± 7 kJ/kg/day, p=0.23). There was a significant difference between patients with a positive or negative N-balance for caloric intake (329 ± 21 vs 174 ± 22 kJ/kg/day), for the ratio caloric intake/TMEE (1.5 ± 0.1 vs 0.8 ± 0.1) and for the energy balance (106 ± 16 vs -37 ± 19 kJ/kg/day)(Table 2).

There was no significant difference in RQ between patients with a positive or negative N-balance (0.89 ± 0.02 vs 0.85 ± 0.02, p=0.19). In 2 patients with a positive N-balance the RQ was >1.0.

In 47% of the patients RQ approximated RQmacr, in 22% the RQ was above the RQmacr and in 31% the RQ was below the RQmacr. The ratio caloric intake/TMEE correlated significantly with RQ (r=0.44, p=0.007). Caloric intake/TMEE correlated slightly better with the difference of RQ-RQmacr (r=0.72, p<0.001).

Table 2 Substrate intake and utilization versus N-balance

	N-balance > 0	N-balance < 0	P-value
Caloric intake (kJ/kg/day)	329 ± 21	174 ± 22	<0.001
TMEE (kJ/kg/day)	223 ± 7	211 ± 8	0.23
Energy balance (kJ/kg/day)	106 ± 16	-37 ± 19	<0.001
Caloric intake/TMEE	1.5 ± 0.06	1.8 ±0.1	<0.001
CHO intake (mg/kg/min)	6.8 ± 0.5	4.8 ± 0.6	0.02
CHO utilization (mg/kg/min)	6.0 ± 0.6	4.4 ± 0.6	0.08
CHO balance (mg/kg/min)	0.8 ± 0.6	0.4 ± 0.3	0.60
Protein intake (g/kg/day)	2.2 ± 0.2	0.9 ± 0.2	<0.001
Protein utilization (g/kg/day)	1.2 ± 0.1	1.9 ± 0.2	<0.001
Protein balance (g/kg/day)	1.0 ± 0.1	-1.0 ± 0.3	<0.001
Fat intake (g/kg/day)	3.4 ± 0.2	1.1 ± 0.3	<0.001
Fat utilization(g/kg/day)	2.1 ± 0.3	2.1 ± 0.4	1.0
Fat balance (g/kg/day)	1.3 ± 0.4	-1.0 ± 0.5	0.001
RQ	0.89 ±0.02	0.85 ± 0.02	0.12

TMEE, total measured energy expenditure; CHO, carbohydrate; RQ, respiratory quotient

There was a significant difference in protein, fat and carbohydrate intake in patients with a positive and negative N-balance. Carbohydrate and fat utilization were not significant different in patients with a positive or negative N-balance but protein utilization was significantly higher in those with a negative N-balance. Protein and fat balance were significantly different between patients with a positive or negative N-balance (Table 2).

DISCUSSION

An accurate way to determine energy requirements is to measure energy expenditure by indirect calorimetry, which we performed in a group of 36 patients with a moderate severity of illness (indicated by low PRISM scores). We confirmed the finding of most studies on critical ill mechanically ventilated children that the measured energy expenditure shows a wide variation between individual patients. Due to this substantial interpatient variability there is a risk of under- and overfeeding in the individual patient. Providing an appropriate amount of calories in different disease states without over- or underfeeding is crucial for optimal patient care. No validated observations in ventilated children were done so far.

In order to provide an appropriate amount of calories, caloric intake should have to be individualized. In our study we showed that feeding according to or in excess of the TMEE could be a guideline because the ratio of caloric intake/TMEE was significantly higher in patients with a positive nitrogen balance (1.5 ± 0.06) as compared to those with a negative nitrogen balance (0.8 ± 0.1) ($p < 0.001$). The energy for growth, which is not included in the TMEE, should be taken into account when calculating the amount of feeding required. For healthy children in the first year of life 30-35% extra energy is needed but in the stressed patient this energy is less because growth will be diminished or even stopped (24).

The RQ reflects the percentage of fat and carbohydrate utilization. The apparent rates of substrates should be interpreted as net rates of "utilization". The apparent rate of carbohydrate oxidation is the sum of the rates of utilization for oxidation and for lipogenesis minus the rate at which carbohydrate is formed from amino acids. The apparent rate of fat oxidation is the difference between the rates of oxidation and synthesis from carbohydrate (25). This has to be taken into account when interpreting the RQ values. In the stressed patient however the RQ may plateau at levels <1.0 despite high levels of carbohydrate infusion because there is continued net utilization of fat for energy. In our study in 3 patients with a carbohydrate intake > 9 mg/kg/min a RQ of 0.98, 0.90 and 0.78 was measured. It is presumed that the glucose intake which is above glucose utilization result in conversion of glucose to glycogen and conversion of glucose in fat (26,27).

Hyperventilation, metabolic acidosis (with buffering of acid generating carbon dioxide), and overfeeding (leading to lipogenesis) may all increase RQ above RQmacr. Hypoventilation or underfeeding with mild starvation ketosis may decrease RQ below RQmacr. Comparison

of the RQ with the RQmacr can probably be helpful in the determination of under- and overfeeding (20,21). In our study in only 47% of the patients RQ approximated RQmacr, in 22% RQ was above the RQmacr suggesting overfeeding and in 31% RQ was below RQmacr suggesting underfeeding or catabolism. Furthermore there was a significant relation between the difference of RQ-RQmacr and the ratio caloric intake/TMEE ($r=0.72$, $p<0.001$). This means in case of a caloric intake which is lower than the TMEE a RQ lower than the RQmacr will suggest lipolysis and in case of a higher caloric intake than the TMEE a RQ higher than the RQmacr will suggest lipogenesis and overfeeding. The difference of RQ and RQmacr depends upon the accuracy with which both variables can be measured, for the RQ an accurate calorimeter is necessary in particular with increased FiO_2 above 0.60 (16).

In acute illness endogenous fat is the main fuel for energy. In 2 studies of mechanically ventilated children receiving only glucose infusion indirect calorimetry showed that relative energy contribution of fat was 53% and 78% respectively (fat utilization rate 2.7 and 4.8 g/kg/day) (7,9). In another study of mechanically ventilated head injured children, also receiving only glucose infusion, a fat utilization rate of 2.3 g/kg/day was measured.

In our study a fat utilization of 2.1 g/kg/day was measured both in patients with a negative and positive N-balance, the relative energy contribution of fat was 38% and 36% respectively. In our study there was a lower energy contribution of fat because not only glucose but also fat was given. The fat intake was significantly higher in patients with a positive N-balance compared with a negative N-balance (3.4 ± 0.2 vs 1.1 ± 0.3 g/kg/day) and these data suggests that in the patients with the negative N-balance endogenous fat was utilized and in patients with the positive N-balance fat storage would occur. It can be concluded that energy-substrate utilization patterns may differ markedly which depends on substrate intake.

In acute illness the accelerated net breakdown of body protein can be decreased by the use of a balanced glucose-lipid regimen as opposed to a glucose regimen. However it is extremely difficult to maintain or replenish body protein during catabolism (29,30,31). Furthermore there is an inability of many patients to efficiently utilize exogenous nutrients during severe catabolic illness which can lead to azotemia (29).

In our study the protein intake of patients with a positive N-balance (2.2 ± 0.2 g/kg/day) was significant higher ($p<0.001$) than in patients with a negative N-balance (0.9 ± 0.2 g/kg/day) but protein utilization was significant lower in the first group (1.3 ± 0.1 vs 2.2 ± 0.2 g/kg/day, $p<0.001$). The lower protein utilization of the first group can be explained by the higher protein intake of these patients and/or by the nitrogen sparing effect of a higher fat intake (glucose utilization were not significantly different in these two groups) (32). The median nitrogen excretion data of our patient group, 230 mg/kg/day (range 68 to 493 mg/kg/day), suggest that a provision of 1.4 g/kg/day of protein (0.4 to 3.1 g/kg/day) should be sufficient to approach nitrogen equilibrium. Previous studies have recommended a protein intake of 1.5 to 2.5 g/kg/day (33,34).

Conclusion

Measurement of the TMEE with indirect calorimetry will give an insight in the accurate energy needs of critically ill mechanically ventilated children. Feeding according to the TMEE is correlated with a positive nitrogen balance. A combination of RQ and RQmacr can be helpful in differentiating under- or overfeeding. Energy-substrate utilization patterns may differ markedly.

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Chapter 4

Energy expenditure and respiratory quotient in mechanically ventilated children

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Addendum to

Comparison of measured and predicted energy expenditure in mechanically ventilated children

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Energy expenditure and substrate utilization in mechanically ventilated children

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ABSTRACT

Introduction

Accurate assessment of energy expenditure provides important information for optimal nutritional support. The purpose of this study was: a) to measure energy expenditure in ventilated critically ill children and compare it with predicted energy expenditure, and b) to compare the respiratory quotient (RQ) with the ratio energy intake/measured energy expenditure and carbohydrate intake.

Methods

In 94 mechanically ventilated children, resting energy expenditure was measured by indirect calorimetry (MREE). The predicted resting energy expenditure (PREE) was calculated with currently recommended equations for healthy children and for critically ill children. Modified bland-Altman analysis and metabolic index [100*(MREE-PREE)/PREE] served to determine accuracy of prediction equations.

Results

None of the prediction equations reliably estimated measured energy expenditure in mechanically ventilated children. Schofield's equation based on weight and height showed the highest accuracy: it predicted energy expenditure within 10% of the MREE in 40% of the children. RQ was correlated with the ratio energy intake/measured energy expenditure and carbohydrate intake.

Conclusions

Prediction equations for energy requirements are not suitable for ventilated, critically ill children. Indirect calorimetry should be used to measure energy expenditure and RQ to accurately assess energy needs of the individual child and to guide nutritional therapy.

INTRODUCTION

Knowledge of energy requirements for critically ill children is essential for the provision of adequate nutrition to prevent the detrimental consequences of over- and underfeeding. Inadequate feeding can increase morbidity and mortality rates [1-2]. Adequate nutritional support can significantly improve physiological stability and outcome [2]. Furthermore, the goal of nutrition in critically ill children is not only to restore a normal functioning level but also to meet the requirements for growth and development.

Nutritional requirements for critically ill children vary widely between individuals. Therefore, measurement of energy expenditure is necessary to tailor optimal nutritional support. Indirect calorimetry is the method of choice to determine energy requirements. However, portable metabolic carts are not always routinely available, so most clinicians estimate energy expenditure using prediction equations [3]. Standard prediction equations are derived from indirect calorimetry measurements in healthy children. The relative difficulty of indirect calorimetry and the poor precision of standard predictive methods have challenged researchers to develop new equations derived from actual energy expenditure measurements of ventilated, critically ill children [4]. However, so far all developed predictive methods have failed to predict energy requirements with acceptable precision for clinical use in ventilated, critically ill children [5-11]. Details of the main studies comparing prediction equations with energy expenditure measurements by indirect calorimetry over the past 10 years are shown in Table 1.

Table 1 Study population characteristics: comparison of measured and predicted energy expenditure in ventilated children with various diagnoses

Author (Year)	Mean age year (range or ± SD)	Nr	Prediction Equation	MREE/ PREE	Mean Bias (kcal/day)	Bias (range or ± SD) (kcal/day)
White [4] 2000	4.5 ± 4.5	100	White I White II	-	-39 -37	-292 to 324 -342 to 398
Briassoulis [8] 2000	7 (0.1-18)	37	Schofield (W/H)	<0.9: 57% 0.9-1.1: 22% >1.1: 21%	-	-
Coss-Bu [11] 2001	5.5 (0.4-17)	33	Talbot	1.2 ± 0.7 (mean ± SD)	-	-
Hardy [7] 2002	4.5 (0-22)	52	Schofield (W)	1.3 0.9-1.1: 36%	-1	-382 to 390
Taylor [10] 2003	8.8 (0.8-16)	57	Schofield (W/H)	<0.9: 51% 0.9-1.1: 37% >1.1: 12%	-92	-484 to 300
Vazquez [9] 2004	4.2 ± 3.7	43	Schofield (W/H)	0.89	-	-
Oosterveld[21] 2006	4 (0-18)	46	Schofield (W/H)	1.0 95% CI (98-103)	-	-
Framson [6] 2007	5.2 (0-17)	44	Schofield (W/H)	<0.9: 22% 0.9-1.1:59% >1.1: 19%	-	-

MREE, measured resting energy expenditure; PREE, predicted resting energy expenditure

The study had a twofold aim: a) to compare measured energy expenditure in mechanically ventilated children with current available prediction equations for use in clinical practice, and b) to correlate the ratio actual caloric intake/measured energy expenditure and carbohydrate intake with the respiratory quotient.

MATERIALS AND METHODS

Patients

Children up to the age of 18 years admitted to our level III multidisciplinary pediatric/surgical ICU were eligible for the study when they met the following criteria: Mechanical ventilation with a Servo ventilator 300 (Siemens-Elema, Solna, Sweden); Inspired oxygen fraction (FiO2) less than 60%, tube leakage <10% (considered not to significantly affect the measurements; determined by comparing inspired and expired tidal volumes measured by the ventilator assuming an absence of air leaks in the patient-ventilator circuit)[12]; Hemodynamic stable condition (blood pressure and heart rate within 2 SD of age-related values)[13]. An exclusion criterion for this study was inclusion into a nutritional intervention study.

The institutional review board of the Erasmus MC approved the study protocol, and written (parental) informed consent was obtained before children entered the study. Clinical data collected included age, gender, weight, height, primary diagnosis, surgical status, days on mechanical ventilation, length of ICU-stay, route of nutritional support, and energy intake. Severity of illness on admission was assessed by the pediatric risk of mortality score (PRISM) [14].

Measured Resting Energy expenditure (MREE) and respiratory quotient (RQ)

Indirect calorimetry measurements were started as soon as technically possible after admission. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and RQ standardized for temperature, barometric pressure, and humidity were measured using the Deltatrac I MBM-100 and Deltatrac II MBM-200 (Datex Division Instrumentarium, Helsinki, Finland) metabolic monitor. Measured resting energy expenditure (MREE) was calculated with the modified Weir formula [15]. The properties of the Deltatrac metabolic monitor have been described previously [5]. Before each study the calorimeter was calibrated with a reference gas mixture (95% O2, 5% CO2, Datex Division Instrumentarium Corp.) The RQ was calculated from the measured oxygen consumption and carbon dioxide levels. Measurements lasted at least 2 hours.

Predicted Resting Energy Expenditure (PREE)

The PREE was calculated with the current equations for healthy children: the Schofield equations based on age and weight (W), the Schofield equations based on age, weight and height

(W/H) [16], and the WHO equations based on weight [17]. In addition, it was calculated with two prediction equations for ventilated critically ill children above 2 months of age; the White equations [4]. Details are provided in Table 2. Results are expressed in kilocalories per day. The PREE was compared with the MREE by means of the metabolic index [18]: [100*(MREE - PREE)/PREE]. The metabolic index represents the relation between MREE and PREE, expressed as a percentage. A negative value (<0) means the PREE overestimated the measured energy expenditure; a positive value (>0) reflects underestimation [18]. The proportion of each PREE falling within 10% of MREE was also used to evaluate prediction accuracy. Based on clinical experience and implicit standards in prior studies we judged that a prediction method capable of predicting within 10% of MREE in the majority of patients would be clinical useful. Other authors use the ratio of MREE/PREE for defining a hypo- or hypermetabolic response: whenever MREE is >110% of PREE of healthy children (for this purpose we used the Schofield (W/H) equation), children are defined as hypermetabolic: when <90%, they are defined as hypometabolic [19].

Table 2 Standard equations used to predict resting energy expenditure in children (kcal/day).

Equation	0-3 year	3-10 year	10-18 year
Schofield (W/H)	0.2 x W + 1516.7 x L - 681,8 (M) 16.3 x W + 1022.7 x L – 413.3 (F)	19.6 x W + 130.2 x L + 414,7 (M) 17,0 x W + 161.7 x L + 371.0 (F)	16.2 x W + 137.1 x L + 515.3 (M) 8.4 x W + 465.4 x L + 200.0 (F)
Schofield (W)	(59.5 x W)–30.3 (M) (58.3xW)-31.1 (F)	(22.7xW)+504 (M) (20.3xW)+486 (F)	(17.5xW)+658 (M) (13.4xW)+692 (F)
WHO	(60.9xW)-54 (M) (61xW)-51 (F)	(22.7xW)+495 (M) (22.5xW)+499 (F)	(17.5xW)+651 (M) (12.2xW)+746 (F)
White I (for children >2 months)	[(20 x age) + (31 x W) + (151 x waz score) + (279 x body temperature) + (122 x days ICU) – 9200 + 0 (head injury) or + 105 (post surgical procedure) or -512 (respiratory illness) or + 98 (other) or – 227 (sepsis)] /4184 Age in months; body temperature in °C; days ICU, the number of days since ICU admission, if >4 then multiply by 4		
White II (for children >2 months)	[(17 x age) + (48 x weight) + (292 x body temperature) – 9677]/4184 Age in months, body temperature in °C		

Schofield (W/H) or (W), Schofield prediction equation based on weight and height or weight; WHO, World Health Organization; Kcal, kilocalories; W, weight in kg; L, length in meters; M, male; F ,female; waz score, weight for age Z score; ICU, intensive care unit

Energy intake

Children were enterally and/or parenterally fed on the guidance of the current feeding protocol as described previously [20] and the judgement of the physician clinically responsible for the individual child, independent of the study. Enteral feeding was started as soon as possible in all patients, either continuously or intermittently through a nasogastric tube (drip or bolus) or nasoduodenal tube (drip). It consisted of human milk or standard formula according to parents' preference. Parenteral feeding was given either by peripheral infusion or by a central venous line. Fluid and electrolyte intakes were adjusted to individual requirements.

Actual total daily energy, carbohydrate and fat intake were derived from patient records on the day of calorimetry.

Statistical analysis

Statistical analyses were performed using SPSS 16.0 for Windows, SPSS software (Chicago, III., USA). Results are expressed as median and range. Spearman's correlation, the metabolic index and modified Bland and Altman comparison served to evaluate the relation between MREE and prediction equations. The mean percentual difference between MREE and PREE represents the performance bias. Two-tailed P-values <0.05 were considered significant.

RESULTS

Clinical Characteristics

The group consisted of 94 children, 51 boys, admitted to the PICU of the Erasmus MC - Sophia Children's Hospital. Key clinical characteristics are shown in Table 3. Median age was 0.46 (0.01-15.2) years, including 63% of the children < 1 year of age. Twenty-two per cent of the children was classified as malnourished (SD-score for WFH<-2.0). The median day of measurement was 2 days (0-69 days) after PICU admission and 2 days (0-15 days) after intubation. All children were on mechanical ventilation and sedated with midazolam and/or morphine. Nine children were treated with neuromuscular blocking agents and 19 children received inotropic drugs. Ventilatory characteristics were as follows: median tube leakage was 4% (0-17), 60 children were on PRVC, 32 on volume support, and 2 on other ventilatory support. There were no known gastrointestinal absorption disturbances. Forty-two children were on full enteral nutrition, 17 on total parenteral nutrition, 28 on a mixture of enteral and parenteral nutrition, and 7 children received only glucose infusion.

Table 3 Patient characteristics

Variable	Number	Median (range)
Gender (M/F)	51/43	
Age (years)		0.46 (0.01-15.2)
Weight (kg)		5.8 (2.3-60.0)
WFH SD score		-0.24 (-4.39-3.14)
PRISM		9 (0-33)
Diagnostic groups:		
Congenital anomalies	10	
Post-operative monitoring	14	
Sepsis or meningitis	16	
Respiratory illness	28	
Cardiac illness	17	
Other	9	

M, male; F, female; WFH SD score, weight for height SD score, PRISM, pediatric risk of mortality.

Comparison of Predicted and Measured Resting Energy Expenditure

For the total population, median MREE was 50 kcal/kg (20-67 kcal/kg), and median RQ was 0.89 (0.67-1.07). The results of predictive energy expenditure calculations in relation with MREE are shown in Table 4. The correlation coefficients between MREE and predictive equations varied between 0.51 and 0.97. The median metabolic index for the different equations ranged from -0.2% to -23%. The Schofield equation (W/H) showed the highest accuracy; it predicted energy expenditure within 10% of the MREE in 40% of the children. Thirty-one percent of the children were classified as hypermetabolic and 29% as hypometabolic. Bland-Altman comparison of MREE and PREE by Schofield (W/H) showed a mean percentual bias of -1.0% and a precision (±1 SD of bias) of 20.7% (Figure 1). The ratio of MREE divided by PREE (using Schofield (W/H) did not differ between the diagnostic groups nor between surgical and non-surgical children. The metabolic index correlated positively with the Z-score for weight for height (r=0.49, p<0.001).

Table 4 Comparison of measured energy expenditure (MREE) and predicted energy expenditure (PREE) in ventilated critically ill children

Prediction Equation	PREE Median (range)	Correlation PREE and MREE (p-value)	[(MREE-PREE)/ PREE]*100% Median (range)	% of children within 10% of MREE
Schofield (W/H)	312 (96-1731)	0.96 (<0.001)	-0.2 (-45 to 76)	40
Schofield (W)	312 (104-1720)	0.97 (<0.001)	-0.9 (-42 to 42)	36
WHO	301 (84-3112)	0.97 (<0.001)	2.5 (-46 to 57)	33
White I (infants<2 mo excluded)	477 (28-8629)	0.51 (<0.001)	-19 (-93 to 705)	16
White II (simplified) (infants <2 mo excluded)	392 (233-1776)	0.93 (<0.001)	-23 (-73 to 42)	19

RQ measurements

For the total population, median RQ was 0.89 (0.67-1.07). RQ was >1.0 in seven children. These seven children had a significantly higher carbohydrate intake than those with a RQ ≤1.0 (9.1 vs 5.1 mg/kg/min, p<0.001). The RQ was also positively correlated with the ratio energy intake/MEE (r=0.45, p<0.001) and carbohydrate intake (r=0.51, p<0.001) (Figure 2).

DISCUSSION

This study shows that all predictive methods fail to reliably estimate measured energy expenditure in mechanically ventilated children. Although all prediction equations were significantly correlated with measured energy expenditure, the metabolic indices showed wide ranges and lack of agreement. This is in accordance with previous studies [5-11]. Schofield's

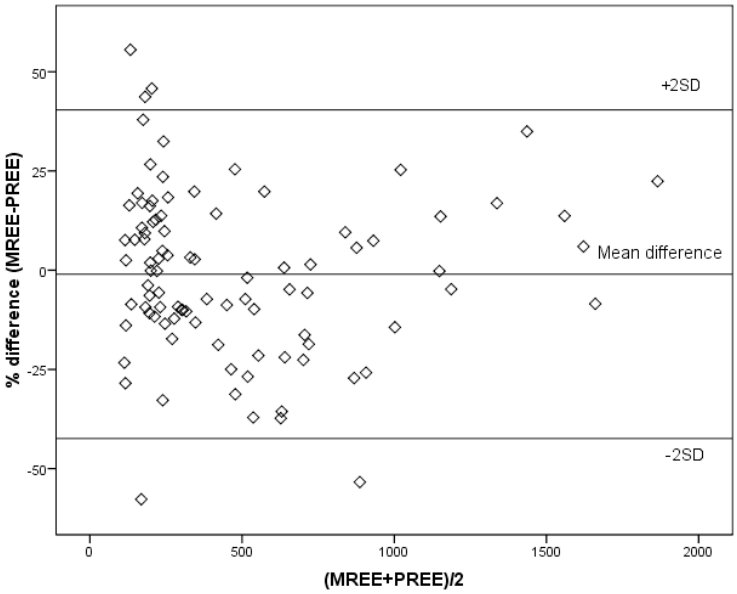

Figure 1. Modified Bland-Altman plot of comparison between measured energy expenditure (MREE) using indirect calorimetry and predicted energy expenditure (PREE) using the Schofield (W/H) equation. The Y-axis, shows the percentual difference between MREE and PREE. A lack of agreement exists between individual predicted energy expenditure and measured energy expenditure values as indicated by the wide 2SD range (-39.4% to 40.4%). The mean values of PREE and MREE are presented in kcal/day.

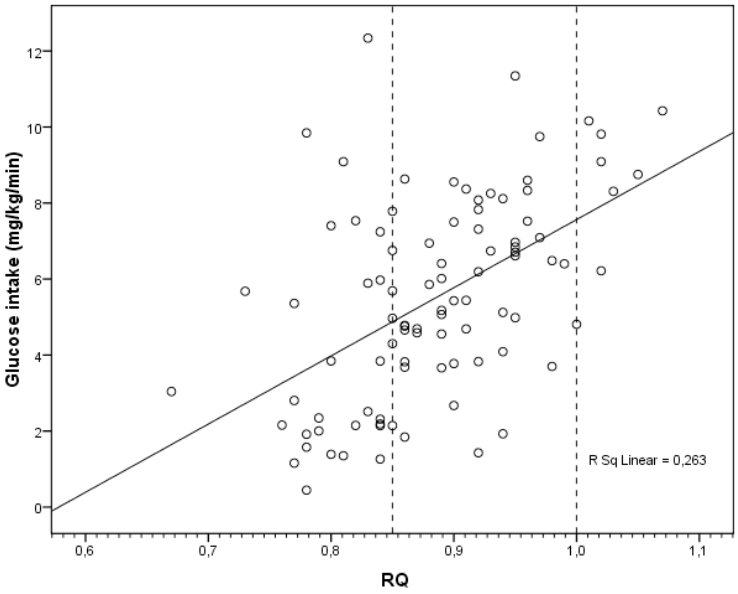

Figure 2. Relation between glucose intake and RQ.

equation (W/H) showed the highest accuracy, as it predicted energy expenditure within 10% of the MREE in 40% of the children. Like in previous studies, Schofield's equation (W) was second best, with 35% of the predictions within 10% of the MREE [6-7]. The two equations developed by White et al. for critically ill mechanically ventilated children yielded the lowest accuracies [4]. The accuracy of the first White (I) equation, derived from 6 patient variables (age, weight, weight for age Z-score, body temperature, number of days after PICU admission and primary reason for admission) was only 16%; that of the simplified version (White II) was 19%. PREE according to the White equations overestimated MREE in most children, which was in accordance with a previous report [6].

There may be several reasons for the inaccuracy of the White equations. One concerns the primary reason for admission: White et al. found the highest MREE in postoperative children, and the lowest MREE in children with respiratory illness. In the present study, however, and in accordance with others, there was no significant difference in MREE between different diagnostic groups with different severity of illness (expressed by PRISM score) or between surgical and medical patients [4,6,8,19,21-23]. Only after severe traumatic brain injury and severe burn injury a hypermetabolic response is reported in the majority of children [22, 24-25]. Second, White used clinical estimations of weight [4], which have been shown to be very unreliable [2]. Some have argued to use ideal body weight for predictive equations [26]. Vazquez-Martinez et al. showed that use of the ideal weight resulted in a higher PREE, but not in improvement of the accuracy of the prediction equations tested [9]. Moreover, actual measured body weight does not always reflect true body mass either, since measured weights are often skewed by edema and rapid loss of lean body mass in the beginning of disease.

However, like White et al. reported, there is a rationale for the use of the Z-score for weight for age in prediction equations for PREE, as it was positively correlated with MREE [4, 8, 27]. MREE will be decreased in children with a low Z-score, because of decreased muscle cell mass. Third, the use of number of days after intensive care admission in the White equation is another questionable parameter as serial measurements of energy expenditure during PICU admission showed no change in energy expenditure over time [6, 8, 21, 28], this will be discussed below. And finally fourth, in both the original White and the simplified White equation the addition of the temperature variable is presumed to increase accuracy. White et al. showed that body temperature was significantly correlated with MREE [4]. Previous studies have shown a 6-12% increase in MREE per degree of increase in body temperature in individual critically ill infants and children [10, 29-30]. However, taking temperature into account will not increase accuracy of a general prediction equation, because the increase in energy expenditure caused by increase in temperature occurs relative to a patient's "baseline" MREE.

Overall, in our study 29% of the children were defined as hypometabolic, 40% as normometabolic and 31% as hypermetabolic based on MREE in comparison with PREE according to Schofield (W/H). This distribution is consistent with previous studies in critically ill children [6, 8-9]. Hypermetabolism in critically ill children is not as frequent as in adults, probably

owing to re-channeling of energy normally used for growth toward energy needs caused by the acute disease state. There are several other reasons for the prevailing hypo- or normometabolic response in critically ill children. Mechanical ventilation decreases the work of breathing, sedation and muscle relaxants decrease physical activity, and continuous feeding as well as treatment in a temperature controlled environment also reduce energy expenditure. Furthermore, it is often assumed that critically ill children resemble adults in their metabolic response to critical illness, showing phases of hypometabolism (Ebb phase) and hypermetabolism (Flow phase). However, serial measurements of energy expenditure during PICU admission showed no change in energy expenditure over time [6, 8, 21, 28]. It is possible that energy expenditure measurements were performed too late to recognize the relative short Ebb phase in critically ill children. Only two studies have evaluated energy expenditure in the first hours after elective surgery. Although a temporary increase in MREE was reported in the first 2-4 hours after surgery, there was no preceding hypometabolic (Ebb) phase in both studies [9, 31]. The lack of intraindividual variation in MREE facilitates monitoring of energy expenditure.

From a clinical viewpoint a single measurement of energy expenditure by indirect calorimetry early during admission may serve to assess the energy needs of the individual child and guide nutritional therapy. An optimal feeding regimen would be defined as a feeding protocol enabling the early restoration of nutritional losses and aiming at achieving normal growth rates. Therefore, caloric amounts should equal the measured energy expenditure in the acute metabolic stress period [32], thereafter energy intake should be increased to account for tissue repair and growth. In the majority of critically ill children, the acute metabolic stress period typically lasts no more than 1 or 2 days. It is not clear, however, how soon energy intake can be increased without the risk of overfeeding [33]. An energy intake of 1.4-1.5 times MREE was suggested to be optimal [28, 34], whereas others considered an energy intake of 1.1 times MREE as overfeeding [35]. Also RQ has been proposed to identify carbohydrate overfeeding (RQ>1.0) and to exclude underfeeding (RQ>0.85). Consistently, we showed that carbohydrate intake in children with a RQ>1.0 was significantly higher than in those with a RQ≤1.0. On the other hand, a high amount of carbohydrates will not always result in a RQ>1.0 (Figure 2), because in the critically ill child there can be ongoing oxidation of fat for energy, resulting in an RQ <1.0.

The question remains whether a prediction equation might be the best alternative to assess energy needs when indirect calorimetry is not possible. If we would have used Schofield's equation (W/H) in the acute phase of illness, energy intake of 30% of the children would have been too low. As pointed out above, energy intake should be increased in 1 or 2 days to account for growth and tissue repair. Increases should be tailored to prevent excessive carbohydrate, protein and fat intakes. Carbohydrate intake can be monitored by serial RQ measurements and blood glucose levels to prevent hyperglycemia. Protein and fat intakes can be monitored by determination of the blood content of urea and trigycerides [36]. The

optimal energy intake after the initial phase of acute illness might be as high as the recommended intake for healthy children [20].

Conclusion

We demonstrated that equations for predicting energy requirements are not suitable for ventilated, critically ill children. These children were frequently hypo- or normometabolic during the first days of PICU admission. Our findings support the use of indirect calorimetry in the individual patient for measurement of energy expenditure early after admission followed by serial RQ measurements. This will lead to greater accuracy and can help avoid under- and overfeeding.

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PART II

HYPERGLYCEMIA

A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty (***Winston Churchill***)

Chapter 5

Pathophysiological aspects of hyperglycemia in children with meningococcal sepsis and septic shock; a prospective, observational cohort study.

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Critical Care (provisionally accepted for publication)

ABSTRACT

Introduction

Children with meningococcal disease show considerable morbidity. Better understanding of pathophysiological mechanisms will improve outcome. The objective of this study was to investigate the occurrence of hyperglycemia and insulin response in critically ill children with meningococcal disease. Setting: Intensive Care Unit in academic children's hospital.

Methods

Seventy-eight children with meningococcal disease were included. The group was classified into shock non-survivors, shock survivors and sepsis survivors. The course of laboratory parameters during 48 hours was assessed. Insulin sensitivity and β-cell function on admission were investigated by relating blood glucose levels to insulin levels and C-peptide levels and by homeostasis model assessment (HOMA).

Results

On admission, hyperglycemia (glucose >8.3 mmol/l (>150 mg/dl)) was present in 33% of the children. Shock and sepsis survivors had higher blood glucose levels compared with shock non-survivors. Blood glucose level on admission correlated positively with plasma insulin, C-peptide, cortisol, age and glucose intake. Multiple regression analysis revealed that both age and plasma insulin on admission were significantly related to blood glucose. On admission 62% of the hyperglycemic children had overt insulin resistance (glucose >8.3 mmol/l and HOMA-%S <50%); 17% had decreased β-cell function (glucose >8.3 mmol/l and HOMA-%B <50%) and 21% had both insulin resistance and decreased β-cell function. Hyperglycemia was present in 11% and 8% of the children at 24 and 48 hours after admission, respectively.

Conclusions

Children with meningococcal disease often show hyperglycemia on admission. Both insulin resistance and decreased β-cell function play a role in the occurrence of hyperglycemia. Normalization of blood glucose levels occurs within 48 hours, typically with normal glucose intake and without insulin treatment.

INTRODUCTION

Critical illness is associated with many endocrine and metabolic changes, including changes in the glucose homeostasis [1-7]. Both hypoglycemia and hyperglycemia may lead to adverse outcome as expressed in length of pediatric intensive care unit (PICU) stay and mortality rates [6-16].

A follow-up study in patients who survived meningococcal septic shock in childhood showed that severe mental retardation was associated with hypoglycemia during admission [17]. Children who died from meningococcal septic shock appeared to have significantly lower levels of blood glucose on admission to the PICU than those who survived, in whom levels were moderately increased [4-5]. The most severely ill children had signs of (relative) adrenal insufficiency on admission. Deficiency of substrate, reduced activity of adrenal enzymes due to endotoxins, cytokines or medication and shock with disseminated intravascular thrombosis can cause necrosis of the adrenal glands resulting in (relative) adrenal insufficiency in children with meningococcal disease [5].

Many children with meningococcal septic shock suffer from hyperglycemia [12, 18-19]. The pathophysiological mechanism leading to hyperglycemia in critically ill children with meningococcal disease may be different from adults. Recently, it was shown that the acute phase of sepsis in children is quite different from adults [18]. It was suggested that hyperglycemia associated with β-cell dysfunction rather than insulin resistance may be the normal pathophysiological response in children with meningococcal septic shock. It was also suggested that treatment of hyperglycemia with exogenous insulin may not be supportive and may even be potentially detrimental in critically ill children [18].

Better insight into pathophysiological mechanisms leading to hyperglycemia is crucial to improve treatment strategies. The gold standard for quantifying insulin sensitivity in vivo is the hyperinsulinemic euglycemic clamp technique [20]. This is a complex and invasive technique, and therefore not easily applied in studies with critically ill children. The search for uncomplicated and inexpensive quantitative tools to evaluate insulin sensitivity has led to the development of other assessments. The fasting glucose-to-insulin ratio and homeostasis model assessment (HOMA) of insulin resistance have been proven to be useful estimates of insulin sensitivity, also in critical illness [21-24]. There is a good correlation between estimates of insulin resistance derived from HOMA (HOMA-%S) and from the hyperinsulinemic euglycemic clamp [24]. The assessment of β-cell function is difficult because the β-cell response to the secretory stimuli is complex. There is no gold standard for β-cell function. The HOMA method for assessing β-cell function (HOMA-%B) is based on measurements of fasting insulin or C-peptide concentration to calculate pre-hepatic insulin secretion in relation with blood glucose levels [24]. The objective of the present study was to investigate the occurrence of hyperglycemia in relation with the insulin response and exogenous factors, such as glucose intake and drug use, in a homogenous group of critically ill children with meningococcal sepsis and/or meningococcal septic shock.

MATERIALS AND METHODS

Patients

The study population consisted of previously healthy children admitted to the PICU of the Erasmus MC-Sophia Children's Hospital between October 1997 and May 2004, suffering from meningococcal sepsis, i.e. sepsis with petechiae/purpura. Sepsis was defined as body temperature of less than 36.0°C or more than 38.5°C with tachycardia and tachypnea [5]. Children were determined to have septic shock if they had persistent hypotension or evidence of poor end-organ perfusion, defined as at least two of the following: a) unexplained metabolic acidosis (pH <7.3 or base excess <-5 mmol/l or plasma lactate levels >2.0 mmol/l); b) arterial hypoxia (PO_2 <75 mm Hg, a PO_2/FiO_2 ratio <250 or transcutaneous oxygen saturation <96%) in patients without overt cardiopulmonary disease; c) acute renal failure (diuresis <0.5 ml/kg/h for at least one hour despite acute volume loading or evidence of adequate intravascular volume without pre-existing renal disease); or d) sudden deterioration of the baseline mental status [5].

Children were not eligible for the study if they had pre-existing diabetes mellitus or had received radiation or chemotherapy within the previous 6 months. Thirty-five of the included 78 children participated in a randomized, double-blinded, placebo-controlled study. They received either placebo or activated protein C concentrate (APC) starting after admission, every 6 hours for the first days of admission, and next every 12 hours to a maximum of 7 days [19]. APC is assumed not to influence the endocrine and metabolic assays [5]. The Erasmus MC Medical Ethics Review Board approved the study and written informed consent was obtained from the parents or legal representatives.

Clinical parameters

Disease severity was assessed by the pediatric risk of mortality (PRISM II) score on day of admission [25]. Glucocorticoid administration, inotropic medication, and use of mechanical ventilation were recorded. Equivalent doses of prednisolone, expressed per body weight (mg/kg) were calculated, using the glucocorticoid equivalents of 20/5/0.75 mg for hydrocortisone, prednisolone and dexamethasone, respectively. Inotropic support was quantified by the vasopressor score developed by Hatherill et al. [26]

Nutrition

The children were fed enterally and/or parenterally according to a standard feeding protocol as previously described [27]. If enteral feeding could not be started on the second day, parenteral feeding was started. On admission at the PICU glucose was administered at a rate of 2-6 mg/kg/min, depending on weight. The initial dose of proteins was 1.0 g/kg/day and that of lipids 1.0 g/kg/day. If clinically possible, nutrition was adjusted to the normal needs according to dietary reference intakes for healthy children on days 3 and 4.

Collection of blood and assays

Arterial blood samples for the determination of blood glucose levels and plasma levels of insulin, C-peptide, cortisol, cytokines, C-reactive protein (CRP), lactate and free fatty acids (FFA) were collected on admission and at 24 and 48 hours thereafter. Assays were used according to manufacturer's instructions. Arterial glucose and lactate were determined on blood gas analyzer (ABL 625, Radiometer, Copenhagen, Denmark). Hypoglycemia was defined as a blood glucose level ≤2.2 mmol/l (≤40 mg/dl), and hyperglycemia as a blood glucose level >8.3 mmol/l (>150 mg/dl)[28]. The reference level for lactate was <2.0 mmol/l. Serum insulin was measured by a two-site chemiluminescent immunometric assay (Immulite 2000, DPC, Los Angeles, USA) with minimum detection level of 35 pmol/l and maximum fasting reference value of 180 pmol/l. Serum C-peptide was measured by a chemiluminescent immunometric method (Immulite 2000, Siemens, Los Angeles, CA). For children under the age of 13 years the reference interval ranged between 0.2 and 2.6 nmol/l (0.6 – 7.8 ng/ml) and for children older than 13 years between 0.4 and 2.6 nmol/l (1.3 – 7.9 ng/ml) [29]. Serum cortisol concentrations were determined with a competitive luminescence immunoassay (Immulite 2000, DPC, Los Angeles, CA). The detection limits of this assay are: 3-1380 nmol/l. Adrenal insufficiency in case of catecholamine-resistant septic shock is assumed at a random total cortisol level <496 nmol/l (<18 mcg/dl) [30]. FFA was determined by enzymatic method (Nefac-kit, Eako, Instruchemie BV). CRP was determined by immunoturbidimetric assay (normal <2 mg/l), and examined on a 912 analyzer (Roche Molecular Biochemicals, Mannheim, Germany). Cytokine levels were analyzed with an enzyme-linked immunosorbent assay (Sanquin, Amsterdam, The Netherlands). The detection limit of interleukin-6 (IL-6) (lowest positive standard) was: 10 pg/ml. The detection limit of tumor necrosis factor-a (TNF-α) was: 5 pg/ml [31].

Outcome measurements

The total sample was divided into three groups: shock non-survivors, shock survivors and sepsis survivors, as we have previously reported striking differences in endocrinological and metabolic responses between survivors and non-survivors [5]. The courses of the main endocrinological, metabolic and immunological laboratory parameters during the first 48 hours of PICU stay were assessed.

The insulin response to hyperglycemia was assessed by investigating insulin response to glucose, and by HOMA modeling [24]. The updated HOMA2 computer model was used to determine insulin sensitivity (%S) and β-cell function (%B) from paired plasma glucose and insulin and C-peptide concentrations on admission. Children were considered to be fasting until admission with subsequently only a continuous glucose infusion without enteral intake for more than 6 hours. Determinations of insulin sensitivity and β-cell function were made on admission only.

Statistical analysis

Analysis was performed with the SPSS statistical software package for Windows (version 16.0; SPSS inc., Chicago, USA). Results are expressed as medians and interquartile range, unless specified otherwise. Between-group comparisons were made using the Mann-Whitney U test for continuous data. Chi-square test was used for comparison of nominal data. Spearman's correlation coefficient was used to evaluate the relationship between different parameters. Multiple linear regression analysis was applied to evaluate the relationship between admission hyperglycemia and various variables. Data were log-transformed for multiple linear regression analysis when necessary. P-values less than 0.05 are considered as statistically significant.

RESULTS

Patient characteristics (Table 1)

Seventy-eight children (32 female) admitted to our PICU with meningococcal disease were included. Their median age was 3.5 years (1.6-9.4 years). Blood cultures revealed Neisseria meningitidis in 65 children, 13 children were diagnosed as having meningococcal disease based on their typical clinical picture. Sixty-seven children were classified as having meningococcal septic shock and 11 as meningococcal sepsis. Nine children with shock died within 24 hours after PICU admission, 1 child with shock died within 48 hours.

The total sample was classified into three groups: shock non-survivors (n=10), shock survivors (n=57) and sepsis survivors (n=11). All children with sepsis survived. Shock non-survivors were significantly younger than shock survivors and sepsis survivors ($p<0.01$). Shock survivors stayed a median 4.1 days (2.7-8.9 days) in the PICU; sepsis survivors a median of 1.1 days (1.0-1.9 days) ($p<0.001$).

Clinical parameters (Table 1)

Median PRISM score was 20 (14-29). PRISM scores and IL-6 levels for shock non-survivors were significantly higher than those for both groups of survivors ($p<0.001$), and those for shock survivors were significantly higher than those for sepsis survivors ($p<0.001$). APC administration did not influence cortisol levels nor coagulation profile (data not shown). Concomitant therapy included antibiotics and administration of fluids in all children. Forty-nine children were mechanically ventilated and 69 children received inotropic support. Thirty-five children were intubated with a single dose of etomidate. Indications for steroid use were catecholamine-resistant septic shock, with or without hypoglycemia, and meningitis. Nine children received glucocorticoids (hydrocortisone or dexamethasone) just before admission to the PICU; 8 of them had catecholamine-resistant septic shock and one had sepsis with meningitis. During admission, another 6 children with septic shock received steroids

(hydrocortisone), because of catecholamine resistant septic shock . One child experienced severe hyperglycemia (glucose >20 mmol/l (>360mg/dl)) after PICU admission, was treated with insulin and excluded from further analysis after admission. The other children did not receive insulin treatment.

Table 1. Patients' characteristics on admission.

	Shock non-survivors	Shock survivors	Sepsis survivors
Number	10	57	11
Sex (F/M)	2F/8M	24F/33M	6F/5M
Age (years)	1.1 (0.6-2.2) *bc	4.1 (1.8-9.3)*a	6.1 (2.8-11.4)*a
PRISM	31 (25-35)**bc	21 (16-28)**ac	9 (8-11)**ab
Inotropic medication (n,%)	10 (100%)	57 (100%)	2 (18%)
Vasopressor score	3 (3-3)	2 (1-3)	0 (0-1)
Mechanical ventilation (n,%)	10 (100%)	37 (65%)	2 (18%)
Steroid treatment (n,%)	2 (20%)	6 (11%)	1 (9%)
Prednisolone equivalents (mg/kg)	0.9 (0.2-1.6)	2.4 (0.6-4.5)	1.0
Glucose intake (mg/kg/min)	3.3 (0-5.8)	3.9 (1.4-5.0)	1.1 (0.6-3.1)

Data expressed as median (25-75 percentile).

F = female, M = male, PRISM = pediatric risk of mortality score, vasopressor score developed by Hatherill et al.[26]

* $p < 0.05$, ** $p < 0.001$

[a] = compared to shock non-survivors, [b] = compared to shock survivors, [c] = compared to sepsis survivors

Nutrition; glucose intake (Table 1)

On admission, median glucose intake was 2.8 mg/kg/min (1.0-5.0 mg/kg/min), which was not significantly different between shock non-survivors, shock survivors and sepsis survivors. Twenty-four hours after admission, median glucose intake in shock survivors was 5.2 mg/kg/min (4.3-6.4 mg/kg/min); 48 hours after admission it was 4.4 mg/kg/min (3.7-6.3 mg/kg/min). Most sepsis survivors were on a partial oral diet at 24 hours after admission, which made it difficult to calculate the exact glucose intake.

Blood analysis

Time course (Table 2)

On admission, 26 of the children (33%) were hyperglycemic; 1 shock non-survivor, 19 shock survivors and 6 sepsis survivors. One child (a shock survivor) was hypoglycemic. In general, shock survivors and sepsis survivors had significantly higher blood glucose levels on admission compared to shock non-survivors. Hyperglycemia was present in 5 shock survivors and 1 shock non-survivor after 24 hours (11%) and in 3 shock survivors after 48 hours (8%). Cortisol and cytokine levels decreased to normal levels within 24 hours.

Table 2. Glucose, insulin, C-peptide, cortisol, FFA, lactate, CRP and cytokines on admission (T_0), at 24 (T_{24}) and at 48 hours (T_{48}).

	Shock non-survivors	Shock Survivors			Sepsis Survivors	
	T_0 (n=10)	T_0 (n=57)	T_{24}# (n=48)	T_{48}# (n=36)	T_0 (n=11)	T_{24} (n=6)
Glucose	4.9*[bc] (2.7-7.0)	7.2*[ac] (5.3-9.0)	6.7 (5.9-7.8)	5.9 (5.3-6.6)	8.8*[ab] (7.5-10.5)	6.6 (4.7-7.1)
Insulin	<35*[bc] (<35-57)	101*[a] (35-197)	111 (71-169)	89 (61-157)	104*[a] (52-226)	136 (51-236)
C-peptide	-	1.1 (0.6-2.7)	2.0 (1.0-3.0)	1.5 (1.0-1.9)	1.0 (0.5-1.8)	1.7 (1.0-2.6)
Cortisol (no glucocorticoids)	615*[bc] (510-930)	954*[a] (713-1241)	603 (430-1409)	554 (501-927)	1140*[a] (1066-1409)	447 (263-657)
FFA	0.3 (0.2-0.5)	0.8 (0.5-1.1)	0.6 (0.4-0.8)	0.3 (0.3-0.6)	0.6 (0.5-0.7)	0.5 (0.4-0.7)
Lactate	6.8**[bc] (5.1-8.0)	3.7**[ac] (2.6-5.4)	2.0 (1.5-2.8)	1.6 (1.2-2.3)	2.1**[ab] (1.6-2.7)	0.8 (0.7-0.9)
CRP	34 *[b]*[c] (23-41)	89*[a] (59-131)	229 (181-274)	223 (159-301)	75**[a] (36-191)	236 (195-273)
IL-6	$120x10^4$**[bc] ($70-160x10^4$)	$3.5x10^4$**[ac] ($1-16x10^4$)	$0.02x10^4$*[c] ($0.01-0.2x10^4$)	$0.01x10^4$ ($0.003-0.03x10^4$)	$0.04x10^4$**[ab] ($82-1x10^4$)	17*[b] ($<10-0.02x10^4$)
TNF-α	42**[b] (20-127)	6**[a] (<5-10.5)	4 (1-12)	-	-	3 (1-10)

Children who received steroids before or on admission were excluded for determination of median cortisol levels

Data expressed as median (25-75 percentile) Glucose (mmol/l), Insulin (pmol/l), C-peptide (nmol/l), Cortisol (nmol/l), FFA, Free Fatty Acids (mmol/l), Lactate (mmol/l), IL-6 (pg/ml), TNF-α (pg/ml) CRP = C-reactive protein (mg/l)

MSS=meningococcal septic shock, MS=meningococcal sepsis

* p< 0.05, **p<0.001

[a] = compared to shock non-survivors, [b] = compared to shock survivors, [c] = compared to sepsis survivors

one patient with insulin therapy excluded

Insulinemic response

Association between glucose and insulin

In figure 1 the association between glucose and insulin levels is shown for the three groups. Hyperglycemic children had significant higher insulin levels (214 pmol/l (128-375 pmol/l)) and C-peptide levels (1.9 nmol/l (0.8-3.7 nmol/l)) than normoglycemic children (insulin 57 pmol/l (18-101pmol/l)), C-peptide 0.7 nmol/l (0.3-1.6 nmol/l), p<0.001 and p=0.02, respectively).

Influence of glucose infusion on insulinemic response

Because blood glucose levels and endogenous insulin production are related to exogenous glucose administration, we assessed intravenous glucose infusion rates at the times when blood glucose and insulin levels were drawn (figure 2). All children received parenteral glucose infusions without enteral intake on admission. Glucose intake rates were not signifi-

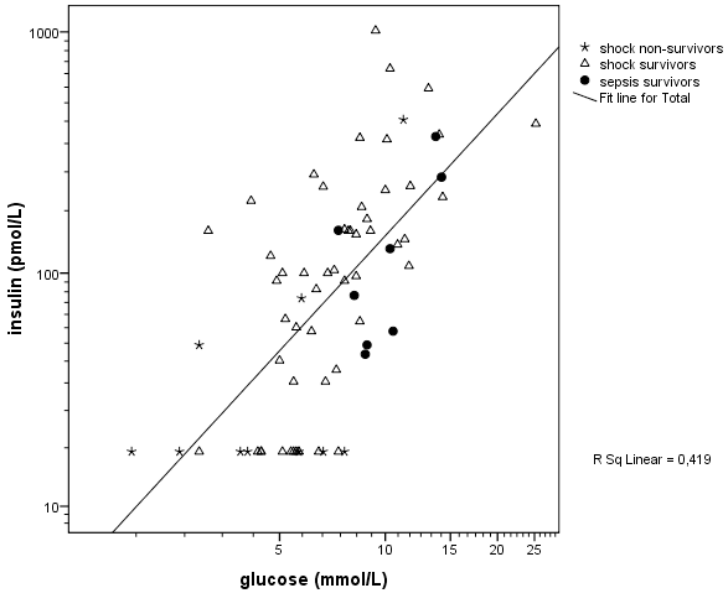

Figure 1. Relation between plasma insulin levels and blood glucose levels on admission in shock non-survivors, shock survivors and sepsis survivors (r=0.67, p<0.001).

cantly different between children with normo- and hyperglycemia (2.4 mg/kg/min (0.8-5.0 mg/kg/min) versus 4.0 mg/kg/min (1.5-6.1 mg/kg/min), respectively, p=0.14) and neither between shock non-survivors, shock survivors and sepsis survivors (Table 1).

Homeostasis model assessment

To determine the occurrence of insulin resistance and decreased β-cell function in hyperglycemic children, HOMA-%S and HOMA-%B were calculated. Paired insulin and glucose levels were used to calculate HOMA-%S. Paired C-peptide (n=35) or insulin levels (n=43) and glucose levels were used to calculate HOMA-%B. In figure 3 the association between glucose and HOMA is shown for the three groups. Figure 3a shows the association between glucose levels and insulin sensitivity (HOMA-%S); figure 3b shows the association between glucose levels and β-cell function (HOMA-%B). The scatter plots are divided into 4 zones by the X-axis reference line representing the maximum reference level for normoglycemia (glucose of 8.3 mmol/l, 150 mg/dl) and a Y-axis reference line at 50% of normal insulin sensitivity (figure 3a) or at 50% of normal β-cell function (figure 3b). Zone D represents children with hyperglycemia and insulin resistance; zone H represents children with hyperglycemia and β-cell dysfunction. Sixty-two percent of hyperglycemic children was insulin resistant, 17% had β-cell dysfunction and 21% had both insulin resistance and β-cell dysfunction. Figure 3a (zone C) shows that insulin resistance also occurred in the children with blood glucose levels below 8.3 mmol/l (<150 mg/dl), but less frequently than in the hyperglycemic children. The

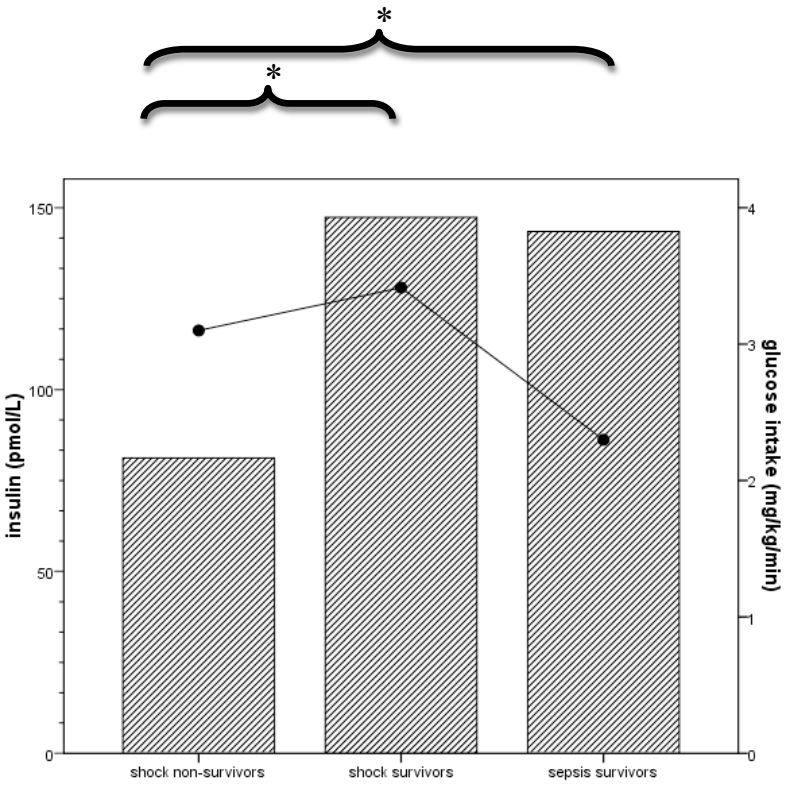

Figure 2 . Mean glucose intake rates and insulin levels on admission in shock non-survivors, shock survivors and sepsis survivors. Bars represent mean insulin levels and dots represent glucose intake rates. Insulin levels in shock survivors and sepsis survivors were significantly higher than in shock non-survivors (* $p<0.05$). There were no differences in glucose intake between the patient categories.

4 children in zone B (figure 3a) all had a decreased β-cell function as they were also located in zone H (figure 3b).

Influence of exogenous factors on glucose homeostasis

Influence of glucocorticoids

Nine children were treated with glucocorticoids just before admission. They tended to have higher blood glucose (8.4 mmol/l, 5.4-12.4 mmol/l, 153 mg/dl, 98-225 mg/dl) and cortisol levels (1308 nmol/l, 615-2094 nmol/l) on admission than the other children (glucose 7.2 mmol/l, 5.3-8.9 mmol/l, 131 mg/dl, 96-162 mg/dl and cortisol 955 nmol/l, 666-1201 nmol/l), but these differences were not significant (p=0.18 and p=0.22, respectively). After admission, an additional 6 children were treated with hydrocortisone (prednisolon equivalent dose of 1.6 mg/kg (0.5-3.1 mg/kg)) within 24 hours. At 24 hours after admission cortisol levels (1824 nmol/l (270-8490 nmol/l)) in the children with glucocorticoid treatment were significantly

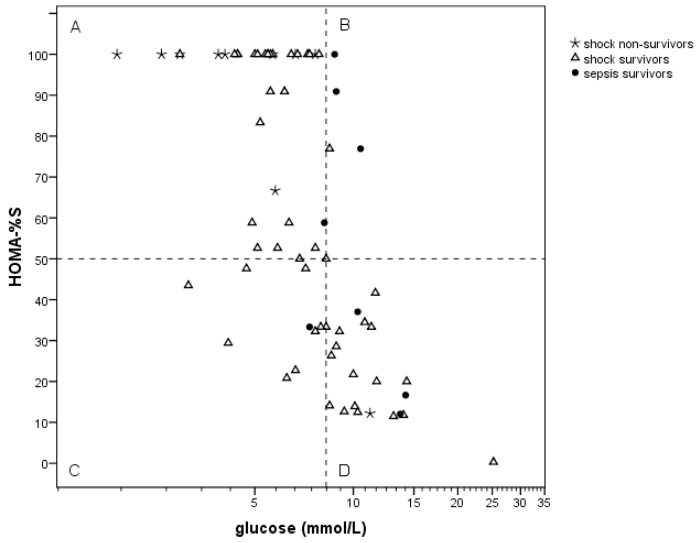

Figure 3a

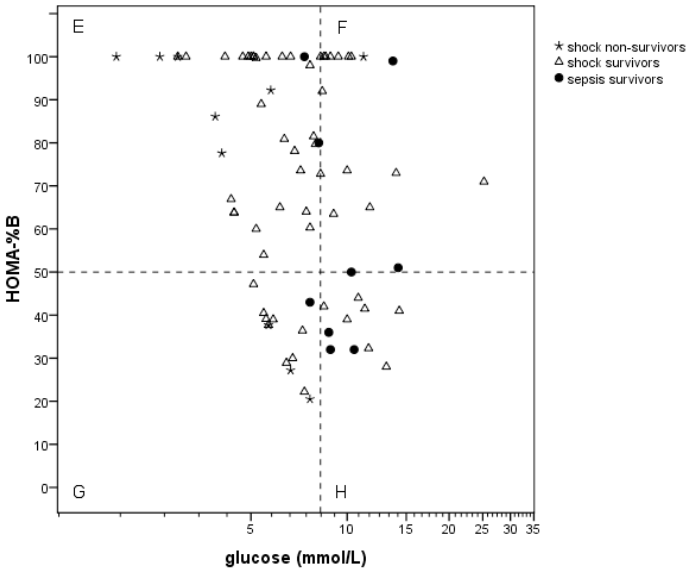

Figure 3b

Figure 3. Relation between HOMA and blood glucose levels on admission in shock non-survivors, shock survivors and sepsis survivors.
a) HOMA-%S, homeostatic model assessment of insulin sensitivity
The vertical, X-axis reference line represents the limit for normoglycemia (8.3 mmol/l, 150 mg/dl)
The horizontal, Y-axis reference line represents 50% of maximum insulin sensitivity.
b) HOMA-%B, homeostatic model assessment of ß-cell function
The vertical, X-axis reference line represents the limit for normoglycemia (8.3 mmol/l, 150 mg/dl)
The horizontal, Y-axis reference line represents 50% of maximum ß-cell function.

higher than in those without glucocorticoid treatment (560 nmol/l (41-8069 nmol/l), p<0.01); blood glucose levels did not differ.

Influence of etomidate

Thirty-five of the children were intubated and had received a single dose of etomidate. As we have previously shown that use of etomidate negatively influenced blood glucose levels, we assessed the influence of etomidate. The children who had received etomidate showed significantly lower glucose and cortisol levels (6.2 mmol/l (4.7-8.5 mmol/l) and 713 nmol/l (555-958 nmol/l), respectively) on admission than the other children (7.7 mmol/l (5.6-10.0 mmol/l) and 1133 nmol/l (953-1342 nmol/l), respectively, p<0.01). At 24 hours after admission, blood glucose levels in etomidate treated children were significantly higher than in the others (7.2 mmol/l vs 6.6 mmol/l, p=0.03), presumably because of a rebound effect. Multiple regression analysis showed that the insulin and age effect on blood glucose levels as described in section 3.4.4 was not influenced by etomidate administration.

Correlations

Blood glucose levels correlated positively with plasma insulin levels (Figure 1; r=0.67, p<0.001), C-peptide levels (r=0.46, p<0.01), cortisol levels (r=0.27, p,0.05), age (r=0.43, p<0.001). Multiple regression analysis revealed that both age and plasma insulin level on admission were factors positively related to blood glucose level (p=0.035 and p<0.001, respectively). These two variables together explained 41% of the variance in blood glucose level on admission. The other variables (glucose intake, cortisol level, (nor)-adrenaline therapy and steroid use) were not significantly related to blood glucose level on admission.

The two outcome parameters, HOMA-%S and insulin to glucose ratio were significantly correlated (r=0.87, p<0.001). C-peptide levels were strongly correlated with insulin levels; r=0.82, p<0.001).

In hyperglycemic children, lactate was inversely correlated with HOMA-%S (r=-0.65, p=0.001).

DISCUSSION

Thirty-three percent of all children in the present study were hyperglycemic on admission and one child was hypoglycemic. Blood glucose levels in shock and sepsis survivors were higher than in shock non-survivors. Hyperglycemic children had significant higher insulin and C-peptide levels than normoglycemic children. Homeostatic model assessment showed a predominance of insulin resistance in hyperglycemic children, although β-cell insufficiency or a combination of insulin resistance and β-cell insufficiency were also seen. Multiple regres-

sion analysis revealed that both age and plasma insulin level on admission were significantly related to blood glucose level.

Hyperglycemia is a common finding in critically ill children and our results are in line with previous studies [8, 11, 14]. Whereas others have reported an association between hyperglycemia and mortality [8-14], in the present study shock non-survivors had the lowest blood glucose levels. This study concerns children with meningococcal sepsis and septic shock, whereas the other studies included children with mixed diagnoses. Only Branco et al. studied children with septic shock (various causes), and showed that a peak glucose level >9.8 mmol/l (>177 mg/dl) was independently associated with an increased risk of death (relative risk: 2.59) [12].

In our study, insulin levels on admission were the lowest in children who did not survive and were closely related to the low blood glucose levels. The association between a lower blood glucose level on admission and mortality in the present study might be explained by the specific features of meningococcal disease like the high risk for relative adrenal insufficiency [5]. This could also explain the positive correlation between blood glucose levels and age, as the youngest children showed the highest mortality rate in combination with the lowest blood glucose levels on admission. Previously we have shown that the concomitant use of therapeutic drugs such as etomidate which was used in almost half of the studied children, influenced blood glucose levels as well [5]. In accordance with previous findings, children intubated with etomidate showed lower glucose and cortisol levels on admission than those without etomidate. Hyperglycemia was associated with elevated insulin levels in half of the children. HOMA showed that insulin resistance as well as β-cell dysfunction resulting in a hypoinsulinemic response resulted in hyperglycemia. Insulin resistance, caused by high levels of counter-regulatory hormones and cytokines, oxidative stress and therapeutic interventions (such as glucocorticoid and catecholamine administration), is the main pathophysiological mechanism of hyperglycemia in critically ill patients [32].

Concerning therapeutic interventions glucocorticoid and catecholamine use in insulin resistant hyperglycemic children was more frequent than in those without insulin resistance. However the numbers were too small to detect significant differences. Serum lactate was negatively correlated to HOMA-%S in hyperglycemic children, which might indicate the negative influence of a compromised circulation on β-cell function. Cortisol level on admission was positively correlated with plasma glucose level in children without previous glucocorticoid treatment, indicating that endogenous cortisol release is a causative factor for hyperglycemia. Sepsis guidelines recommend glucocorticoids for the treatment of vasopressor-dependent septic shock [15]. Glucocorticoids stimulate hepatic glucose production mainly by mobilizing substrate for hepatic gluconeogenesis and activation of key hepatic gluconeogenic enzymes. Furthermore, glucocorticoid excess reduces glucose uptake and utilization by peripheral tissues, due in part to direct inhibition of glucose transport into the cells [33]. Hyperglycemic episodes were more common in adult septic shock patients who

received hydrocortisone in bolus therapy as compared to those who received continuous infusion with equivalent dose [34]. This important side effect of glucocorticoid treatment has not yet been addressed in studies in critically ill children

Another important causative factor of hyperglycemia might be the amount of glucose intake. In the present study children were considered as fasting on admission, because they only received a continuous glucose infusion without enteral intake. Glucose intake did not differ between normo-and hyperglycemic children. In critically ill adults an association was shown between hyperglycemia and a high glucose infusion rate (> 5 mg/kg/min) [35]. On the other hand, low-caloric parenteral nutrition in adult surgical trauma patients resulted in less hyperglycemic events and lower insulin requirements [36]. Maximum glucose oxidation rates in severely burned children approximate 5 mg/kg/min [37]. Exogenous glucose in excess of this amount enters nonoxidative pathways and is unlikely to improve energy balance and lipogenesis and may result in hyperglycemia [38-39].

Two studies have suggested that a hypoinsulinemic response in critically ill children might result in hyperglycemia [18,40]. First, Van Waardenburg et al. studied 16 children with meningococcal disease on the third day of admission (10 shock survivors and 6 sepsis survivors) [18]. While most children were normoglycemic, shock survivors had lower insulin levels (50 pmol/l) and insulin to glucose ratios (8 pmol insulin per mmol glucose) than sepsis survivors (130 pmol/l and 24 pmol insulin per mmol glucose, respectively), suggesting normal or enhanced insulin sensitivity in shock survivors. Second, Preissig and Rigby [40] showed relatively low C-peptide levels (1.5 nmol/l, 4.4 ng/ml) within 48 hours after admission in hyperglycemic critically ill children with respiratory and cardiovascular failure. Accordingly, the present study also showed relatively low C-peptide levels for shock survivors and sepsis survivors during admission (1.0 -1.7 nmol/l, 3.0-5.1 ng/ml). Homeostatic model assessment of β-cell function based on paired C-peptide, insulin and glucose levels showed β-cell dysfunction of the pancreas in 38% of hyperglycemic children, both shock and sepsis survivors. The cause of pancreatic dysfunction could be multifactorial, including elevations in pro-inflammatory cytokines, catecholamines and glucocorticoids. It was hypothesized that β-cells become dysfunctional if physiological changes occur acutely. When the same changes occur more gradually this might allow β-cells to adapt and function at supraphysiological levels over time, resulting in insulin resistance. Also β-cell exhaustion is a known phenomenon characterized by an ability to increase secretion up to a certain level and thereafter fail in response to further demand.

Finally, proinflammatory cytokines are important mediators of the hyperglycemic stress response. We did not find correlations between cytokines and insulin levels or HOMA-%S in hyperglycemic children, presumably because of the relatively small sample size.

Forty-eight hours after admission the percentage of children with hyperglycemia had decreased from 33 to 8% without insulin therapy. In contrast, in critically ill adult patients hyperglycemia may persist for days to weeks with or without insulin therapy [41]. This differ-

ence might be due to the rapid resolution of the acute stress response that is seen in severely ill children with meningococcal disease [5]. The present data also show that the elevated cortisol and cytokine levels on admission decrease to normal values within 24 hours.

There are several limitiations to this study. The hyperinsulinemic euglycemic clamp technique is the "gold standard" for quantifying insulin sensitivity in vivo because it directly measures the effects of insulin to promote glucose utilization under steady state conditions. It is not easily implemented, however, in large studies with critically ill children. In the present study, therefore, insulin sensitivity was indirectly assessed by investigating the insulin response to glucose, and by homeostatic model assessment. Diabetes studies and epidemiological studies on glucose tolerance have frequently used HOMA and recent reports have shown its value for assessment of insulin sensitivity in critically ill [22-23].

Conclusions

Hyperglycemia with blood glucose level >8.3 mmol/L (>150 mg/dL) on admission is frequently seen in children with meningococcal sepsis and septic shock, hypoglycemia is also seen but less frequently. Blood glucose levels in most children spontaneously normalize within 48 hours, at normal glucose intake and without insulin treatment. Both insulin resistance as well as β-cell dysfunction may contribute to the occurrence of hyperglycemia in critically ill children with meningococcal sepsis and septic shock.

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Chapter 6

Disturbance of glucose homeostasis after pediatric cardiac surgery

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SUMMARY

The objective was to evaluate the time course of peri-operative blood glucose levels in children undergoing cardiac surgery for congenital heart disease in relation with endogenous stress hormones, inflammatory mediators and exogenous factors such as caloric intake and glucocorticoid use. Forty-nine children undergoing cardiac surgery were prospectively included. Blood glucose levels, hormonal alterations and inflammatory responses were investigated before and at end of surgery and 12 and 24 hours thereafter. In general, blood glucose levels were highest at the end of surgery. Hyperglycemia, defined as glucose >8.3 mmol/L (>150 mg/dL), was present in 52% of the children at end of surgery. Spontaneous normalisation of blood glucose occurred in 94% of children within 24 hours. During surgery glucocorticoids were administered to 65% of all children and this was the main factor associated with hyperglycemia at the end of surgery (determined by univariate analysis of variance). Hyperglycemia disappeared spontaneously, without insulin therapy, within 12 to 24 hours in the majority of children. Postoperative morbidity was low in the study group, so the presumed positive effects of glucocorticoids seemed to outweigh the adverse effects of iatrogenic hyperglycemia.

INTRODUCTION

Hyperglycemia is a regular phenomenon in critically ill children following surgical repair or palliation of congenital heart defects. Some recent studies showed an association between hyperglycemia and increased postoperative morbidity and mortality in these children [7,18,35].

In the adult literature there is a debate on the usefulness of intensive insulin therapy for glucose control to improve morbidity and mortality in cardiac surgical patients [8,13]. The only randomized controlled study in critically ill children showed improved short-term outcome after treatment with intensive insulin therapy targeting blood glucose levels to age-adjusted normal fasting concentrations [31], but there is debate on the harm of insulin induced hypoglycemic events [11].

For glucose control protocols to be most efficient, they should be based on pathophysiological mechanisms [30]. While several studies have addressed this topic for critically ill adults [15-16, 26], such studies in critically ill children are lacking.

Hyperglycemia in critically ill children is caused by multiple factors, among which endogenous stress hormones [2], inflammatory mediators, oxidative stress and therapeutic interventions such as glucose and drug administration, are the main causative factors.

Children undergoing cardiopulmonary bypass surgery often receive perioperative glucocorticoids to attenuate the systematic inflammatory response, but so far no clinical benefit has been shown [22]. However, hyperglycemia is a well-known side effect of glucocorticoid

use. We hypothesize that in some settings the adverse effects of steroid induced hyperglycemia could outweigh the anticipated benefits.

The objective of the present study was to evaluate blood glucose levels in children undergoing open-heart surgery in relation with stress-induced endogenous hormonal production, inflammatory mediators and exogenous factors such as caloric intake and glucocorticoid use.

MATERIAL AND METHODS

Patients

Eligible subjects were consecutive children with congenital heart disease who underwent open-heart surgery in the Erasmus MC in a two-year period.
Children were not eligible for the study if they had endocrine or chromosomal abnormalities or had received radiation or chemotherapy within the previous 6 months.
The Erasmus MC Medical Ethics Review Board approved the study (196.429/2000/222) and written informed consent was obtained from the parents or legal representatives of each child and of all children aged >12 years.

Clinical parameters

Anthropometric measurements were taken the day before cardiac surgery. Children were fasted before and during surgery and received glucose intravenously (4-6 mg/kg/min) after surgery according to protocol. Enteral nutrition was initiated at the first post-operative day if clinically possible.

Severity of illness was assessed by RACHS (Risk Adjustment for Congenital Heart Surgery) [10], PRISM-score (pediatric risk of mortality score) [19], PELOD-score (pediatric logistic organ dysfunction score) [14] and levels of established biomarkers, such as interleukin-6 (IL-6) and interleukin-10 (IL-10) and arterial lactate.

Congestive heart failure was defined by the criteria of Van der Kuip et al. adjusted for age [27]. The presence of cyanotic heart disease, duration of cardiopulmonary bypass (CPB) and aorta cross clamp time were recorded.

Most children received mild hypothermia (median 31°C) and one (aged 16.6 years) received deep hypothermia (22.5°C) during cardiac surgery. All children received standardized analgesia during and after surgery. Glucocorticoids were administered at the discretion of the attending anaesthesist. The decision to administer glucocorticoids was made before start of surgery and independent of the operative course. Standardized protocols were used for administration of inotropes and weaning from the ventilator. The weighted inotropic (WI) score based on maximum inotropic support during surgery and ICU (intensive care unit) stay was calculated [33]. Duration of mechanical ventilation, as well as wound infections, length of ICU and hospital stay and survival were recorded.

Collection of blood and assays

Arterial blood samples were obtained at start of surgery after induction of anaesthesia, at the end of surgery after sternal closure, and at 12 and 24 hours thereafter. All laboratory parameters were determined immediately, except cytokines. Serum and plasma were stored at -80° C until assayed.

Glucose and lactate were determined on an ABL 725 blood gas analyser (Radiometer Copenhagen, Denmark) in a certified clinical chemistry laboratory (ISO 17025 and 9001). Hypoglycemia was defined as a blood glucose level ≤2.2 mmol/L (≤40 mg/dL), and hyperglycemia as a blood glucose level >8.3 mmol/L (>150 mg/dL) (30). Normal value for lactate was <2.0 mmol/L.

Serum insulin concentrations were determined with an immunoradiometric assay on an Immulite 2000 (DPC) with a minimum detection level of 35 pmol/L [6]. In our laboratory the maximum fasting reference value for insulin is 180 pmol/L. The insulin/glucose ratio was calculated to assess insulin sensitivity. To date there are no strict reference values for the (non)-fasting glucose-to-insulin ratio. In our study the maximum reference value for insulin/glucose ratio was defined as 18 pmol/mmol. This value was derived from current literature data, taking into account the differences between insulin assays and units of analysis [5,28,32].

Serum cortisol concentrations were determined with an Immulite 2000 competitive luminescence immunoassay (DPC, Los Angeles, CA) with detection limits of 3-1380 nmol/L. Normal level of cortisol during stress was defined as cortisol > 496 nmol/L [17]. Plasma ACTH (adrenocorticotrope hormone) concentrations were determined by an immunoradiometric assay (Bio International, Gif sur Yvette, France). The within- and between-assay variation coefficients for the assays of cortisol and ACTH were less than 7%.

Plasma cytokine levels were analyzed with an enzyme-linked immunosorbent assay (Sanquin, Amsterdam, The Netherlands). The detection limit of IL-6 (lowest positive standard) was 10 pg/ml ; that of IL-10 was 25 pg/ml.

Statistics

Data were analysed with SPSS 16.0. Results are expressed as median (interquartile range), unless specified otherwise. Mann-Whitney U, Chi-square test and Fisher's Exact Test were used for group comparison. Univariate Analysis of Variance was used to assess relationships between glucose, steroid use, disease severity as expressed by WI-score and cardiopulmonary bypass time. Data were log-transformed when necessary. Two-tailed P-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

The study group consisted of 49 children (24 boys), aged 2 months to 18 years. They had surgery for left-right shunt patch closure of ventricular septal defect (n=13 (including six with combined closure of atrial septal defect and one with additional repair of tricuspid valve); closure of atrial septal defect, n=7; patch closure of aortopulmonary window together with reimplantation of anomalous left coronary artery from pulmonary artery, n=1); corrective surgery for Tetralogy of Fallot (n=9), univentricular heart (partial cavo-pulmonary connection, n=4; total cavo-pulmonary connection, n=2), left ventricular outflow tract obstruction (enucleation, n=4; pulmonary autograft, n=2; allograft aortic root replacement, n=2), right ventricular outflow tract obstruction (infundibulectomy, n=2; pulmonary allograft, n=1), mitral valve insufficiency (mitral valve annuloplasty, n=2).

Clinical parameters

All children underwent elective cardiac surgery upon cardiopulmonary bypass support (CPB) and 45 of them underwent cardioplegic arrest. All survived.

Thirty children were on inotropic support at the end of surgery; 16 of them received dopamine, 6 received dobutamine, 7 received both dopamine and dobutamine and 1 patient received noradrenalin.

Thirty-two (65%) children received one bolus of glucocorticoids during cardiac surgery. Twelve children received their bolus after induction before surgical incision, 8 at start of heparinisation before cardiopulmonary bypass and 12 at aortic cross clamping. All children but 2 received methylprednisolone (30 mg/kg); 1 received dexamethasone (1 mg/kg) and 1 received hydrocortisone (2 mg/kg). For the purpose of this study we created two groups: those treated with glucocorticoids (n=32) and those without glucocorticoid treatment (n=17). No wound infections occurred. None of the patients received insulin during surgery or ICU stay.

Clinical parameters are depicted in Table 1.

Time courses of laboratory parameters

Laboratory results at start of surgery, end of surgery and at 12 and 24 hours after end of surgery for the group as a whole, are shown in Table 2.

Glucose

Table 2 shows blood glucose levels from start of surgery up to 24 hours after end of surgery. Hypoglycemia ≤2.2 mmol/L (≤40 mg/dL) did not occur. In general, blood glucose levels were highest at the end of surgery.

Table 1 Clinical parameters

Variable	Glucocorticoids (n=32)	No glucocorticoids (n=17)	All patients (n=49)
Demographic data			
Age (years)	1.4 (0.5-6.2)	3.2 (0.6-13.3)	1.7 (0.5-8.7)
Sex (F/M)	15/17	10/7	25/24
Weight (kg)	8.7 (6.6-18.2)	13.0 (6.3-42.0)	12.3 (6.6-24.4)
Body mass index	14.8 (13.6-15.9)	15.1 (14.3-17.5)	14.9 (14.1-16.3)
Illness Severity			
Congestive heart failure (%)	11/32 (34%)	3/17 (18%)	14/49 (29%)
Cyanotic heart disease (%)	10/32 (31%)[a]	1/17 (6%)	11/49 (22%)
RACHS	3 (2-3)	2 (1-3)	3 (2-3)
PRISM-score	14 (11-17)	13 (11-17)	13 (11-17)
PELOD-score	11(1-11)	6 (1-11)	11 (1-11)
WI score	38 (22-54)[a]	3 (0-28)	30 (0-45)
Operative course			
CPB time (min)	78 (55-126)	64 (44-117)	73 (50-120)
Aortic crossclamp time (min)	50 (37-90)	39 (25-83)	45 (34-86)
Hypothermia (°C)	30.0 (28.7-31.7)	32.4 (29.8-34.1)	31.0 (28.8-33.0)
Postoperative course			
Glucose Intake (mg/kg/min)	3.5 (1.8-7.4)	3.3 (1.0-6.2)	3.4 (1.8-6.5)
Ventilation duration (hours)	11 (7-25)	7 (6-11)	9 (6-17)
Inotropes (%)	24/32 (75%)	6/17 (35%)	30/49 (61%)
Length of ICU stay (days)	2 (2-2)	2 (2-2)	2 (2-2)
Length of hospital stay (days)	7 (7-9)	7 (7-8)	7 (7-8)

Data are expressed as median (interquartile range) or numbers (percentage).
RACHS, risk adjustment for congenital heart surgery
PRISM-score, pediatric risk of mortality score
PELOD-score, paediatric logistic organ dysfunction score
WI score, weighted inotropic score based on maximum inotropic support during surgery and ICU stay
CPB, cardiopulmonary bypass
Glucose intake, started at ICU admission
[a]denotes significant difference between patients treated with and without glucocorticoids, $p<0.05$.

At start of surgery, hyperglycemia >8.3 mmol/L (>150mg/dL) was present in 1 patient. At the end of surgery, hyperglycemia was present in 52% (25/48) of the children, decreasing to 11% (5/47) after 12 hours and 6 % (3/47) after 24 hours. Thus almost all children were normoglycemic after 24 hours. Hyperglycemia was not associated with ventilation days, nor with length of ICU and hospital stay.

Plasma insulin and insulin/glucose ratios

Table 2 shows endogenous plasma insulin levels and the insulin/glucose ratios from start of surgery up to 24 hours after end of surgery.

Table 2 Time course of laboratory parameters for patients with and without glucocorticoid treatment.

Variable	Glucocorticoids				No glucocorticoids				All patients			
	Start	**End**	**12h**	**24h**	**Start**	**End**	**12h**	**24h**	**Start**	**End**	**12h**	**24h**
Glucose	4.8	9.5 [a]	6.8	6.2	4.6	7.4 [a]	5.5	6.6	4.7	8.5	6.3	6.2
(mmol/L)	(4.1-5.1)	(7.6-10.8)	(4.9-7.5)	(5.4-7.2)	(4.2-4.9)	(5.9-8.2)	(4.5-7.1)	(5.2-7.4)	(4.1-5.0)	(6.7-10.4)	(4.9-7.4)	(5.4-7.2)
Insulin	15	59	36	63	17	41	33	75	15	54	34	66
(pmol/L)	(14-20)	(39-76)	(14-71)	(29-94)	(14-34)	(27-57)	(14-60)	(22-140)	(14-21)	(28-74)	(14-64)	(29-101)
Insulin/Glucose	3	6	5	10	4	5	7	10	4	6	5	10
(pmol/mmol)	(3-4)	(4-8)	(3-9)	(5-15)	(3-6)	(4-10)	(3-12)	(4-19)	(3-5)	(4-9)	(3-9)	(5-15)
Cortisol	213	6972 [b]	1185	352	156	250 [b]	1037	627	203	5455	1158	590
(nmol/L)	(165-308)	(5409-8327)	(549-1729)	(170-1077)	(109-274)	(111-516)	(581-1497)	(447-917)	(130-302)	(340-7280)	(549-1713)	(222-943)
ACTH	2.2	3.6	2.1 [b]	2.1	2.2	2.6	3.6 [b]	2.2	2.2	3.3	2.2	2.1
(pmol/L)	(2.1-2.8)	(1.5-10.7)	(1.0-2.2)	(1.0-2.2)	(2.1-2.6)	(2.1-7.1)	(2.4-7.9)	(1.2-2.5)	(2.1-2.8)	(1.9-8.3)	(1.4-3.6)	(1.0-2.2.)
Cortisol/ACTH	90 [a]	1485 [b]	590 [b]	239	58 [a]	61 [b]	263 [b]	293	80	557	489	276
(KM/M)	(66-135)	(522-3126)	(309-1184)	(109-547)	(43-104)	(36-96)	(91-489)	(169-463)	(56-115)	(79-2197)	(228-823)	(116-504)
Lactate	0.9	1.7	1.3	1.3	0.90	1.6	1.3	1.3	0.9	1.6	1.3	1.3
(mmol/L)	(0.7-1.1)	(1.3-2.6)	(1.0-1.8)	(0.9-1.5)	(0.8-1.1)	(1.1-1.9)	(1.1-1.6)	(1.0-1.6)	(0.7-1.1)	(1.3-2.4)	(1.0-1.8)	(1.3-1.5)
IL-6	10	21	27 [b]	18 [a]	10	26	56 [b]	41 [a]	<10	22	38	19
(pg/ml)		(10-35)	(15-44)	(10-26)		(10-43)	(40-90)	(21-48)		(10-40)	(20-55)	(10-40)
IL-10	25	274 [b]	25	25	25	61 [b]	25	25	25	157	25	25
(pg/ml)		(101-363)	(25-37)	(25-25)		(27-82)	(25-25)	(25-25)	(25-25)	(69-294)	(25-28)	(25-25)

Laboratory parameters at start of surgery, end of surgery and 12 and 24 hours after surgery of patients treated with and without glucocorticoids.

Data are expressed as median (interquartile range)

ACTH, adrenocorticotrope hormone

IL, interleucine

[a] denotes significant difference between patients treated with and without glucocorticoids, $p<0.05$.

[b] denotes significant difference between patients treated with and without glucocorticoids, $p<0.001$.

At start of surgery, plasma levels of insulin in all children were below the maximum fasting reference level. In all but one of the children (98%) the insulin/glucose ratios were below the maximum reference value.

At the end of surgery, plasma levels of insulin in 6% (3/48) of the children were above maximum reference level. The insulin/glucose ratio was increased >18 pmol/mmol in 9% (4/47) of the children. They had blood glucose levels varying between 7.4 and 10.8 mmol/L. In the remaining children with an insulin/glucose ratio ≤18 pmol/mmol, hyperglycemia was seen in 53% (23/43) of them.

Twelve hours after surgery, none of the children had plasma insulin levels and insulin/glucose ratio above maximum reference value.

Twenty-four hours after surgery, the insulin levels and insulin/glucose ratios were highest. Plasma insulin levels in 9% (4/46) of the children were above maximum reference level. The insulin/glucose ratio was increased >18 pmol/mmol in 20% (9/46) of the children, but only three of them were hyperglycemic. In the remaining children with an insulin/glucose ratio <18 pmol/mmol, hyperglycemia did not occur.

Influence of glucocorticoids

Sixty-five percent (32/49) of the children were treated with glucocorticoids during surgery. Clinical parameters before surgery did not differ between children with and without glucocorticoid treatment, except for the prevalence of cyanotic heart disease and the WI-score, which both were significantly higher in children with steroid treatment (Table 1). Laboratory results at the various time points are shown in Table 2 and Figure 1.

Blood glucose levels at the start of surgery, before glucocorticoid treatment, did not differ between the groups (Figure 1A). At the end of surgery blood glucose levels in children treated with glucocorticoids were significantly higher than levels in those without glucocorticoid treatment. Hyperglycemia occurred significantly more often (p=0.001) in the group with glucocorticoid treatment. The effect of glucocorticoid treatment on blood glucose levels at the end of surgery was independent of other parameters such as glucose intake, the presence of cyanotic heart disease, WI-score and cardiopulmonary bypass time. At twelve and twenty-four hours after surgery median blood glucose levels did not differ between the groups.

Insulin levels and insulin/glucose ratios at all time points did not differ between the groups (Figure 1B and C).

The maximum peak cortisol levels were found at the end of surgery, with significantly higher cortisol levels and cortisol/ACTH ratios in children treated with glucocoricoids (Figure 1D). At twelve and twenty-four hours after surgery, cortisol levels and cortisol/ACTH ratios of children with glucocorticoid treatment had spontaneously decreased to the levels in children without glucocorticoid treatment. In both groups, however, cortisol levels were still higher than levels at the start of surgery.

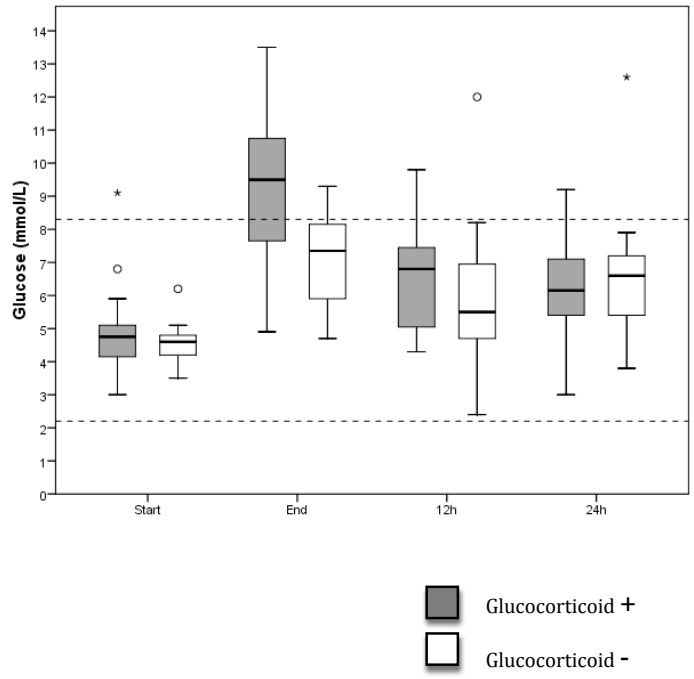

Figure 1A

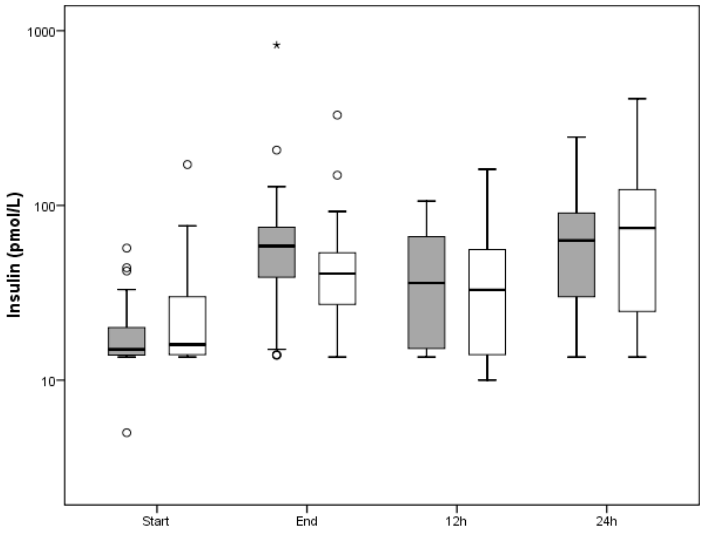

Figure 1B

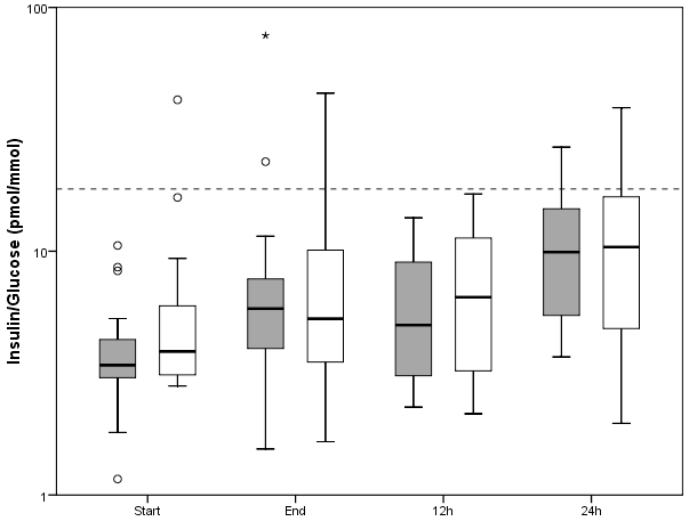

Figure 1C

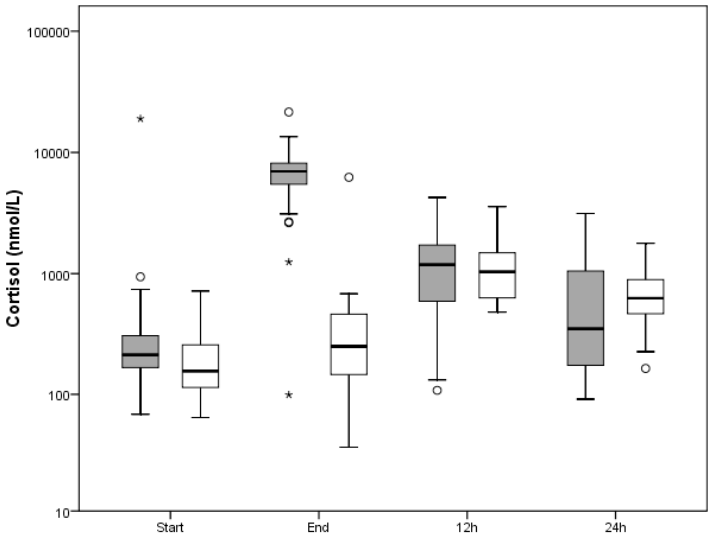

Figure 1D

Figure 1. Time course of blood glucose (A), insulin (B), insulin/glucose ratio (C) and cortisol (D) for patients with and without glucocorticoid treatment.

Time course of blood levels of glucose (A), insulin (B), insulin/glucose ratios (C) and cortisol (D) at start of surgery, end of surgery and 12 and 24 hours after surgery for patients treated with glucocorticoids and without glucocorticoids. Box-whisker-plots: the boxes indicate 25 to 75 percentile with the median and the attached whiskers the complete range *(with exclusion of outliers (o) and extremes (*))*.

IL-6 at 12 and 24 hours after surgery was significantly lower in the children treated with glucocorticoids. IL-10 at the end of surgery and at 12 hours after surgery was significantly higher in children treated with glucocorticoids. There were no other differences in laboratory parameters between both groups.

DISCUSSION

Our study shows that treatment with glucocorticoids during surgery was the main factor associated with the occurrence of hyperglycemia at the end of cardiopulmonary bypass surgery for congenital heart defects. Hyperglycemia frequently occurred with the highest blood glucose levels at the end of surgery. Hyperglycemia disappeared spontaneously (without insulin therapy) within 12 to 24 hours in the majority of the children without significant postoperative morbidity. The occurrence of hyperglycemia was not associated with increased morbidity in terms of duration of ventilation, ICU stay or hospital stay. Moreover, overall morbidity in our population was low. Median duration of mechanical ventilation was 9 hours, while length of ICU and hospital stay were 2 and 7 days respectively. Wound infections, renal dialysis and extracorporeal life support (ECLS) did not occur and all patients survived.

Hyperglycemia in critically ill children is caused by multiple proposed mechanisms, including counterregulatory hormone-mediated upregulation of gluconeogenesis and glycogenolysis, and downregulation of glucose transporters with decreased peripheral utilization of glucose by tissues such as skeletal muscle and liver [29]. In the present study we evaluated how many hyperglycemic patients showed signs of insulin resistance, as this is described as the main causative factor in development of hyperglycemia in critically ill adults [23,26,36]. In only 4 children (9%) an increased insulin/glucose ratio (>18 pmol/mmol) was seen at the end of surgery. The other hyperglycemic children showed a normal or (relatively) decreased insulin/glucose ratio. Plasma insulin levels increased 24 hours after surgery, which might be due to the fact that most patients were detubated and already on enteral nutrition. The increase in insulin levels can be interpreted as a recovery response to the administered enteral feeding.

The decreased insulin response after surgery might be due to the fact that critically ill children seem to be more vulnerable than adults to develop beta-cell dysfunction. Preissig et al. hypothesized that beta-cells, known to be exquisitely sensitive to rapid physiological changes, may become dysfunctional if these changes acutely occur above a certain threshold [20]. These changes may be induced by multiple factors like hypothermia, vasopressors, elevations of pro-inflammatory cytokines and use of glucocorticoids [1,9,12,20]. In the study by Preissig et al. in critically ill children with respiratory and cardiovascular failure [20], the vasopressor score was inversely correlated with c-peptide level, indicating beta-cell dysfunction due to the suppressing effect of exogeneous catecholamines. In our study the use of vasopressors

was low, with only one patient on noradrenalin. This might explain the relatively normal plasma insulin levels at the end of surgery. Another explanation for the less pronounced hypoinsulinemic response in our study might be the mild effect of cardiac surgery on the inflammatory response as shown by the low levels of Il-6 and mild increased IL-10 at the end of surgery in the patients without glucocorticoid treatment. Perioperative administration of glucocorticoids was associated with decreased IL-6 and increased IL-10 levels after CPB. This is in accordance with adult studies, which have shown that glucocorticoids may decrease the inflammatory response during the CPB procedure [3]. However, for pediatric patients with congenital heart disease undergoing cardiopulmonary bypass surgery, the clinical benefit of this suppressed cytokine response remains unclear.

There is debate about the positive effects of steroid use during cardiopulmonary bypass in pediatric patients and whether the potential positive effects of corticosteroid treatment during cardiopulmonary bypass surgery outweigh the potential adverse effects, such as hyperglycemia [4,22]. High blood glucose levels at the end of CPB surgery for congenital heart defects were also found in previous studies [1,7,21,24]. We found a spontaneous normalisation of blood glucose levels within 24 hours postoperatively, which is in line with one other study [24], whereas in a few other studies a more gradual decrease in blood glucose levels over 3 days was shown [18,35]. This could be related to our relatively low postoperative morbidity as compared with other studies, with comparable pre-operative illness severity as expressed by RACHS. Other authors [21] reported increased length of ICU stay (median 3-6 days), mechanical ventilation (4.4 days), dialysis (1.1-4%), ECLS (3-8%) and mortality (4-11%). Vlasselaers et al. reported their results from a prospective randomized controlled trial treating critically ill children (75% were patients after cardiac surgery for congenital heart defects). Intensive insulin therapy for hyperglycemia improved morbidity and reduced mortality [31], but there is debate on the harm of insulin induced hypoglycaemic events [11]. It is important to realize that not only hyperglycemia, but also hypoglycemia is associated with adverse outcome [7,25,34-35].

In general it can be stated that there are important differences in morbidity and mortality after pediatric cardiac surgery between centres. In our study none of the patients were treated with insulin for hyperglycemia and overall morbidity was low, so there is no need for the standard use intensive insulin therapy for tight glycemic control.

A limitation of this study was that glucocorticoids were administered at the discretion of the attending anaesthesist. Although treatment was not randomized, glucocorticoids were administered before aortic clamping and thus independent of the operative course. Moreover, there were no differences in age, clinical course and duration of cardiopulmonary bypass time between patients with and without glucocorticoid treatment. Furthermore, although patients with cyanotic heart disease were more likely to receive glucocorticoids and the median WI score was higher in the glucocorticoid treated patients, univariate analysis

of variance showed that preoperatively administered glucocorticoids were independently associated with increased blood glucose levels at the end of surgery.

In summary, we showed that the development of hyperglycemia at the end of cardiac surgery for congenital heart disease was associated with glucocorticoid administration during surgery. Postoperative hyperglycemia was frequent, but in almost all cases (94%) blood glucose levels spontaneously normalized within 24 hours, without the use of insulin administration and without significant morbidity or mortality. Standard use of intensive insulin therapy for tight glycemic control is not needed in this patient group. In contrast with our hypothesis, we conclude that since postoperative morbidity was low in the study group, the presumed positive effects of glucocorticoids seemed to outweigh the adverse effects of iatrogenic hyperglycemia.

Future research should focus on the value of corticosteroid therapy during pediatric cardiac surgery to weigh both the pros and cons of either hyperglycemia and corticosteroid therapy.

Acknowledgements

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PART III

GLYCEMIC CONTROL

The fact that your patient gets well does not prove that your therapy was correct (***vrij naar Samuel J. Meltier***)

Chapter 7

Insulin/Glucose ratio as a marker for insulin therapy in critically ill children

Jennifer J. Verhoeven, Marianne Koenraads, Wim C.J. Hop, Jeannette B. Brand, Mirjam M. van de Polder, Koen F.M. Joosten

Nutrition (provisionally accepted for publication)

ABSTRACT

Objective

To investigate the endogenous insulin response in critically ill children with hyperglycemia and to explore the relationship between insulin response and clinical outcome.

Research Methods & Procedures

Sixty-four consecutively admitted critically ill children with hyperglycemia, defined as blood glucose >8 mmol/L (>145 mg/dL), and treated with insulin according to a glucose control protocol were included. Demographic data and clinical and laboratory parameters were collected. Insulin sensitivity was investigated by relating blood glucose levels to endogenous insulin levels just before start of insulin administration. Results are expressed as median (range).

Results

64 children (24 girls), age 7.0 yrs (0.3-16.9 yrs) with various diagnoses were included. A hyperinsulinemic response, indicated by elevated insulin/glucose ratios (>18 pmol/mmol), was seen in 55% of the children. Duration of insulin therapy, mechanical ventilation and PICU length of stay in children with a hyperinsulinemic response was longer than in children with a hypoinsulinemic response.

Conclusion

Both a hyper- and a hypoinsulinemic response play a role in the occurrence of hyperglycemia in critically ill children. The insulin/glucose ratio in relation with the clinical picture might be used to judge about the usefulness of insulin therapy for the individual child.

INTRODUCTION

Critical illness is associated with many endocrine, metabolic and immunologic changes [1]. One of these is hyperglycemia, caused by a complex interaction of endogenous and exogenous factors. Hepatic insulin resistance and the resulting excessive gluconeogenesis together with impaired glucose use in peripheral tissues are considered to be the driving forces behind stress hyperglycemia in critically ill adults [2-3]. Studies in critically ill children have reported an association between hyperglycemia and morbidity (e.g. longer length of stay in the intensive care unit (ICU), duration of ventilator use and adverse neurological outcome) [4-12].

The underlying mechanisms of hyperglycemia and risk factors in critically ill children have been little studied and in small groups of patients only [13-14]. Waardenburg et al. proposed that hyperglycemia associated with hypoinsulinemia rather than insulin resistance may be the common pathophysiological response at least in children with meningococcal septic shock [13]. Preissig and Rigby reported a different aetiology of hyperglycemia in critically ill children dependent on the presence of respiratory and/or cardiovascular failure. Insulin resistance, as defined by elevated C-peptide/glucose ratio's was the prominent cause of hyperglycemia in children with respiratory failure only, versus primary beta-cell dysfunction in children with both respiratory and cardiovascular failure [14].

Intensive insulin therapy in critically ill children (targeting blood glucose concentrations of 2.8-4.4 mmol/L (50-80 mg/dL) in infants and 3.9-5.5 mmol/L (70-100 mg/dL) in older children) resulted in shorter ICU stay and fewer secondary infections [15]. We have successfully implemented a nurse-driven glucose control protocol for critically ill children of all ages with hyperglycemia, defined as blood glucose level >8 mmol/L (>145mg/dL) at any time during admission. This resulted in normoglycemia within 12 hours for 94% of the children involved without episodes of hypoglycemia ≤2.2 mmol/L [16].

Better insight into pathophysiological mechanisms leading to hyperglycemia might even improve treatment strategies like these. We studied the endogenous insulin response in relation with hormonal, metabolic and immunologic parameters in critically ill children with hyperglycemia just before start of insulin therapy, and hypothesized that both a hyper- and a hypoinsulinemic response play a role in the occurrence of hyperglycemia. The objective of this study was to explore the relationship between insulin response and clinical characteristics and outcome of critically ill children.

MATERIALS AND METHODS

Setting

The Pediatric Intensive Care Unit of the university children's hospital is a tertiary 34-bed multidisciplinary unit providing for high acute medical and surgical conditions in children aged up to 18 years.

Design

Prospective evaluation of critically ill children aged 2 weeks to 18 years consecutively admitted to the PICU of the Erasmus MC-Sophia Children's Hospital from January 2006 till July 2009 and showing hyperglycemia (defined as blood glucose level exceeding the value of 8 mmol/L (>145 mg/dL)) meeting the criteria for insulin treatment [16]. Children with diabetes mellitus were excluded. The local Medical Ethics Review Board approved the study.

Clinical characteristics and outcome parameters

Patients' baseline characteristics and other clinical information were recorded. Anthropometric measurements were taken on the day of admission.

Disease severity was determined by the Pediatric Risk of Mortality score (PRISM II) and the Pediatric Logistic Organ Dysfunction (PELOD) scoring system [17-18].

Respiratory and inotropic support, use of glucocorticoids and antimicrobiological agents were recorded. Inotropic support was quantified by the vasopressor score developed by Hatherill et al. [19]. We calculated equivalent doses of prednisolone, expressed per body weight (mg/kg), using the glucocorticoid equivalent potencies 20/5/0.75 for hydrocortisone, prednisolone and dexamethasone, respectively.

Children received standardized analgesia, sedation and nutritional support [20]. The glucose control protocol prescribes glucose intake rates dependent on bodyweight and insulin dose dependent on the actual blood glucose level. Actual glucose intake was calculated. All children were on continuous enteral and/or parenteral feeding.

Laboratory tests

A standard care physician-initiated, nurse-driven glucose control protocol was used to screen and treat all hyperglycemic patients [16]. Blood glucose measurements were obtained as soon as possible after admission. In case of hyperglycemia >8 mmol/L (>145 mg/dL) measurements were repeated every hour and further according to the protocol. Blood was collected from an indwelling arterial or venous catheter or from capillary puncture. Arterial blood samples for the determination of glucose, insulin, cortisol, C-reactive protein (CRP), lactate, cholesterol, free fatty acids (FFA), triglycerides, creatinin, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and prothrombin time (PT) were taken at the start of insulin therapy. All laboratory parameters were determined immediately in a certified

laboratory of clinical chemistry (ISO 17025 and 9001). Assays were performed according to manufacturer's instructions.

Blood glucose was measured on either a blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) or by a bedside capillary glucose measurement with a point of care system (HemoCue AB, Sweden). Blood glucose levels of <2.6 mmol/L (<47 mg/dL) or >15 mmol/L (>272 mg/dL) obtained by the latter method were considered to be unreliable. Measurements were then repeated on the blood gas analyzer. Hypoglycemia was defined as a blood glucose level ≤2.2 mmol/L (≤40 mg/dL), and hyperglycemia as a blood glucose level >8.0 mmol/L (>150 mg/dL) [16].

Serum insulin was measured by a two-site chemiluminescent immunometric assay (Immulite 2000, DPC, Los Angeles, USA) with minimum detection level of 35 pmol/L. The maximum fasting reference value for insulin was set at 180 pmol/L. The insulin/glucose ratio was calculated to assess insulin sensitivity. The maximum reference value for insulin/glucose ratio was defined as 18 pmol/mmol. This value was derived from current literature data, taking into account the differences between insulin assays and units of analysis [13, 21-22]. Insulin sensitivity was also measured using the homeostasis model assessment method (HOMA). Scores ≥ 4 indicate decreased insulin sensitivity [23].

Serum cortisol concentrations were determined with a competitive luminescence immunoassay (Immulite 2000, DPC, Los Angeles, CA). The detection limits of this assay are: 3-1380 nmol/L. Nonstressed reference values for cortisol were between 200 and 800 nmol/l. Although there are no strict definitions on adrenal insufficiency assessment in critically ill children, adrenal insufficiency in the case of catecholamine-resistant septic shock may be assumed at a random level < 496 nmol/L [24].

Arterial lactate was determined on blood gas analyzer (ABL 625, Radiometer, Copenhagen, Denmark). The reference level for lactate was <2.0 mmol/L. Serum CRP was determined by immunoturbidimetric assay (normal <2 mg/l), and examined on a 912 analyzer (Roche Molecular Biochemicals, Mannheim, Germany).

Plasma FFA concentrations were determined by enzymatic method (Nefac-kit, Wako, Instruchemie BV). Reference levels for FFA for children between 4 months- 10 years: 0.3-1.1 mmol/L, children >10 years: 0.2-0.8 mmol/L.

Statistics

Data were analysed with SPSS 16.0. Results are expressed as median (range), unless specified otherwise. Data were log-transformed when necessary. Mann-Whitney U test was used for group comparison. Chi-square test was used for comparison of nominal data. In the between-group comparison and analysis of correlations on duration of insulin therapy, ventilation days, PICU and hospital length of stay, children who died during insulin therapy, mechanical ventilation, PICU and/or hospital stay, respectively, were excluded from analysis. None of the

children died during glucocorticoid treatment. Two-tailed P-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The study group consisted of 64 children (24 girls), median age 7.0 years (0.3 – 16.9) with various diagnoses. Fifty-one had respiratory or cardiovascular failure, for which they were mechanically ventilated or received inotropic support. None of all children had severe hepatic failure. One child was admitted with acute renal insufficiency requiring dialysis therapy. Eleven children (17%) died during PICU admission. Five of them died during insulin therapy. Patients' characteristics just before start of insulin therapy are shown in table 1.

Table 1 Patients' characteristics at start of insulin treatment

Variable	Insulin/Glucose <18 (n=29)	Insulin/Glucose >18 (n=35)	P-value
Gender (M/F)	18/11	22/11	
Age (years)	7.0 (0.3-16.4)	6.9 (0.2.-17.0)	0.55
Weight (kg)	20.0 (4.5-85.0)	24.0 (3.2-80.0)	0.63
Diagnostic category			NA
Infectious	9	14	
Cardiac Surgery	5	4	
Trauma	5	4	
Neurologic	6	3	
Respiratory	1	5	
Surgery	3	3	
Other	0	2	
PRISM	14 (1-44)	12 (2-36)	0.50
PELOD	12 (0-61)	11 (0-50)	0.54
MV (%)	16 (55%)	31 (88%)	0.004**
Inotropics (%)	12 (41%)	17 (49%)	0.62
VAS score	1 (0-3)	1 (0-3)	NA
Antibiotics (%)	15 (52%)	23 (66%)	0.31
Nutrition (%)			NA
Parenteral	23 (79%)	23 (66%)	
Enteral	0	4 (11%)	
Parenteral/Enteral	6 (21%)	8 (23%)	
Glucocorticoids (%)	11 (38%)	11 (31%)	0.61
Prednisolone equivalents (mg/kg)	0.6 (0.03-1.0)	0.6 (0.2-8.0)	0.49

Data are expressed as median (range) or numbers.

PRISM, pediatric risk of mortality; PELOD, Pediatric Logistic Organ Dysfunction; MV, mechanical ventilation; VAS, vasopressor score developed by Hatherill et al. [19]

* significant ($p<0.05$) difference between children with hypo- and hyperinsulinemic response

** significant ($p<0.001$) difference between children with hypo- and hyperinsulinemic response

Insulinemic response

Blood samples were taken just before start of insulin treatment. The group median blood glucose level at start of therapy was 9.9 mmol/L (5.7-43.3) (180, 104-787 mg/dL). Median plasma insulin level was 235 pmol/L (<35-3803). Insulin levels were below detection level in 3 patients. Median insulin/glucose ratio was 20 pmol/mmol (1-235). Median HOMA was 13 (2-385).

A hyperinsulinemic response as expressed by an elevated insulin/glucose ratio >18 pmol/mmol was seen in 35 children (55%). The other 29 children (45%) with an insulin/glucose ratio <18 pmol/mmol were classified as having a hypoinsulinemic response. Children with a hyperinsulinemic response had similar baseline clinical parameters as compared to those with a hypoinsulinemic response (Table 1). All children with a hyperinsulinemic response had a HOMA score ≥ 4.

Laboratory parameters (Table 2) did not differ between children with a hyperinsulinemic response and those with a hypoinsulinemic response. Although free fatty acids were significantly elevated in children with hypoinsulinemic response versus those with a hyperinsulinemic response, results were below maximum reference levels in both groups; 0.53 (0.23-1.29) versus 0.28 (0.09-0.83) mmol/L, respectively.

Table 2 Laboratory parameters at start of insulin therapy

Variable	Insulin/Glucose <18 (n=29)	Insulin/Glucose >18 (n=35)	P-value
Glucose (mmol/L)	10.3 (5.7-43.3)	9.7 (7.1-21.7)	0.60
Insulin (pmol/L)	79 (<35-351)	364 (166-3803)	<0.001**
Insulin/Glucose	9 (1-16)	41 (19-24)	<0.001**
HOMA	5 (2-80)	25 (9-385)	<0.001**
Cortisol (nmol/L)	560 (28-2715)	648 (40-4442)	0.74
CRP (mg/L)	30 (1-366)	67 (1-314)	0.12
FFA (mmol/L)	0.5 (0.2-1.3)	0.3 (0.09-0.83)	<0.001**
TG (mmol/L)	0.8 (0.2-9.7)	1.1 (0.3-6.6)	0.31
Cholesterol (mmol/L)	2.5 (0.7-6.2)	2.6 (0.7-4.8)	0.90
Lactate (mmol/L)	2.4 (0.7-8.3)	2.5 (0.9-11.7)	0.95
Ureum (mmol/L)	5.2 (1.6-20.1)	5.2 (1.8-45.1)	0.48
Creatinin (µmol/L)	41 (20-324)	56 (11-995)	0.11
PT (sec)	17 (12-39)	18 (13-52)	0.42
AST (IU/L)	96 (19-2145)	69 (18-1375)	0.84
ALT (IU/L)	26 (12-372)	47 (5-468)	0.75
Trombocyte (IEx10^9/L)	169 (5-332)	183 (13-572)	0.35
Leucocyte (IEx10^9/L)	9 (1-26)	10 (1-21)	0.84

Data are expressed as median (range) or numbers.

CRP, C-reactive protein; FFA, Free Fatty Acids; TG, triglycerides; PT, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

* significant ($p<0.05$) difference between children with hypo- and hyperinsulinemic response

** significant ($p<0.001$) difference between children with hypo- and hyperinsulinemic response

Clinical outcome parameters are shown in Table 3. The two groups significantly differed on glucose intake (3.4 vs 4.2 mg/kg/min), duration of insulin therapy (10 vs 33 hours), mechanical ventilation (2 vs 5 days) and PICU length of stay (5 vs 11 days). Non-ventilated children with an insulin/glucose ratio <18 pmol/mmol (n=10) were treated with insulin for 8 hours (0.2 -124); the others for 32 hours (2-540, p<0.05).

Table 3 Patients' characteristics during PICU stay

Variable	Insulin/Glucose <18 (n=29)	Insulin/Glucose >18 (n=35)	P-value
Days from admission to hyperglycemia	0.5 (0.03-2.8)	0.6 (0.1-60.4)	0.13
Glucose control protocol characteristics:			
Glucose intake (mg/kg/min)	3.4 (0.0-6.2)	4.2 (0.4-19.3)	0.03*
Time from start of insulin infusion to normoglycemia (hrs)	4 (0.2-17)	4 (0.8-759)	0.93
Max insulin dose, (mIU/kg/hrs)	50 (3-140)	70 (20-200)	0.20
Duration of insulin therapy (hrs)	10 (0.2-124)	33 (3-540)	0.005**
Glucocorticoids (days)	2 (0.04-11)	2 (0.04-8)	0.78
MV (days)	2 (0-18)	5 (0-35)	0.04*
PICU LOS (days)	5 (1-22)	11 (2-106)	0.02*
Hospital LOS (days)	7 (1-96)	17 (1-155)	0.28
PICU Survival (n)	23 (79%)	26 (74%)	0.53

Data are expressed as median (range) or numbers.
MV, mechanical ventilation; PICU LOS, pediatric intensive care unit length of stay
* significant (p<0.05) difference between children with hypo- and hyperinsulinemic response
** significant (p<0.001) difference between children with hypo- and hyperinsulinemic response

Correlations

Insulin/glucose ratio was significantly correlated with HOMA (r=0.79, p<0.001). There were weak but statistically significant correlations between insulin/glucose ratio and duration of insulin therapy (r=0.39, p<0.01), duration of mechanical ventilation (r=0.34, p<0.05), and PICU LOS (r=0.34, p<0.05). Duration of insulin therapy was also positively correlated with duration of steroid treatment (r=0.60, p<0.01), maximum insulin dose (r=0.54, p<0.01), PICU LOS (r=0.37, p<0.01), insulin level (r=0.35, p<0.01) and CRP level (r=0.32, p<0.05).

DISCUSSION

In this study, children with a hyperinsulinemic response were more often mechanically ventilated, had a significant longer duration of insulin therapy, mechanical ventilation and PICU stay, than children with a hypoinsulinemic response. Duration of hospital stay, mortality and other clinical outcome parameters did not differ between both groups. A recent study in critically ill adults found no differences in morbidity or mortality between patients with overt insulin resistance and patients who were insulin sensitive [3]. The authors suggested that severity of illness and the underlying inflammatory response, rather than hyperglycemia or insulin resistance, may be the main contributor to outcome of severely ill patients [3]. However, in our study we did find differences in morbidity (duration of mechanical ventilation and PICU length of stay) between patients with a hyperinsulinemic response compared with those with a hypoinsulinemic response. Our finding that a hyperinsulinemic response was associated with respiratory failure, is in line with findings from Preissig and Rigby [14]. These authors reported signs of insulin resistance, measured by C-peptide levels in children with respiratory failure. On the other hand, they also reported primary beta-cell dysfunction as the prominent cause of hyperglycemia in children with both respiratory and cardiovascular failure at the same time, whereas in the present study both a hyper-and a hypoinsulinemic response were seen in children with cardiovascular failure. They postulated that especially noradrenalin has a deleterious effect on beta-cell function. Lower vasopressor scores in our study population is a possible explanation of the finding of a decreased insulin response to hyperglycemia in only a minority of our patients. Preissig and Rigby unfortunately did not report these scores.

Adult studies have yielded many factors that may influence the insulin and glucose response to critical illness. Hyperglycemia associated with elevated insulin levels may result from higher glucose intake, as well as the presence of excessive amounts of counterregulatory hormones (noradrenalin, adrenalin, glucagon, glucocorticoids, and growth hormone) and cytokines (tumor necrosis factor-α, interleukin-1 and interleukin-6) [2]. With regard to drug-induced hyperglycemia, both steroid therapy and vasopressors have a negative effect on insulin sensitivity [25].

Concerning glucose intake, we found higher glucose intake rates, without significant differences in bodyweight, in children with a hyperinsulinemic response compared to those with a hypoinsulinemic response. A study in critically ill adults reported a strong association between the amount of infused glucose and intensive care outcome in a situation without insulin treatment and without active glucose control. As, in our study, all children were treated with insulin for hyperglycemia, this unfavourable association does not apply to our population [26].

Concerning the use of vasopressors, we did not find a correlation between the vasopressor score and beta-cell dysfunction as expressed by insulin/glucose ratio. Regarding glucocor-

ticoid use, duration of glucocorticoid treatment was strongly correlated with duration of insulin therapy, which might reflect the depressing effect of glucocorticoids on insulin sensitivity. This is supported by the correlations found between duration of insulin therapy and insulin level, insulin/glucose ratio and peak insulin dose. Also, the strong correlation between duration of glucocorticoid therapy and insulin therapy is in accordance with pharmacological studies, which have reported decreased insulin sensitivity from 4 hours after the start of glucocorticoid infusion, which did not change for a further 2 months of glucocorticoid treatment [27]. It would be interesting for future studies to determine blood levels of glucose, cortisol, C-peptide and insulin during glucocorticoid treatment.

A limitation of this study is the fact that insulin sensitivity was measured indirectly by insulin/glucose ratio and HOMA. The hyperinsulinemic euglycemic clamp technique is the "gold standard" for quantifying insulin sensitivity in vivo because it directly measures the effects of insulin to promote glucose utilization under steady state conditions. We resorted to the indirect methods, because the clamp technique is not easily implemented in large studies with critically ill children. As glucagon is the primary hormonal stimulator of hepatic gluconeogenesis during critical illness which is resistant to the inhibitory effect of physiological concentrations of insulin [28], the ratio of insulin to glucagon may have additional value in future studies on hormonal response to hyperglycemia.

From previous studies [14], as well as from this study, it has become obvious that many critically ill children are treated with exogenous insulin for a relatively short period of time. In this study it was a median duration of 23 hours (7-55). As the duration in the group of non-ventilated children with an insulin/glucose ratio <18 pmol/mmol, was significantly shorter than in the other children, it might be postulated that in these children the acute stress response is rather brief, so that consequently the hyperglycemic state lasts shortly. Therefore, the value of insulin therapy in these children could be questioned. Without insulin therapy, their hyperglycemia would probably also have normalized within a day without adverse effects on morbidity, as occurred in young children after surgery [29]. It would be worthwhile to investigate if the insulinemic response to hyperglycemia, determined by insulin/glucose ratio or HOMA in combination with type of organ dysfunction, could be used in clinical practice to determine the need of exogenous insulin treatment.

Conclusions

Both a hyper- and a hypoinsulinemic response play a role in the occurrence of hyperglycemia in critically ill children. Children with a hyperinsulinemic response had a longer duration of insulin therapy, mechanical ventilation and PICU length of stay compared with those with a hypoinsulinemic response. Most of the children without respiratory failure showed relatively low insulin levels and insulin/glucose ratios, in combination with a short duration of insulin therapy.

Future research should focus on pathophysiological mechanisms of hyperglycemia in critically ill children. It would be challenging to develop predictor equations that could foretell in advance which hyperglycemic children would benefit from insulin therapy and which would not.

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Chapter 8

Management of hyperglycemia in the pediatric intensive care unit; implementation of a glucose control protocol

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ABSTRACT

Objective

To evaluate a stepwise nurse-driven glucose control protocol for the treatment of hyperglycemia in critically ill pediatric patients.

Setting

Academic pediatric intensive care unit.

Design

Prospective observational study.

Patients

50 consecutively admitted critically ill children with hyperglycemia above 8 mmol/L (145 mg/dL) were included and treated according to the glucose control protocol.

Methods

Demographic data and clinical parameters were collected and different steps in the protocol were evaluated. Data were expressed as medians with interquartile ranges.

Main Results

Fifty children (28 boys), age 3.5 yrs (1.2 -9.3 yrs) were treated in 18 months. 42 children had multiple organ failure. Eight children died. Insulin treatment was initiated 4 hours after the first episode of hyperglycemia was documented (median blood glucose 11.4 mmol/L (207 mg/dL) (9.7-14.5 mmol/L, 176-264 mg/dL)). Blood glucose was <8 mmol/L (145 mg/dL) within 12 hours of initiating insulin therapy in 47/50 children (94%) (median 5 hrs). Duration of treatment was 34 hr (17-72 hrs) and the maximum insulin dose ranged between 20 and 200 mIU/kg/hr (median 70 mIU/kg/hr). Episodes of severe hypoglycemia <2.2 mmol/L (47 mg/dL) did not occur.

Conclusion

The use of a stepwise nurse-driven glucose control protocol resulted in normoglycemia within 12 hours for 94% of the children involved. Episodes of severe hypoglycemia did not occur. We conclude that the glucose control protocol is effective in treating hyperglycemia in critically ill children. Further studies are necessary to assess safety before the protocol could also be implemented in other PICU's.

INTRODUCTION

Hyperglycemia and insulin resistance are universal findings in critically ill adult patients. In the acute stress state this metabolic response could be regarded as an adaptive response. Nevertheless, several studies in adults and children have observed associations of both initial hyperglycemia and prolonged hyperglycemia with adverse outcomes (1-12).

Since then, several studies on the management of hyperglycemia in critically ill adults by intensive insulin therapy have reported conflicting results (13-15).

The Leuven investigators showed that intensive insulin therapy reduced mortality in surgical patients and in medical patients staying in the ICU for at least 3 days (13, 14). They also showed beneficial effects on a variety of indicators of morbidity, such as a reduction in nosocomial infections, acute renal failure, critical illness polyneuropathy, and anemia, as well as shorter duration of mechanical ventilation and overall length of ICU stay. A multicenter, randomized trial showed no significant benefits of intensive insulin therapy in the rate of death or the mean score for organ failure. Moreover, the use of intensive insulin therapy was associated with an increased risk for serious adverse events related to hypoglycemia (15). Studies in critically ill children which have shown an association between hyperglycemia and greater morbidity and mortality, were mostly retrospective and could not demonstrate causality between glucose levels and outcome measures (1-12).

The overall hypothesis regarding treatment of hyperglycemia is that critically ill children will benefit from maintaining normoglycemia with exogenous insulin, as in critically ill adults (13, 14). Two studies in a small group of children with severe burns reported beneficial effects of insulin treatment on survival, infection rates and inflammatory response (16, 17). The insulin treatment protocol was not published. Such a protocol for critically ill children with hyperglycemia would obviously have to be both safe and effective. Factors like time to normoglycemia, target blood glucose level, occurrence of hypoglycemia, practical feasability and workload are some of the aspects to be taken into account.

So far no studies have published results of implementation of an insulin treatment protocol in critically ill children in relation with different blood glucose levels. The present study documents experiences with the implementation of such a glucose control protocol in our pediatric intensive care unit (PICU).

MATERIALS AND METHODS

Patients

All children with single or multiple organ failure consecutively admitted to the PICU of the Erasmus MC-Sophia Children's Hospital from January 2006 to June 2007 with hyperglycemia (defined as blood glucose level exceeding the value of 8 mmol/L (145 mg/dL)) at any time

during admission meeting the criteria for insulin treatment, were prospectively evaluated (see below). This hospital is a tertiary care center embedded in the Erasmus University Medical Center, Rotterdam, the Netherlands. Children with diabetes mellitus were excluded. The Medical Ethics Committee of the Erasmus MC approved the study**.**

Insulin protocol (Figure 1)

On admission, children with bodyweight ≤30 kg received intravenous glucose at a rate of 4–6 mg/kg/min; the rate for those with body weight >30 kg was 2-4 mg/kg/min. To achieve the target glucose infusion rates, 5% and 10% dextrose infusions were given.

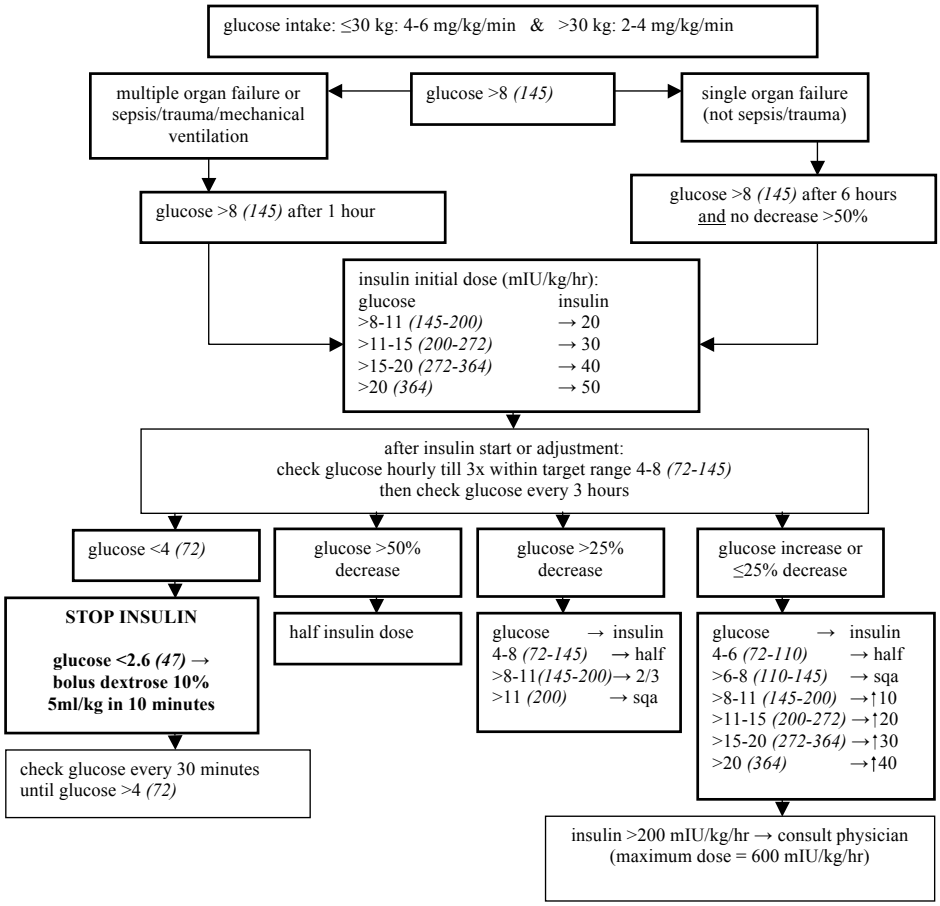
Children with sepsis, trauma, multi-organ failure and/or receiving mechanical ventilation were included in the protocol when two consecutive blood or capillary glucose values at a 1-hr interval were >8 mmol/L (145 mg/dL). Children with single organ failure were included when blood glucose levels were >8 mmol/L (145 mg/dL) for more than 6 hours and decreased less than 50% during the following 6 hours.

The glucose control protocol was initiated by the attending physician at a dose dependent on the actual blood glucose level. Thereafter, nursing staff was allowed to adjust the insulin rate according to the rate of increase or decrease of blood glucose level. Initially blood glucose level was measured every hour until it had reached the target range with values between 4 and 8 mmol/L (72-145 mg/dL). After three consecutive measurements had shown glucose levels within the target range, glucose level was measured every 3 hours. Frequency of measurements was intensified again to once hourly for 3 hours when continuous enteral feeding was started and parenteral glucose administration had been reduced by more than 50%.

When insulin dose exceeded 200 mIU/kg/hour the protocol required nurses to consult with the attending physician. Maximum insulin dose was 600 mIU/kg/hour. Stop criteria were defined as: a) blood glucose level <4 mmol/L (72 mg/dL); b) insulin rate <15 mIU/kg/hr at any time or <30 mIU/kg/hr for more than 24 hours; c) start enteral bolus feeding and or interruption of continuous feeding or dextrose infusions; d) discharge from the PICU. When blood glucose decreased < 2.6 mmol/L (47 mg/dL), a bolus infusion of dextrose 10% of 5ml/kg was administered intravenously.

Insulin infusion was restarted after discontinuation when blood glucose rose to >8 mmol/L (145 mg/dL), at the "insulin initial dose" level shown in figure 1.

Time to reach goal blood glucose level was defined as the time elapsed from start of insulin infusion until the first measurement showing that blood glucose level had dropped to ≤8 mmol/L (145 mg/dL). Hypoglycemia was defined as blood glucose level either <4 mmol/L (72 mg/dL) with hypoglycemic symptoms or <2.6 mmol/L (47 mg/dL) regardless of symptoms. Severe hypoglycemia was defined as blood glucose <2.2 mmol/L (40 mg/dL) in accordance with most studies in literature. Neurological sequelae were monitored by clinical assessment.



Stop criteria:

-blood glucose <4 mmol/L (72 mg/dL)
-insulin rate <15 mIU/kg/hr at any time or < 30 mIU/kg/hr during 24 hours
-start enteral bolus feeding
-interruption of continuous feeding or dextrose infusions
-discharge from PICU\

Figure 1 Glucose control protocol
Glucose = blood glucose level in mmol/L *(mg/dL)*.
Insulin = insulin dose in mIU/kg/hr.
(↑10 = increase current dose with 10 mIU/kg/hr, 2/3 = continue with 2/3 of current dose)

Clinical parameters

Disease severity was determined by the Pediatric Risk of Mortality score (PRISM II) during the first 6 hours of admission. Respiratory and inotropic support, use of glucocorticoids and antibiotics were recorded.

Collection of blood samples and analysis

Blood glucose measurements were obtained as soon as possible after admission. In case of hyperglycemia >8 mmol/L (145 mg/dL) measurements were repeated every hour and further according to the protocol. Blood was collected from an indwelling arterial or venous catheter or from capillary puncture. Blood glucose was measured on either a blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) or by a bedside capillary glucose measurement with a point of care system (HemoCue AB, Sweden). Blood glucose levels of <2.6 mmol/L (47 mg/dL) or >15 mmol/L (272 mg/dL) obtained by the latter method were reconfirmed with the blood gas analyzer. Hypoglycemia <2.6 mmol/L (47 mg/dL) was treated with dextrose bolus prior to reconfirmation.

Statistics

Results are expressed as medians with interquartile range unless specified otherwise. Statistical analysis was performed with a statistical analysis software program (SPSS 13.0 for WINDOWS, SPSS, Inc, Chicago, IL). Comparisons between children with one- or multi- organ failure were made with the Mann-Whitney U-test. A p-value < 0.05 was considered to be significant.

RESULTS

In an 18-month study period 50 children (28 boys), age 3.5 yrs (1.2-9.3 yrs) with various diagnoses received insulin treatment and were eligible for inclusion in the study (tables 1 and 2). Forty-two children had multiple organ failure. Median PRISM score was 12 (8-22). Eight children died, of whom three died during insulin treatment.

Concomitant therapy on admission included inotropic agents in 26 children (12 children were treated with dobutamine, 12 with dobutamine and noradrenaline, one with noradrenaline, and one with dopamine, dobutamine and noradrenaline). Forty children were mechanically ventilated and received benzodiazepines and/or morphine for sedation. Twenty-one patients received steroids (different doses and types) during insulin treatment. The duration of steroid treatment was positively correlated with the duration of insulin treatment ($r=0.65$, $p=0.001$).

Insulin protocol

Glucose intake in children ≤30 kg and >30 kg was 4.3 (2.4-5.7) and 2.6 (0.8-3.7) mg/kg/min, respectively. Five patients received full continuous enteral feeding at start of insulin treatment, 22 patients were fully parenterally fed and 23 patients received partial continuous enteral and partial parenteral feeding.

Table 1 Clinical diagnoses

Diagnosis	Number of patients
Sepsis	13
Surgical	10
Status epilepticus	6
Pneumonia	5
Status asthmaticus	4
Trauma	3
Congenital heart defect	2
Guillain Barre	2
Acute renal failure	2
Acute renal/liver failure	1
Intracerebral hemorrhage	1
Coma	1

Table 2 Characteristics of all children and those with multiple or single organ failure

	Multiple organ failure N=42	Single organ failure N=8	All children N=50
Age (yrs)	2.8 (1.0-9.0)*	11.5 (6.3-14.9)*	3.5 (1.2-9.3)
Female (%)	45%	38%	44%
PRISM	14 (7-23)	11 (8-15)	12 (8-22)
Steroid use	15 (33%)	6 (75%)	21 (42%)
Glucose intake (mg/kg/min)	3.8 (2.2-5.3)	2.7 (0.7-5.3)	3.7 (2.0-5.3)
Time from 1st episode of hyperglycemia to start insulin infusion (hrs)	3.8 (2.0-8.0)	7.5 (3.5-9.0)	4 (2.0-8.1)
Time from start of insulin infusion to normoglycemia (hrs)	5.0 (2.8-8.0)	5.5 (3.3-6.2)	5 (3.0-7.3)
Glucose at start of insulin infusion			
(mmol/L)	11.0 (9.5-13.8)	13.0 (11.7-15.3)	11.4 (9.7-14.5)
(mg/dL)	200 (173-251)	236 (213-278)	207 (176-264)
Max insulin dose (mIU/kg/hr)	70 (40-90)	70 (40-100)	70 (40-100)
Hypoglycemic events			
<4 mmol/L (72 mg/dL)	15 (33%)	0	15 (30%)
<2.6 mmol/L (47 mg/dL)	3 (7%)	0	3 (6%)
<2.2 mmol/L (40 mg/dL)	0	0	0
Duration of therapy (hrs)	36 (16-78)	21 (18-45)	34 (17-72)

Data are expressed as medians with interquartile ranges

*$p<0.05$

Insulin treatment was initiated 3.8 hours (2.0-8.0 hrs) after the first episode of hyperglycemia occurred in children with multiple organ failure. Insulin treatment was initiated 7.5 hours (3.5-9.0 hrs) after the first episode of hyperglycemia in children with single organ failure. Blood glucose level at initiation of therapy was 11.4 mmol/L (207 mg/dL) (9.7-14.5 mmol/L, 176-264 mg/dL).

Within 12 hours after initiation of therapy blood glucose had dropped to ≤8 mmol/L (145 mg/dL) in 47/50 children (94%). Median time needed to reach goal level was 5.0 hrs (3.0-7.3 hrs). The maximum dose of insulin ranged from 20 to 200 mIU/kg/hr (median 70 mIU/kg/hr).

Duration of treatment (the 3 children who died during treatment excluded) was 34 hrs (17-72 hrs). Thirteen children received insulin for more than 72 hrs.

Rebound hyperglycemia >8mmol/L (145 mg/dL) during insulin therapy occurred in 25 patients. Median blood glucose level during rebound was 8.9 mmol/L (162 mg/dL) (8.3-9.7 mmol/L, 150-176 mg/dL) with a duration of 1 hour (1-3 hours). There was no relation between the occurrence of rebound hyperglycemia and either blood glucose level at start of treatment or the length of time to glucose control. Duration of insulin therapy (51 vs 19 hours, $p<0.01$) and maximum insulin dose during treatment (80 vs 44 mIU/kg/uur, $p<0.05$) in the rebound group were significantly higher than in the patients without rebound hyperglycemia.

Hypoglycemia <4 mmol/L (72 mg/dL) was noted in 3.5% of all blood samples (in 15 children). Hypoglycemia <2.6 mmol/L (47 mg/dL) was noted in 0.4% of all samples (in 3 children, all without clinical symptoms). Episodes of severe hypoglycemia <2.2 mmol/L (40 mg/dL) did not occur. The occurrence of hypoglycemia was associated with the following findings: delayed glucose measurement (4 times, leading to hypoglycemia <2.6 mmol/L (47 mg/dL) in 3 cases), incorrect insulin adjustment (4 times), change of parenteral to enteral nutrition without insulin dose adjustment (3 times), and other reasons (4 times).

Various reasons to stop insulin treatment were (table 3): Blood glucose <4 mmol/L (72 mg/dL) (11 times), insulin dose <15 mIU/kg/hr (15 times), insulin dose <30 mIU/kg/hr for more than 24 hours (5 times), start enteral bolus feeding (4 times), death during treatment (3 times), or discharge (2 times). In 10 instances the reason had not been documented.

Table 3 Reasons to stop insulin treatment

Reason	Number of patients (percentage)
Hypoglycemia <4 mmol/L (72 mg/dL)	11 (22%)
Insulin dose <15 mIU/kg/hrs	15 (30%)
Insulin dose <30 mIU/kg/hr more than 24 hrs	5 (10%)
Start enteral bolus feeding	4 (8%)
Death during insulin therapy	3 (6%)
Discharge from PICU	2 (4%)
Unknown reasons	10 (20%)

Problems encountered with implementation of the protocol

Several protocol violations were encountered. Glucose was not always administered according to the protocol. At start of the insulin treatment, intake was too low in 17 children (34%) and too high in 10 children (20%).

Insulin treatment was initiated in time in 9 children (21%) with multiple organ failure and in 3 children (38%) with single organ failure. The insulin starting dose was correct in 39 children

(78%). Nine children (18%) started with an insulin dose that was too low (10 mIU/kg/hr (10-20 mIU/kg/hr) below the recommended dose). Two children (4%) started with a dose that was too high (10 mIU/kg/hr above the recommended dose).

Glucose measurements were done more frequently than was necessary according to the protocol. The median number of glucose measurements per hour until normoglycemia was 1.2 (1.0-1.6). It dropped to 0.5 (0.3-0.8) in the period after normoglycemia until discontinuation of insulin treatment. In the period until normoglycemia, the number of adjustments of insulin dosage was 3 (1-7), i.e. 0.5 adjustments per hour (0.3-0.8).

In 42% (120/285) of occasions the adjustments were done incorrectly. Regarding those insulin adjustments that were done incorrectly, insulin infusion rate was too low in the majority (63%, 76/120) of the occasions. The median insulin infusion rate was 10 mIU/kg/hr (10-20 mIU/kg/hr) below the recommended dose according to the protocol. Insulin infusion rate was too high in 37% (44/120) of the occasions, with a median insulin rate of 10 mIU/kg/hr (10-20 mIU/kg/hr) above the recommended dose according to the protocol.

DISCUSSION

This study showed that implementation of a stepwise nurse-driven protocol enabled achievement of normoglycemia within 12 hours after initiation of insulin therapy in 94% of the children. Severe hypoglycemia <2.2 mmol/L (40 mg/dL) did not occur.

Studies in critically ill children have defined different blood glucose thresholds for hyperglycemia (18). Levels >8.3 mmol/L (>150 mg/dl) seem to have the strongest association between hyperglycemia and increased morbidity and mortality (4, 8, 19). Based on these studies, we defined the threshold for hyperglycemia as blood glucose level >8 mmol/L (145 mg/dL). Consequently, the target range for blood glucose level was established at 4 to 8 mmol/L (72-145 mg/dL). This range differs from the range used in clinical trials in adults, from 4 to 6.1 mmol/L (72-110 mg/dL). We opted for a slightly higher target range, because critically ill children are believed to be at a higher risk of developing hypoglycemia. The time elapsed until normoglycemia was reached was relatively short (5 hours), suggesting that the glucose control protocol was well designed. Still, as only 58% of the adjustments until normoglycemia were correct, an even faster time until normoglycemia could have been reached.

Although severe hypoglycemia <2.2 mmol/L (40 mg/dL) did not occur, hypoglycemia <4 mmol/L (72 mg/dL) was seen in 15 of the 50 children (30%). The most plausible explanations for the occurrence of hypoglycemia were: delayed glucose measurements, incorrect insulin adjustments and change of parenteral to enteral nutrition without insulin dose adjustments. These findings accentuated the importance of adherence to the protocol. Serious concerns have arisen about the consequences of hypoglycemia in critically ill adults on intensive insulin therapy (20, 21). While it is clear that severe and prolonged hypoglycemia

is harmful for individuals of any age, there has been no evaluation to date of the effect of brief hypoglycemia on PICU outcome. In adult studies the incidence of severe hypoglycemia was four to seven times greater in critically ill patients treated with intensive insulin therapy as compared to control groups (13-15, 22). Adult studies which evaluated the association between hypoglycemia and risk of death show conflicting results (20, 23). Larger prospective studies are needed to evaluate outcome after hypoglycemia in the (P)ICU.

The protocol intensified nursing workload, notably during acute admissions. Frequencies of blood glucose determinations and adjustments of insulin infusion rates were highest during the period from start of insulin treatment to normoglycemia occurred. Previous surveys among nurses revealed that the frequency of blood glucose sampling was considered as the most common reason for the increased workload (24).

The nursing burden was not quantified explicitly, which can be considered a limitation of this study. A second limitation of this study is that blood glucose measurements were done by either of two methods, and that the type of blood was capillary, arterial or venous. Values found could differ as to the method and type of blood used.

This study was not designed to show beneficial effects on morbidity or mortality. It appeared, however, that 37 of the 50 children were treated for less than three 3 days. The question is, whether it will be possible to study the effects on morbidity and mortality in children whose insulin treatment is very short. Future studies should elucidate which children might benefit from insulin treatment. Furthermore, a computer decision support system for glucose control could exhibit even more efficient glucose control with less occurrence of hypoglycemia (25).

Conclusions

In this study we showed that a stepwise, nurse-driven protocol enabled achievement of normoglycemia within 12 hours after initiation of insulin therapy in almost all of the patients.

Although there were many protocol violations, these were mostly of minor importance and severe hypoglycemia <2.2 mmol/L (40 mg/dL) did not occur. We conclude that the glucose control protocol is effective in treating hyperglycemia in critically ill children. Further studies are necessary to assess safety before the protocol could also be implemented in other PICU's.

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Management of hyperglycemia in the pediatric intensive care unit

LETTER TO THE EDITOR AND AUTHOR'S REPLY

Mark R. Rigby, Catherine M. Preissig

Pediatric Critical Care Medicine 2010; 11: 163

Jennifer J. Verhoeven, Koen F.M. Joosten

Pediatric Critical Care Medicine 2010; 11: 317

Letter to the Editor

Management of hyperglycemia in the pediatric intensive care unit

To the Editor:

We were very excited to see the recent publication by Dr. Verhoeven et al describing another experience of active glycemic control in critically ill children (1). This study describes the implementation of a protocolized approach to control hyperglycemia in children with single or multiple organ failures admitted to their pediatric intensive care unit in Rotterdam, Netherlands. Patients with sepsis, trauma, multiple organ failure, and/or receiving mechanical ventilation were included in this study, and the glycemic control protocol was initiated when blood glucose (BG) was >145 mg/dL on two consecutive readings in 6 hrs (in those with single organ failure) or one reading (in those with >2 organ failures). Those with known diabetes mellitus were excluded and there were no apparent age restrictions. Goal BG levels were targeted at <145 mg/dL, using a nurse-driven, weight-based insulin infusion algorithm, and all patients received routine glucose infusions. Although the authors report no occurrence of severe hypoglycemia (defined as BG <40 mg/dL), no data on how successful their approach was at maintaining their target glycemic goal is provided. Although the authors indicate "So far,no studies have published results of implementation of an insulin treatment protocol in critically ill children . . .," theirs is in fact the third peer-reviewed description of an active approach to glycemic control in a pediatric intensive care unit. In November 2008, our group published our experience, using a physician-initiated, nurse-driven approach to hyperglycemia detection and management (2). We showed that we could effectively maintain BG levels in our target range of 80 to 140 mg/dL with little to no increase in baseline hypoglycemic episodes. In addition, we have also shown and recently published that hyperglycemia prevalence and severity are correlated with certain illness-severity risk factors (3). In February 2009, Vlasselaers et al published a groundbreaking, randomized, controlled trial in pediatric critical care, where strict glycemic control (in age-adjusted fasting ranges) was compared with more conservative control (180–214 mg/dL) (4). Although there wasoutcome benefit (including decreased mortality) in the strict control arm, hypoglycemic rates of ~ 25% in that group raises concerns and likely obviates this approach into standard practice. Reports describing successful protocols and suggesting that glycemic control can be accomplished safely and effectively is important as many pediatric intensivists cite fear of hypoglycemia as a primary concern when considering adopting such an approach. Likely, only after experience with such safe, effective approaches can convincing outcome studies be conducted

which will provide the evidence needed to truly support the routine practice of glycemic control in pediatric critical care.

The authors have not disclosed any potential conflicts of interest.

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Pediatr Crit Care Med 2010 Vol. 11, No.1,163

Letter to the Editor

Management of hyperglycemia in the pediatric intensive care unit

The authors reply:

We would like to thank Catherine Preissig and Mark Rigby for their additional remarks in the January issue of *PCCM* about our recent publication on management of hyperglycemia in the pediatric intensive care by implementation of our glucose control protocol (1).

Today, our protocol is indeed the third peer-reviewed description of an active approach to glycemic control in the pediatric intensive care. Preissig et al (2) and Vlasselaers et al (3) have recently published their protocolized approach to control hyperglycemia in critically ill children. In addition, at this moment, there is a large multicenter study in England investigating if strict blood glucose control in pediatric intensive care units is beneficial when compared to current standard practices (Control of Hyperglycemia in Pediatric intensive care, CHiP trial) (4).

There are some notable differences between the protocolized approaches to control hyperglycemia that need to be discussed. First, although our glucose control protocol is designed for all ages (same as the work of Vlasselaers et al and CHiP trial), Preissig et al only use their protocol for pediatric intensive care patients aged >6 months and weighing >5 kg. Second, different target ranges for plasma glucose levels are being used: 4.4 –7.7 mmol/L (80–140 mg/dL) by Preissig et al, 2.8–4.4 mmol/L (51–80 mg/dL) for infants aged 0–1 yr and 3.9 –5.5 mmol/L (71–100 mg/dL) for children aged 1–16 yrs by Vlasselaers et al, 4–7 mmol/L (72–128 mg/dL) in the CHiP trial and 4–8 mmol/L (72–145 mg/dL) in our study. Third, in the study by Preissig et al and CHiP trial, no glucose intake ranges are recommended, whereas we advocate to start with a standard glucose regimen, in children ≤30 kg: 4–6 mg/kg/min and in children >30 kg: 2–4 mg/kg/min. In the study of Vlasselaers et al, median glucose intake on day 1 after admission was only 3.5 mg/kg/min for infants <1 yr of age and 2.8 mg/kg/min for children 1–16 yrs of age. Fourth, we start with an insulin infusion rate depending on the exact glucose level varying between 0.02 IU/kg/hr and 0.05 IU/kg/hr, whereas the other protocols use one or two starting doses, which are considerably higher than our insulin starting doses: 0.05 IU/kg/hr by Preissig et al, 0.1 IU/kg/hr to 0.2 IU/kg/hr depending on initial blood glucose level by Vlasselaers et al and CHiP trial. It should be further investigated whether one or more of the above issues are associated with early achievement of normoglycemia, the prevalence of hypoglycemia (especially in infants), and most importantly beneficial outcome. We agree with Preissig and Rigby that hypoglycemic rates of 25%, as described in the randomized control trial by Vlasselaers et al, with

the majority of hypoglycemias in infants <1 yr (70 infants and 17 children), raises concerns. With our approach, no hypoglycemia ≤2.2 mmol/L (≤40 mg/dL) occurred, and Preissig et al also showed that, with their approach, the occurrence rate of hypoglycemia was very low (4%). At this moment, we have treated 323 children with our glucose control protocol, and an ad hoc analysis of 7195 blood glucose samples showed hypoglycemia of ≤2.2 mmol/L (≤40 mg/dL) in only 0.3% of the samples, corresponding with 4% of the patients. Furthermore, mean time until target blood glucose level was 5 hrs with both our and Preissigs' approach. Concerning the issue on how successful our approach was to maintain the target glucose ranges of 4 – 8 mmol/L (72–145 mg/dL), we found in 50% of the patients a rebound hyperglycemia with median blood glucose levels of 8.9 mmol/L (162 mg/dL). However, duration of this rebound was relatively short with a median of 1 hr. Interestingly, there is a marked discrepancy between the duration of insulin treatment in our group in comparison with other studies. Although we only treated patients for a mean of 2.1 days, Preissig et al treated patients for 6.3 days and Vlasselaers et al treated patients with intensive insulin therapy throughout intensive care stay for 5.5 days. This might be due to the strict stopping criteria for insulin administration in our protocol.

In conclusion, we agree with Drs. Preissig and Rigby that it is important to describe efficient protocols for glycemic control in pediatric critically ill patients, which do not increase the occurrence of hypoglycemic events. Vlasselaers et al reported a beneficial short-term outcome in pediatric patients treated with intensive insulin therapy. However, the majority (75%) of their patients was admitted after cardiac surgery, which means that further research is necessary to establish the beneficial effects of insulin therapy in all disease categories affecting critically ill children.

The authors have not disclosed any potential conflicts of interest.

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Pediatr Crit Care Med 2010 Vol. 11, No. 2, 317

CHAPTER 9
Glycemic control in pediatric critical care

LETTER TO THE EDITOR AND AUTHOR'S REPLY

Koen F.M. Joosten, Sascha C. Verbruggen, Jennifer J. Verhoeven

The Lancet 2009; 373: 1423-1424

Greet van den Berghe, Dirk Vlasselaers, Lars Desmet et al.

The Lancet 2009; 373: 1424

Letter to the Editor

Glycaemic control in paediatric critical care

To the Editor:

A major concern in the study by Dirk Vlasselaers and colleagues[1] is the high incidence of hypoglycaemic events in the intervention group (70 infants, 17 children [25%]). In a large Australian cohort,[2] a U-shaped outcome curve showed that both high and low glucose concentrations worsen outcome. There could be several reasons for the high incidence of hypoglycaemia in the study. First, the target ranges for plasma glucose concentrations were low (2·8–4·4 mmol/L for infants and 3·9–5·6 mmol/L for children). Second, the infants' glucose intake was lower than recommended (median 3·5 mg/kg/min on day 1 compared with 5·5 mg/kg/min according to guidelines from the European Society for Paediatric Gastroenterology, Hepatology and Nutrition). Third, the treatment algorithm for insulin was adjusted by the nurses on the basis of their experience. In our institution, hyperglycaemia is treated (target glucose concentrations 4–8 mmol/L[3]) by use of a detailed stepwise algorithm to adjust insulin therapy.[4] None of our patients has had a plasma glucose concentration of less than 2·2 mmol/L. Additionally, in adults in intensive care, use of a computer-assisted glucose control protocol was shown to maintain the incidence of hypoglycaemia (<2·2 mmol/L) at only 0·86%.[5] Finally, the starting dose of insulin was high (0·1–0·2 IU/kg/h), whereas a lower starting dose of 0·02–0·05 IU/kg/h would seem to be safer.[5] An appropriate glucose intake, especially in infants, according to weight and age, in combination with a stepwise (computer-assisted) insulin adjustment protocol and slightly higher glucose target concentrations might decrease the incidence of hypoglycaemia without losing the beneficial effects of insulin therapy in critically ill children.

We declare that we have no conflicts of interest. Koen Joosten, Sascha C Verbruggen and Jennifer J Verhoeven Erasmus Medical Center/Sophia Children's Hospital, Dr Molewaterplein 60, 3015 GJ Rotterdam, Netherlands

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The Lancet, Volume 373, Issue 9673, 25 April 2009-1 May 2009, Page 1423-1424.

Letter to the Editor

Glycaemic control in paediatric critical care

Authors'reply:

Coert Zuurbier and colleagues argue that the glycaemic targets chosen for the control groups in randomised controlled trials investigating intensive insulin therapy in patients in intensive-care units (ICUs) should be more closely examined. We could not agree more. Variable control targets might indeed partly explain the variable results of studies in adults.[1]

Zuurbier and colleagues suggest that in the control group of our paediatric ICU study we should have targeted 7–8 mmol/L instead of 12 mmol/L, since this would better reflect a "modern conventional" group. By contrast, Catherine Preissig and Mark Rigby make the opposite argument, claiming we should have targeted 7–8 mmol/L in the intervention group. Both suggestions are worth investigating.

There is ample evidence for adverse outcomes associated with hyperglycaemia in adult and paediatric ICU patients. This association follows a J-shaped curve, the nadir being the "normal level" for age, and a linear rise in risk of death for levels exceeding the upper normal range. Association does not necessarily mean causality, however.[2] Indeed, hyperglycaemia could merely reflect severity of illness, a beneficial adaptation to illness, or, as in diabetes mellitus, it can induce complications.

To differentiate between these three possibilities, a randomised controlled trial is the only option. In children, no such trials addressing this question had been done before ours, so there was no evidence for any glycaemia target in paediatric ICU patients. In any first study, the control group should reflect this ignorance. This is exactly why we did the study, to investigate whether the "naturally" occurring hyperglycaemic response to illness is beneficial or harmful. In the light of "primum non nocere", the control group preferably gets no treatment. However, the only undisputable adverse effect of hyperglycaemia in any condition is glucosuria and concomitant hypovolaemia when blood glucose concentrations exceed the renal threshold of 12 mmol/L. Hence, a "don't touch" approach unless this level is reached was chosen for the control group in our three randomised trials.[3], [4] and [5] This is the only correct choice for a first study in a specific patient population. As a target for the intervention group, we chose "normal for age". Whether another (higher than normal) target, as suggested by Preissig and Rigby and by Koen Joosten and colleagues, is equally effective and avoids risk of hypoglycaemia should be studied by a randomised trial. Also the eventual benefit of additional glucose infusion in infants, or a computerised closed-loop system, remains to be studied. The opposing viewpoints of these correspondents nicely illustrate how clinical practice often

evolves in opposite directions on the basis of expert opinions instead of evidence. We provided the first bit of evidence. Clearly, this is only the beginning.

We declare that we have no conflicts of interest.

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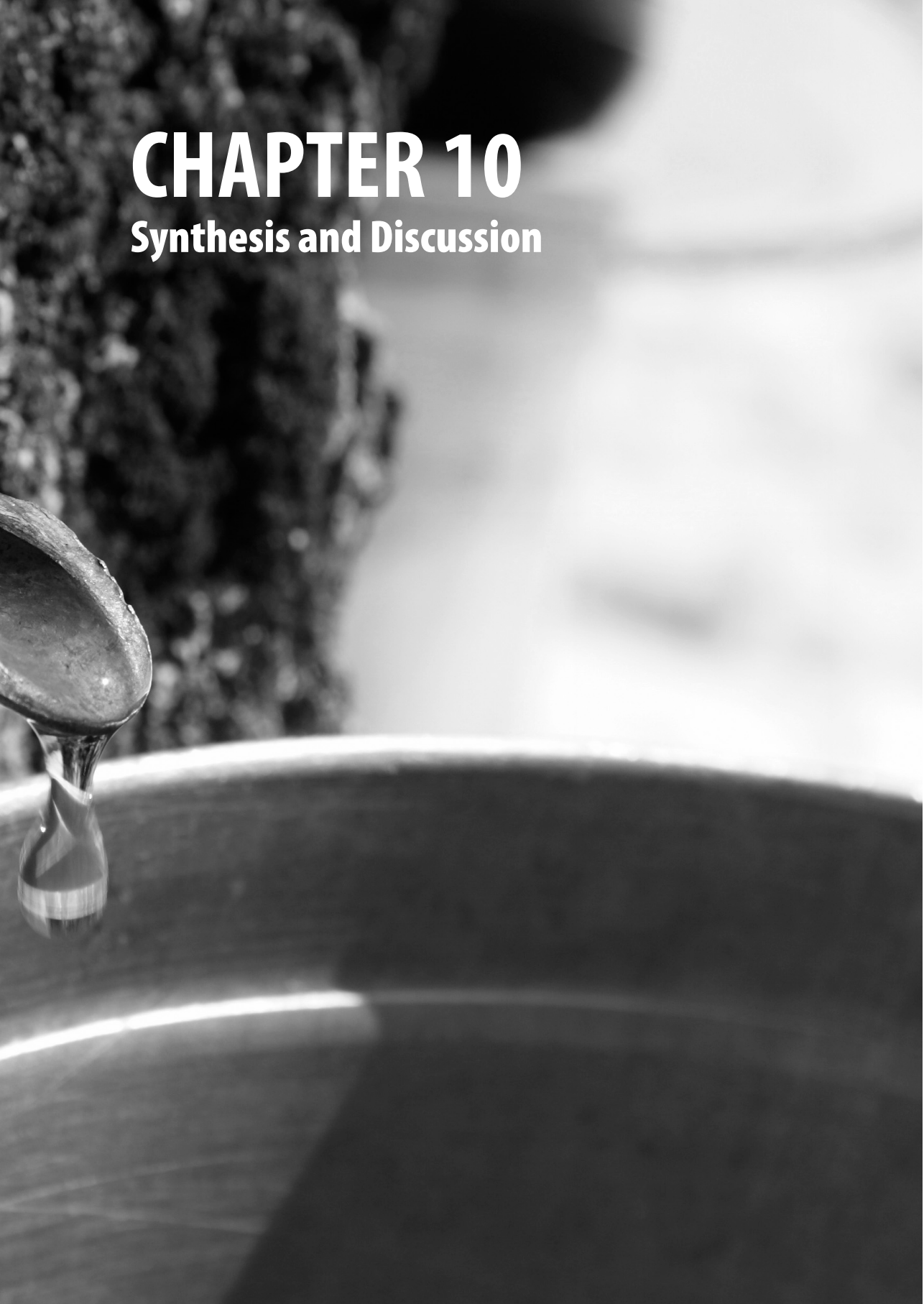

CHAPTER 10
Synthesis and Discussion

In **Chapter 1** we describe the background and initial goals of the studies presented in this thesis:
a) Energy requirements of critically ill children assessed by measurements of energy expenditure and substrate utilization (chapters 2,3,4).
b) Pathophysiological aspects of stress hyperglycemia in two diagnostic groups (critically ill children with meningococcal sepsis and septic shock and critically ill children after cardiac surgery for congenital heart defects, chapters 5,6).
c) Insulin/glucose ratio as a marker for insulin therapy in critically ill children with hyperglycemia (chapter 7).
d) Experiences with the development and implementation of a glucose control protocol in the pediatric intensive care unit (chapter 8).

ENERGY REQUIREMENTS IN CRITICALLY ILL CHILDREN

During critical illness and recovery thereafter, adequate nutritional support is an important aspect of the clinical management of pediatric intensive care patients. Adequate nutrition in critically ill children is needed for survival, growth and development. Despite the growing attention for nutrition, many hospitalized children suffer from both acute and chronic malnutrition. Also, severe underfeeding and overfeeding may occur during hospital stay. [1-4] There is a high incidence of protein energy malnutrition in children with (congenital) heart disease, due to decreased intake, increased energy expenditure (attributable to cardiac failure or increased work of breathing), and malabsorption (attributable to altered gastrointestinal function by lower cardiac output).[5] Another group at risk for malnutrition includes children with burn injuries. In these children a hypermetabolic stress response and poor intake result in energy deficits, and the negative effects on nutritional status may persist for months after injury.[6-7] An increased risk of malnutrition is also evident in preterm neonates and in children with chronic disease, major congenital anomalies, chronic lung disease (e.g. cystic fibrosis and broncho-pulmonary dysplasia), diseases of the gastro-intestinal tract (e.g. intestinal atresia, short bowel syndrome, inflammatory bowel disease), cancer, HIV-infection, renal disease, or cerebral palsy.[8-11] Both underfeeding and overfeeding may lead to in-hospital complications and post discharge adverse effects, as described in the introduction to this thesis. Evaluation of nutritional support is best done by assessing of both energy intake and energy expenditure.

In 1995, when we started to measure energy expenditure and substrate utilization in critically ill children by indirect calorimetry, research on this subject was still in its infancy. However, the importance of oxygen in metabolism and indeed life itself, was first revealed by the work of the Anglo-Irish scientist Robert Boyle (1627-1691), who established the concept of the chemical elements. Crucially, Boyle demonstrated that when a lighted candle went out in a closed chamber, a mouse confined to the same chamber rapidly died.

In **Chapter 2** we present the results of the first energy expenditure measurements in 50 mechanically ventilated children (median age 7 months (range 2 days to 13 years) with mixed diagnoses (median PRISM score 6 (range 0 to 13)). There was a close correlation between the measured resting energy expenditure (MREE) and predicted resting energy expenditure (PREE) by the Schofield formula for weight, age and sex, but Bland-Altman analysis showed lack of agreement between individual MREE and PREE. We therefore concluded that standard prediction equations are not appropriate to calculate energy needs and energy expenditure should be measured in the individual child. Since then, the relative difficulty of indirect calorimetry and the poor precision of standard predictive methods have inspired researchers to develop new prediction equations derived from energy expenditure measurements of ventilated, critically ill children. In **chapter 4,** energy expenditure was measured in 94 mechanically ventilated children (median age 6 months (range 2 days to 15 years) with mixed diagnoses (median PRISM score 9 (range 0 to 33)). Schofield's equation for weight, height, age and sex showed the highest accuracy by predicting energy expenditure within 10% of the MREE in 40% of the children. The lowest accuracies (16% and 19%) were found using the equations developed by White et al.[12] for mechanically ventilated children. We have elaborated on the most plausible explanations for failure of the White equations to accurately predict REE. The first White equation includes 6 variables: age, weight, weight for age Z-score, body temperature, number of days after PICU, and primary reason for admission. An important caveat in the White equations is the use of estimated weights, which generally are known not to be reliable.[13] White et al. reported the highest levels of energy expenditure in children after surgery: the lowest in children with respiratory illness.[12] However, others did not find differences in MREE between children with sepsis, brain injury, respiratory failure, transplant and cardiac surgery.[14] Moreover, we found, in accordance with others, a lack of agreement between MREE within diagnostic groups.[15-18] Only after severe traumatic brain injury and after severe burn injury a hypermetabolic response is seen in the majority of children.[18-21] Apparently, comorbidities and varying clinical conditions, such as catecholamine use, mechanical ventilation, sedation, neuromuscular blockade and a thermoneutral environment, are important factors significantly influencing MREE. Body temperature, too, greatly influences energy expenditure in infants and children, as shown from a 6-12% increase in resting energy expenditure per degree increment in body temperature.[22-23] Although this should be taken into account when calculating energy expenditure in the individual patient, it will not increase accuracy of a general prediction equation. In **chapters 2,3 and 4** we reported a normo- or hypometabolic response in 70% of the children, which is in accordance with other reports in critically ill children.[14, 16, 24] Serial energy expenditure measurements during PICU admission have shown a small coefficient of variation in measurements over one week.[25] Therefore, the parameter "number of days after intensive care admission" is another questionable parameter in the first White equation.

In **Chapter 3** we determined the value of indirect calorimetry combined with nitrogen balance in 36 mechanically ventilated children (median age 10 months (range 1 week to 13 years) with mixed diagnoses (median PRISM score 7 (range 0 to 17)). In only 47% of the patients measured RQ approximated the calculated RQ of the macronutrients administered (RQ macr), in 22% RQ was above RQmacr, suggesting overfeeding, and in 31% RQ was below RQmacr, suggesting underfeeding. The ratio of caloric intake/MEE was significantly higher in children with a positive nitrogen balance compared to those with a negative nitrogen balance. Thus, feeding according to or in excess of MEE can be a guideline for providing adequate caloric intake. In the children with a positive nitrogen balance, the caloric intake exceeded MEE by 40%. The optimal caloric intake in critically ill children is still being debated. Obviously, caloric intake should equal measured energy expenditure in the acute phase of disease, clinically characterized by hemodynamic and respiratory instability. The acute metabolic stress period, with its increased levels of stress (catabolic) hormones, such as cortisol, catecholamines and glucagon, usually lasts no longer than 1 or 2 days in the critically ill children.[26-27] After the acute catabolic phase, caloric intake should be increased to account for tissue repair and growth. Previous studies in mechanically ventilated children showed that adequate energy intake was in the range of 1.2 to 1.5 times measured energy expenditure.[14, 28-31] We have previously shown that cumulative deficits in energy and protein intake relative to recommended dietary reference intakes (DRI) for healthy children resulted in a decrease in body weight and upper arm circumference. One could speculate, therefore, that energy requirements for critically ill children in the recovery phase of disease should be close to or even above DRI levels.[32-33] We recommend to tailor the daily increase in energy intake to prevent excessive carbohydrate, protein and fat intake. Carbohydrate intake can be monitored by daily calculations of glucose intake, serial RQ measurements and blood glucose levels. Protein and fat intake can be monitored by urea and triglyceride levels. Moreover, C-reactive protein (CRP) can be used as an indicator for anabolic restoration. The inflammatory response to infection, accidental or surgical trauma, or burn injury plays a crucial role in the catabolic stress response. When the underlying disease is cured, inflammation goes down and the recovery phase ensues characterized by decreasing levels of cytokines, decreased CRP and increasing anabolic hormonal action. In this phase, energy and dietary proteins are necessary to restore the protein lost in the acute phase of the disease and for (catch) up growth.[34]

Although the metabolic monitor is considered the best clinical ("golden") standard for the assessment of energy expenditure, there are no randomized controlled clinical trials showing that indirect calorimetry improves outcomes. Indirect calorimetry still has probably a greater role in research than in guiding daily clinical patient care. Nevertheless, we have been using indirect calorimetry for 15 years on our PICU. On the basis of our experiences, a review of the literature, and the results of our data analysis, we propose an algorithm (Figure 1) for performing nutritional assessment and nutritional support in clinical daily practice based on previous work of our group[35] and ESPGHAN guidelines on parenteral nutrition 2006.[36-37]

HYPERGLYCEMIA IN CRITICALLY ILL CHILDREN

Hyperglycemia occurring during critical illness results from a stress response modulated by the hypothalamic-pituitary-adrenal axis, the autonomic nervous system and cytokines. In critically ill children, the hyperglycemic response to stress is complex and not well clarified. Various factors play an important role in this process. For example, the presence of excessive counter-regulatory hormones (glucagon, growth hormone, catecholamines, cortisol) and cytokines (IL-1, IL-6, and TNF-α); exogenous administration of catecholamines, glucocorticoids, dextrose; and the nature of nutritional support together with relative insulin deficiency.[38] In part II of this thesis we tried to obtain a better insight into pathophysiological mechanisms leading to hyperglycemia.

Meningococcal sepsis and septic shock

The study presented in **Chapter 5** describes pathophysiological aspects of the occurrence of hyperglycemia in 78 children with meningococcal sepsis and septic shock (median age 3.5 years (range 0.1 to 16.1 years), median PRISM score 20 (range 4 to 43)). The objective of this study was to investigate the occurrence of hyperglycemia in relation with the insulin response and exogenous factors, such as glucose intake and drug use, in particular glucocorticoids, vasopressors and inotropes. Insulin sensitivity and β-cell function on admission were investigated by relating blood glucose levels to insulin levels and C-peptide levels and homeostasis model assessment (HOMA). One third of the children proved hyperglycemic (glucose level >8.3 mmol/L) on admission. For the majority of children spontaneous normalization of blood glucose levels occurred within 48 hours, without insulin treatment. Insulin resistance was predominant in hyperglycemic children, although β-cell insufficiency or a combination of insulin resistance and β-cell insufficiency were also seen. Insulin resistance is the main pathophysiological mechanism of hyperglycemia in critically ill patients. It may be caused by high levels of counter-regulatory hormones and cytokines, and by therapeutic interventions. Regarding therapeutic interventions, we found a trend towards higher cortisol and glucose levels in the glucocorticoid treated children versus those without glucocorticoids. The administration of glucocorticoids is often indispensable in children with refractory shock and/or hypoglycemia. On the other hand, it may induce hyperglycemia, which will sustain with prolonged glucocorticoid use. The glucose administration rate did not have a significant effect on the occurrence of hyperglycemia. Presumably glucose intake was too low (4 mg/kg/min in hyperglycemic children (range 0.2 to 10.4 mg/kg/min) to demonstrate the effect on glucose levels. In critically ill adults a glucose infusion rate >5mg/kg/min was associated with hyperglycemia and in critically ill children an association was seen between increased RQ (>1.0) and a glucose infusion rate of >8 mg/kg/min. Thus, although early administration of adequate amounts of carbohydrates in the acute phase of illness is necessary to

On admission (day 1)

Anthropometry
- Weight (SDS)
- Length (SDS)
- MUAC/CC
- Head circumference (SDS,<1yr)

Laboratory parameters
- Glucose*
- CRP
- Micronutrients (Mg, Ca, P)
- Tg
- (Insulin if BG>8 mmol/l (Future?))

After admission

Anthropometry
- Weight -2x/ week
- Length -1x/week (<1yr)
- Head cf -1x/week (<1yr)
- MUAC/CC -weekly

Laboratory parameters
- Glucose* } - daily
- CRP } - daily
- TG } - daily
- Urea } - daily
- Micronutrients } - daily
- N-balance -on indication

Energy expenditure

MREE: Indirect calorimetry — ASAP after admission and 2x/wk (to adjust intake based on RQ)

PREE: Schofield formula — If indirect calorimetry not possible

0-3 year	3-10 year	10-18 year
0,2 x W + 1516,7 x L - 681,8 (♂)	19,6 x W + 130,2 x L + 414,7 (♂)	16,2 x W + 137,1 x L + 515,3 (♂)
16,3 x W + 1022,7 x L – 413,3 (♀)	17,0 x W + 161,7 x L + 371,0 (♀)	8,4 x W + 465,4 x L + 200,0 (♀)

*** Glucose >8 mmol/l → glucose algorithm (go to Figure 3)**

Figure 1a

prevent hypoglycemia, excessive carbohydrate administration may result in hyperglycemia and concomitant adverse effects.

Other research groups have reported reported low insulin/glucose ratios in children with meningococcal septic shock,[39] and low C-peptide levels in hyperglycemic critically ill children with respiratory and circulatory failure.[40]

In accordance with our findings, they suggested that pancreatic β-cell dysfunction may be a cause of hyperglycemia. This complex phenomenon has been seldom evaluated in critical illness. Even in diabetes mellitus the pathophysiological mechanisms of the development of β-cell dysfunction are not fully understood. In vitro studies have shown that proinflammatory

Energy requirements

Day 1	Glucose intake	≤ 30kg 4-6 mg/kg/min
		> 30kg 2-4 mg/kg/min
Day 2-3	Start enteral feeding or parenteral feeding if enteral feeding not possible	
	Energy intake according to MREE or PREE	
Day 3-6	Increase energy intake to 2 x MREE or 2 x PREE or RDA (33)	

Daily adjustment of intake

- **Daily caloric intake calculations**

- **Carbohydrate**

Enteral	60% of total energy intake
Parenteral	10-18 g/kg/day

Indirect calorimetry
RQ >1.0 → decrease carbohydrate or energy intake
RQ <0.85 → consider increasing energy intake

Blood glucose >8 mmol/l → glucose algorithm (figure 2)

- **Protein**

Enteral and parenteral	9-15% of total energy intake 1.5-4.0 g/kg/day

- **Fat**

Enteral	40% of total energy intake
Parenteral	
infants	3-4 g/kg/day
older children	2-3 g/kg/day

Weekly evaluation of growth
Minimal growth targets:
- 100-200 g/week for infants (keep up growth chart)
- no weight loss in older children

Figure 1b

Figure 1. Proposed standard of nutritional assessment (1a) and nutritional support (1b) for critically ill children admitted to the PICU with an expected stay of more than24 hours.
ASAP, as soon as possible; BG, blood glucose level; CC, calf circumference; CRP, C-reactive protein; MREE, measured resting energy expenditure; MUAC, mid upper arm circumference; N-balance, nitrogen balance; PREE, predicted resting energy expenditure; RQ, respiratory quotient; SDS, standard deviation score; W, weight in kg; L, length in meters; RDA, recommended daily allowances (optimal requirement for healthy children allowing for energy needed for growth and recovery)

cytokines (e.g. IL-1 and TNF-α) mediate inhibition of insulin secretion by pancreatic β-cells.[41-42] Furthermore, β-cells were found exquisitely sensitive to rapid physiological changes and may be at risk of becoming dysfunctional if these changes acutely occur above a certain threshold, like in the ebb phase of the metabolic stress response.[40] These changes may be induced by multiple factors like hypothermia, vasopressors, elevations of pro-inflammatory cytokines and use of glucocorticoids.[40, 43] Also β-cell exhaustion is a reported phenomenon in critically ill adults with multi-organ dysfunction syndrome, characterized by increasing secretion up to a certain level and thereafter failing in response to further demand.[44-45]

In general, we confirmed the short duration of the acute metabolic stress response. Temporarily increased on admission, pro-inflammatory cytokines and cortisol levels, both decreased rapidly after the first day of illness.[26] This early resolution of the acute stress response, might also have influenced the insulin resistant state and would explain the low indices hyperglycemia after 48 hours in the children studied. Hyperglycemia may persist for days or weeks in critically ill adults.

Cardiac surgery for congenital heart disease

Since dysregulation of glucose homeostasis is common in children undergoing cardiac surger,[46-50] we chose this patient group for further research on the pathophysiological aspects of hyperglycemia. In **Chapter 6** we evaluated the time course of peri-operative blood glucose levels in 49 children undergoing cardiac surgery for congenital heart disease (median age 1.7 years (range 2 months -18 years, median PRISM 13 score (range 5-31)).

Hyperglycemia was present in 52% of the children at the end of surgery associated with normal or (relatively) decreased insulin/glucose ratio in almost all of them. In contrast, adults often show postoperative hyperglycemia due to an increase in insulin resistance induced by surgical trauma.[51]

Moreover, spontaneous normalization of blood glucose occurred in almost all (94%) of children within 24 hours, without the use of insulin and without significantly longer duration of ventilation, ICU or hospital stay. This was in line with one other study on glycemic profile in infants after the arterial switch operation.[49] Others reported a more gradual decrease in blood glucose levels over 3-5 days following comparable cardiac surgery for congenital heart defects.[46, 48, 50]

We showed that the administration of glucocorticoids (in 65% of the children) during surgery was the main factor associated with hyperglycemia at the end of surgery. This was in accordance with findings in adults after coronary bypass surgery,[52] showing a considerable hyperglycemic effect associated with the administration of dexamethasone. Glucocorticoids inhibit the inflammatory response induced by cardiopulmonary bypass and may thus ameliorate its adverse effects. The use of glucocorticoids in cardiac surgery is controversial for its risk of important adverse effects that may occur.[53] Since postoperative morbidity in our study was low, we concluded that the presumed positive effects of glucocorticoids seemed to have

outweighed the adverse effects of iatrogenic hyperglycemia. Future research should focus on the value of glucocorticoid therapy during pediatric cardiac surgery to weigh both the pros and cons of either hyperglycemia and glucocorticoid therapy, preferably in large randomized controlled trials .

In general, three major conclusions can be drawn from both studies on glucose homeostasis:

a) Hyperglycemia is a frequent, but spontaneously normalizes in the majority of children with meningococcal sepsis or septic shock and children after cardiac surgery for congenital heart defects.

b) Both insulin resistance and (relative) β-cell dysfunction play a role in the occurrence of hyperglycemia in critically ill children.

c) Exogenous factors such as glucose intake and glucocorticoid administration significantly influence blood glucose levels.

These conclusions raise some important questions:

- Does insulin therapy have an additional positive effect on outcome in these diagnostic categories, considering that hyperglycemia normalizes spontaneously within 24-48 hours?
- Is the presence of a hypo-or hyperinsulinemic response helpful in assessing dose or duration of insulin therapy?
- Is it possible to predict which children or patient groups with hyperglycemia could benefit from insulin therapy or not?

To answer these questions, we performed a study to explore the relationship between insulin response to hyperglycemia and clinical outcome in critically ill hyperglycemic children. This study is presented in Part III, **chapter 7**.

Methodological considerations

A limitation of the studies presented in **chapter 5** and **6** was the inability to assess the exact insulin sensitivity, because it was measured indirectly by insulin/glucose ratio and HOMA. The hyperinsulinemic euglycemic clamp technique is the "golden standard" for quantifying insulin sensitivity in vivo because it directly measures the effects of insulin to promote glucose utilization under steady state conditions. We resorted to indirect methods, because the clamp technique is not very practical in clinical settings and not easily and safely implemented in large studies with critically ill children. Therefore, as also previously described by others, we used levels of insulin and/or C-peptide and HOMA in relation with blood glucose levels and glucose intake rates to determine insulin sensitivity and β-cell function.[39-40 54-56] There is a good correlation between estimates of insulin resistance derived from HOMA and from the hyperinsulinemic clamp.[57] β-cell function assessment is more difficult because the β-cell response to the secretory stimuli is complex and there is no gold standard.[57] Fasting levels of insulin or C-peptide are the most reliable parameters (both for HOMA and insulin/glucose or C-peptide/glucose ratios) for comparison between individuals and between

study populations. However, in critically ill patients it is rather difficult to achieve a fasting state. For one, gastric emptying is delayed, and glucose absorption will therefore continue for several hours after last feed.[58] Second, as glucose is necessary to cover energy requirements of organs and tissues, exclusively dependent on glucose, such as the brain, glucose administration should not be stopped. Another justification for the use of non-fasting insulin, C-peptide and glucose levels is based on the finding that exogenous glucose administration diminishes endogenous glucose production. The endogenous glucose production declines with increasing rate of intravenous glucose until it is almost completely suppressed.[59] This was also seen in children after craniofacial surgery (unpublished data of our own). Assuming that the endogenous insulin secretion response is similar to endogenous and exogenous glucose, this suggests that the insulin/glucose ratio and HOMA are independent of glucose infusion rate. However, these issues seem to be more complicated, as others have shown that administration of glucose, even in larger amounts, to critically ill adults, failed to suppress endogenous glucose production.[60] There are no data concerning endogenous glucose production in relation with the amount of administered glucose in critically ill children.

In conclusion, HOMA, insulin/glucose ratio and C-peptide/glucose are useful markers of insulin sensitivity and/or β-cell function, also in critical illness, [54-55, 57, 61] but taking into account the following limitations:

- Reaching a fasting state is often not possible in clinical practice; in this case a continuous IV or enteral glucose infusion should be given to reach steady state glucose and insulin levels.
- Results need to be interpreted in relation with glucose intake and paired blood glucose level.
- Normal fasting values have not been validated for critically ill children. Quantifying the precise level of insulin sensitivity in individual critically ill patients is advised against, therefore. Only the presence or absence of insulin resistance should be established.

GLYCEMIC CONTROL IN CRITICALLY ILL CHILDREN

As stated in the introduction to this thesis, treatment of hyperglycemia in critically ill adults has become standard of care.[62] Nevertheless, strict glycemic control in PICUs remains controversial because outcome data are lacking. Indeed, even in adult care it is not clear which patients should be treated with strict glycemic control. Furthermore, the major adverse effect of glucose control in adults and children is hypoglycemia, which may be more deleterious in the pediatric population, as sustained low blood glucose may impact brain development.

In **chapter 7** the relationship is presented between insulin response to hyperglycemia and clinical outcome in critically ill hyperglycemic children treated with insulin. We hypothesized that the presence of a hypo-or hyperinsulinemic response could be helpful in predicting

which children or patient groups with hyperglycemia could benefit from insulin therapy. Sixty-four children with hyperglycemia meeting the criteria for insulin treatment (discussed in **chapter 8**) were included (median age 7.0 years (range 2 weeks to 17 years), median PRISM score 14 (range 0 to 36), mixed diagnoses). Blood samples for stress hormonal, metabolic and immunological parameters were drawn just before start of insulin infusion. We found that children with a hyperinsulinemic response were more often mechanically ventilated, had a longer duration of insulin therapy, mechanical ventilation and PICU stay than children with a hypoinsulinemic response. Duration of glucocorticoid use was strongly correlated with duration of insulin therapy, which might reflect the depressing effect of glucocorticoids on insulin sensitivity.

On the other hand, a hypoinsulinemic response in combination with a short duration of insulin therapy was present in over three quarters (78%) of the children without respiratory failure. Therefore, the value of insulin therapy in these children is questionable. Their hyperglycemia would probably also have normalized within a day without insulin therapy and without negative effects on morbidity. This suggests that critically ill children without respiratory failure and without overt insulin "resistance" would not benefit much from insulin therapy. Likely, these children might be at risk of hypoglycemia when treated with insulin. A randomized controlled trial in critically ill children with hyperglycemia should be performed to prove our hypothesis that the presence of a hypo- or hyperinsulinemic response can predict dose and duration of insulin therapy. With the rapid and highly sensitive immunoradiometric assay for insulin, the insulin/glucose ratio or HOMA could be suitable for use in clinical practice.[63]

The glucose control protocol

Awaiting the results of randomized controlled trials to assess outcome in hyperglycemic children treated with insulin, we were one of the first to develop a glucose control protocol for the treatment of hyperglycemia in critically ill children. In **chapter 8** we describe our experiences with the implementation of this protocol on our PICU (figure 2. Algorithm A). We included 50 critically ill hyperglycemic children (median age 3.5 years (range 1 month to 15 years), median PRISM score 12 (range 8 to 22), mixed diagnoses). It appeared that the stepwise nurse-driven protocol enabled to achieve normoglycemia (target glucose 4-8 mmol/L) within 12 hours after initiation of insulin therapy in 94% of the children. Although there were many protocol violations, these were mostly of minor importance and severe hypoglycemia <2.2 mmol/L did not occur. Three quarters of the children were treated with insulin for <3 days. The question is whether these children will benefit from insulin therapy, as the Leuven group reported a reduction in mortality only in a subgroup of medical adult patients who stayed and were treated with insulin in ICU for > 3days.[64]

Since our publication, other authors have reported on their experiences with other protocols for critically ill children.[47, 65-69] The main features of the current protocols are summarized

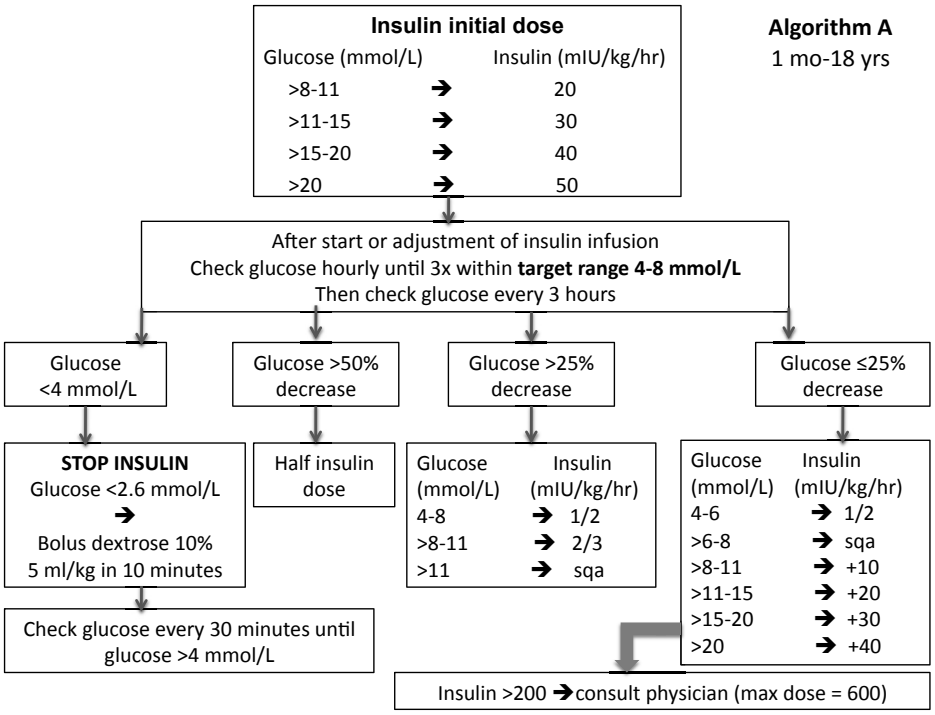

Figure 2. Algorithm A
Glucose control protocol for infants and children (1 mo- 18 years)

in Table 1. There are some notable differences between the protocolized approaches to control hyperglycemia that need to be discussed (**chapters 9 and 10**). First, different target ranges for plasma glucose levels are being used. Most obvious is the lowest minimal target level of 2.8 mmol/L accepted for children of 0-1 yr by Vlasselaers et al.[65] Second, none of the authors defined glucose intake ranges, whereas we advocate to start with a standard glucose regimen: 4-6 mg/kg/min in children <30 kg; : 2-4 mg/kg/min in children >30 kg. Third, our protocol and the recently published Pediatric Yale Insulin Infusion Protocol (PYIIP)[67] are the only ones to start with a moderate insulin infusion rate depending on the exact glucose

level, whereas the other protocols use one or two starting doses, which are considerably higher than ours. Fourth, we have defined strict stopping criteria in contrast with the other protocols. It should be further investigated whether one or more of the above issues are associated with early achievement of normoglycemia, the presence of hypoglycemia and most importantly beneficial outcome. Mean time until target blood glucose level was 5 hours with both our and Preissig's approach[47] and 10 hrs with PYIIP.[67]

The high hypoglycemia rate (blood glucose ≤ 2.2 mmol/L) of 25%, as described by Vlasselaers et al. and Jeschke et al. raises concerns.[65, 69] Hypoglycemia rate in the PYIIP[67] was 10%, which was still higher than with our approach. Analysis of 7195 blood samples of 323 children in our population showed hypoglycemia in only 0.3% of the samples, corresponding with 4% of the children, as on Preissig's approach.[47] In randomized controlled trials investigating clinical effects of glycemic control in adults the occurrence of hypoglycemia varied between 5 and 19%.[70] Risk factors for hypoglycemia in critically ill patients include a previous diagnosis of diabetes mellitus, sepsis, shock, liver failure, the need for renal replacement therapy and decrease of nutrition without adjustment for insulin infusion.[71-72] Hyperglycemic children with a hypoinsulinemic response are probably at increased risk of hypoglycemia during insulin therapy compared to children with insulin resistance. Moreover, hypoglycemia symptoms in PICU patients may go unnoticed as they are nonspecific and may be obscured by sedation and neuromuscular blockade.

Concerning glycemic control with insulin therapy, two specific patient groups have to be taken into account: neonates below 28 days of age and children after traumatic brain injury. Since neonates and infants are at increased risk for hypoglycemia because of less mature regulatory capacities in glucose and insulin metabolism, we have evaluated our glucose protocol specifically in this young population. Although our protocol was equally effective in young infants and in older children, hypoglycemia occurred more frequently in infants (7%). Therefore we have adjusted some parts of the protocol for critically ill neonates (up to 28 days of age), such that the initial insulin starting doses decreased by 10 mIU/kg/hour and the minimum insulin dose as stop criteria decreased to insulin rate <5 mIU/kg/kg/hour at any time, or <20 mIU/kg/hour during 24 hours (Figure 2. Algorithm B).

The brain is an obligate glucose consumer that depends almost entirely on the availability of systemic glucose to maintain normal energy metabolism. Children with severe acute brain disease may have increased susceptibility to both hyper- and hypoglycemia. After acute brain injury, hyperglycemia (blood glucose >11 mmol/L) exacerbates secondary brain injury and independently predicts poor neurological outcome in adults and children.[73-74] Control of blood glucose is therefore recommended for the treatment of brain-injured patients, although its pathophysiology remains unclear. It is not known whether this association is due to direct detrimental effects of hyperglycemia or represents a marker of severe brain injury. On the other hand, brain metabolism is highly dependent on constant supply of glucose. As a consequence, the acutely injured brain is particularly sensitive to hypoglycemia, which can

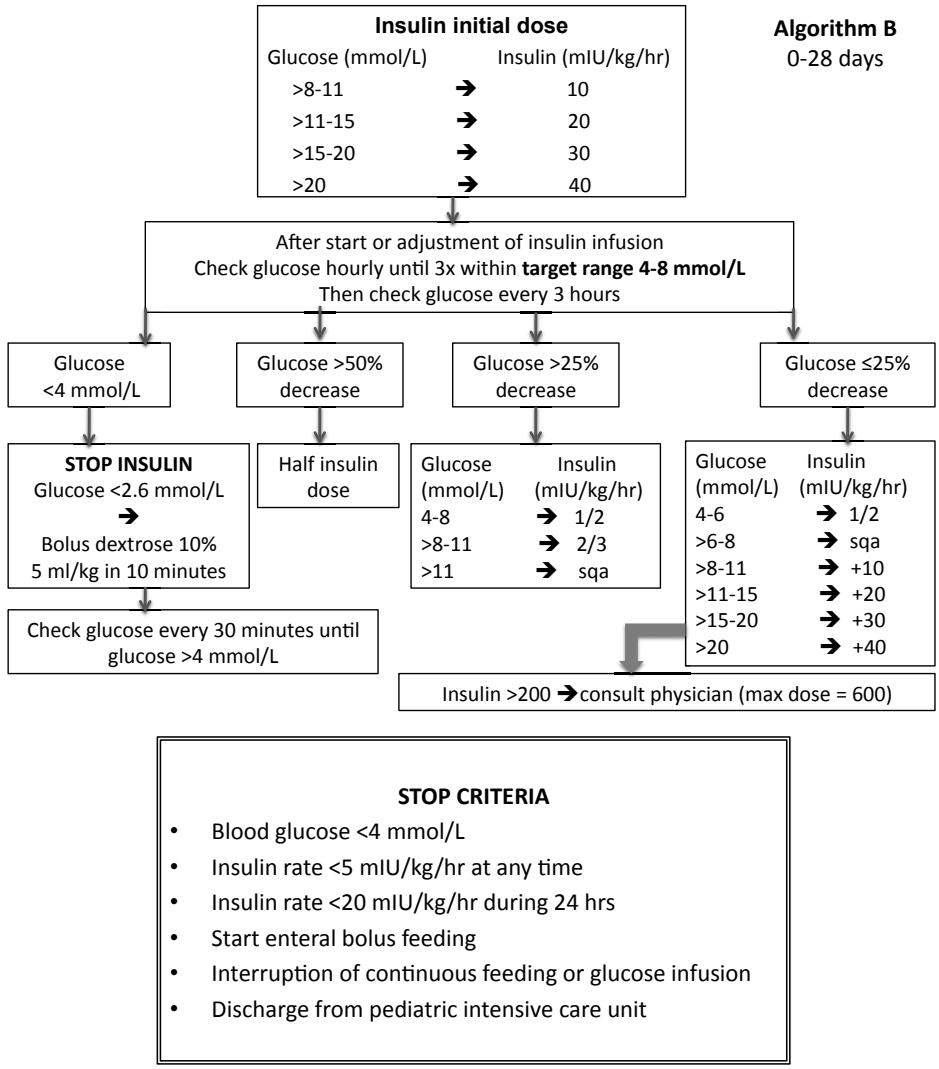

Figure 2. Algorithm B
Glucose control protocol for neonates (0-28 days)

induce a state of energy failure (metabolic crisis). Experimental studies (in cats) have shown that insulin-induced reduction of systemic glucose below 6-8 mmol/L closely correlated with a decrease in brain glucose levels and a concomitant increase of cerebral lactate, together with a significant elevation of peri-ischemic cortical depolarizations. These findings suggest that the use of intensive insulin therapy might carry a risk of relative "neuroglucopenia", which in turn might lead to energy dysfunction and thus may further contribute to exacerbating secondary brain injury.[75] There is clearly a lower limit of systemic glucose below which the availability of substrate might become harmful in the setting of severe brain injury. This

Table 1 Insulin titration guidelines in the pediatric intensive care unit, main features

Author (year)	Population (age,weight) [diagnosis]	Target BG (mmol/L)	Glucose Intake (mg/kg/min)	Insulin Start Dose (IU/kg/hr)	Insulin adjustment (IU/kg/hr)	Stop insulin when	Stop insulin and give glucose when
Preissig[47] (2008)	(>6 mo, >5kg) [all, except severe liver insufficiency or DM]	4.4-7.7	-	BG>7.7 **0.05**	Check after 1 hr, Continue or decrease or increase by 50% depending on BG change	BG<7.7 for 6 hours on 0.02 IU/kg/h	Not defined
Verhoeven (2009)[89]	(0-16 yrs) [all, except DM]	4.0-8.0	≤30kg: 4-6 >30kg: 2-4	BG>8-11 **0.02** BG>11-15 **0.03** BG>15-20 **0.04** BG>20 **0.05**	Check after 1 hour Continue or decrease or increase depending on BG change	BG<4, insulin <0.015 IU/kg/h, insulin <0.03IU/kg/h for 24 hours, start enteral bolus feeding, interruption of continuous feeding or dextrose infusions, discharge from PICU	<2.6mmol/L
Vlasselaers (2009)[65]	(0-16) [all]	0-1 yr: 2.8-4.4 1-16 yrs: 3.9-5.5	-	BG>upper normal **0.1** BG>2x upper normal **0.2**	**0.02-1** depending on BG level	0–1 year: <2.8 mmol/L 1–16 year: <3.9 mmol/L	0-1 year: <1.7mmol/L 1-16 year: <2.2 mmol/L
Macrae CHiPtrial (2010)[66]	(≥ 36weeks corrected gestation - 16 yrs [receiving both mechanical ventilation and vasoactive drugs, except DM, inborn error of metabolism]	4-7	-	BG>7 **0.05** BG>14 **0.1**	Check after 30 minutes Depending on increase or decline and actual BG	Decline ≥ 50% or glucose 2.5-4.9 mmol/L	<2.5 mmol/L
Faraon-Pogaceanu PYIIP (2010)[67]	(0-18 yrs) [receiving MV or vasoactive drugs]	5-6.6	-	BG>7.8 **>0.014,** depending on BG	Check after 1 hour, unless BG <3.9 then check every 15-30 min **0.02-0.2** depending on BG, hourly rate of BG change & insulin infusion rate	BG<3.8, Achievement of target range without insulin, Stop MV or vasoactive drugs	BG<2.8 BG 2.8-3.8 + symptoms
Fram (2010)[68]	(4-18 yrs) [total BSA burned ≥40% requiring skin grafting]	4.4-6.1	Continuous feeding	**0.05**	Every hour Depending on BG	BG<4.4	Not defined
Jeschke (2010)[69]	(0-18 yrs) [total BSA burned ≥30% except DM]	4.4-6.1	Continuous feeding	**0.1**	Every 15 minutes until stable **0.1-1.0** depending on BG	BG<4.4 interruption of continuous feeding	BG<4.4

was confirmed in patients with TBI treated with intensive insulin therapy whose outcome tended to be worse than for those treated with conventional insulin therapy.[76] The amount of cerebral damage due to hypoglycemia is likely to be both dose and time dependent, and hypoglycemia should, therefore, be treated promptly. Plasma glucose levels above 11 mmol/L are widely accepted to be harmful in patients with traumatic brain injury, but the optimal range for systemic glucose control has not yet been clearly established. Since the prevalence of severe traumatic brain injury has decreased, it is difficult to perform prospective trials with enough power to evaluate the precise impact of intensive insulin therapy on brain glucose metabolism and outcome. Awaiting the results of such trials, we recommend a cautious use of insulin therapy aiming at a more liberal target for systemic glucose control (6-10 mmol/L) in brain-injured children.

In summary, although various experts and regulatory agencies have called for tight glycemic control in critically ill adults. The supporting data remain somewhat incomplete and conflicting, however. So far one randomized controlled trial of glycemic control in pediatric intensive care patients has shown improved short-term outcome, in terms of shorter PICU stay, and less mortality in infants and children treated with intensive insulin therapy targeting blood glucose levels to age-adjusted normal fasting concentrations.[65] A second randomized controlled trial, in a selected group of severely burned children, showed lower incidences of infection and sepsis with the use of glycemic control.[69]

The survival benefit of tight glycemic control in critically ill children is unknown, because of lack of large randomized controlled studies in critically ill children with various diagnoses. There are two multicenter trials currently addressing this issue. The CHiP (Control of Hyperglycemia in Pediatric Intensive Care) Trial[66] in the United Kingdom is enrolling children on mechanical ventilation and vasoactive agent infusion (ISRCTN61735247, EudraCT 2006-005715-10); the SPECS (Safe Pediatric Euglycemia in Cardiac Surgery) Trial in the United States is randomizing children undergoing cardiopulmonary bypass for cardiac surgery (ClinicalTrials.gov.Id:NCT00443599). Awaiting the results of these and hopefully other studies we recommend to apply the algorithm depicted in Figure 3.

RECOMMENDATIONS FOR FUTURE RESEARCH

Research on hyperglycemia in critically ill children should focus on pathophysiological mechanisms. By defining laboratory parameters (e.g. HOMA, insulin/glucose ratio, cytokine and/or CRP response) or clinical factors (e.g. diagnostic category, age and/or glucocorticoid or catecholamine use), that independently determine insulin requirements, it will be possible to develop equations that will predict which hyperglycemic children would benefit from insulin therapy and which would not.

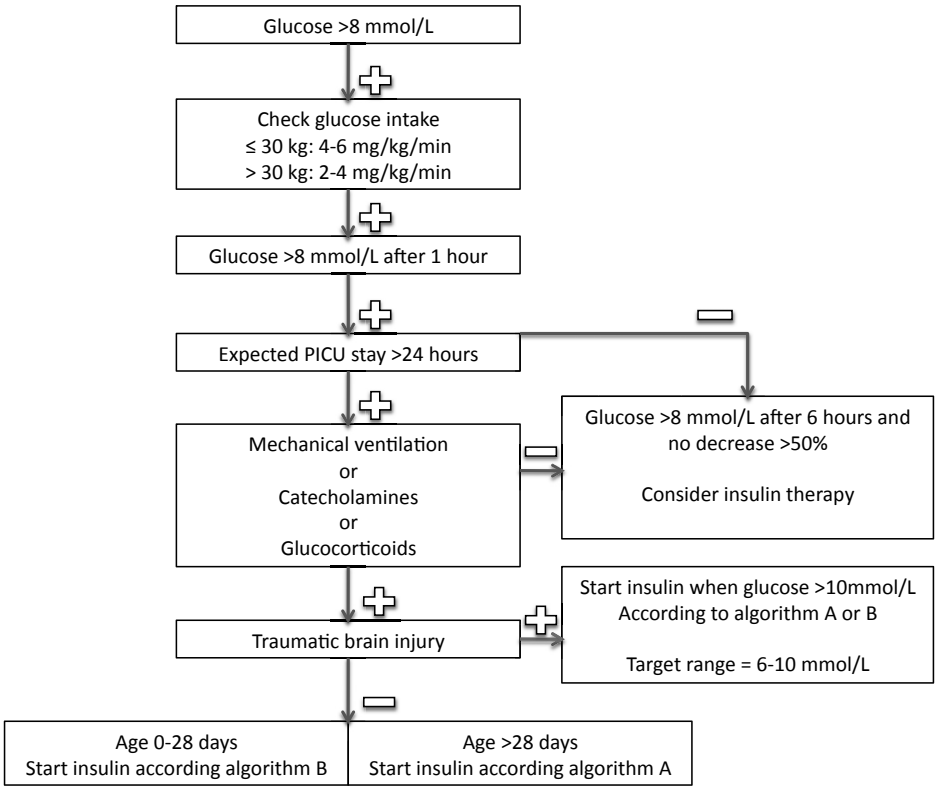

Figure 3. Algorithm for hyperglycemia >8 mmol/L

Future studies are needed to validate HOMA, insulin/glucose ratio and C-peptide/glucose ratio in comparison with the hyperinsulinemic euglycemic clamp technique in critically ill children. A simple manner would be to determine levels of insulin, C-peptide and glucose just before start of clamping. Moreover, serial measurements should be performed to evaluate reliability of paired blood samples at certain time points. Moreover, future studies may employ other methods or a combination of methods to more directly assess insulin sensitivity, such as hyperinsulinemic euglycemic clamping techniques. The ratio of insulin to glucagon may have additional value in studies on hormonal response to hyperglycemia. Glucagon is the primary hormonal stimulator of hepatic gluconeogenesis, which is resistant to the inhibitory effect of physiological concentrations of insulin during critical illness.[77]

To define the optimal glucose intake in critically ill children of all ages and with various diagnoses, endogenous glucose kinetics should be qualified with stable isotope assays. In addition, energy expenditure and substrate use should be determined by indirect calorimetry. This will lead to a better understanding of the causes of hyperglycemia in critically ill children and will help to develop new guidelines on parenteral and enteral glucose intake.

Research on the effectiveness of insulin therapy for critically ill hyperglycemic children should focus on children receiving respiratory and/or cardiovascular support. Moreover, effectiveness and safety should be evaluated for surgical versus non-surgical children, specific diagnostic categories and for different ages. Outcomes to be assessed are the incidence of nosocomial infections, duration of PICU stay, duration of hospital stay, duration of endotracheal intubation, mortality, cardiac function, immune function, endocrine function, nutritional status, and neurodevelopmental evaluation with longitudinal follow-up.

Study the usefulness of techniques for continuous glucose measurements. The currently available main techniques to measure subcutaneous glucose concentration are the microdialysis technique and the platinum electrode. The advantage of a platinum electrode over a microdialysis system, is that it is much smaller and therefore more practical for use in neonates and infants. Moreover, results are probably less influenced by the local inflammatory reaction that is caused by the subcutaneous insertion of the probe.[78] [79-85]

Hormonal treatment of hyperglycemia could be of interest. Glucagon-like peptide-1 (GLP-1) has recently been introduced in diabetic literature.[86-87] In adults with type 1 and 2 diabetes, GLP-1 works as an adjunctive agent as a result of stimulation of insulin secretion, suppression of glucagon secretion and slowing of gastric emptying. Because the effects on insulin and glucagon are glucose-dependent, the use of GLP-1 does not appear to increase the risk of hypoglycemia. GLP-1 reduced the amount of exogenous insulin to control plasma glucose levels in 24 severely burned pediatric patients.[88] Thus, GLP-1 potentially represents a novel agent to attenuate hyperglycemia in critically ill children.

FINAL REMARKS

Nutritional support of critically ill children is of major importance. In this thesis energy requirements of critically ill children in the acute phase of disease were assessed with resultant practical recommendations for clinical use. Furthermore we elaborated on the causes and consequences of hyperglycemia. Emphasis should be on measures preventing hyperglycemia. A number of algorithms for daily clinical practice were developed (Figure 1,2,3), which should be implemented and can be considered as standard of care. In this way an optimal glucose supply (for important organs like the brain) can be guaranteed and the chances of complete recovery and normal functioning of the critically ill child can be increased.

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Chapter 11

Summary

Samenvatting

SUMMARY

A variety of metabolic disturbances characterize the condition of critical illness, including hyperglycemia, dyslipidemia and increased protein turnover. This hypercatabolic state puts children at risk for protein-energy malnutrition. Malnourished children have a higher risk of complications, resulting in longer hospital stay and increased mortality. Furthermore, hyperglycemia has been identified as an independent risk factor for adverse outcome. The efficacy of strict glycemic control with insulin therapy has been much debated. In **Chapter 1** we describe the background and initial goals of the studies presented in this thesis. The focus is on energy requirements in critically ill children in the acute phase of disease in relation with the hyperglycemic response to stress. Furthermore we elaborate on the causes and consequences of hyperglycemia against the background of finding optimal strategies to control blood glucose levels.

This thesis is built up of three parts. Part I is dedicated to energy requirements of critically ill children. Energy expenditure of mechanically ventilated children was measured by indirect calorimetry.

In **Chapter 2** we present the results of energy expenditure measurements in 50 mechanically ventilated children with mixed diagnoses. There was a close correlation between the measured resting energy expenditure (MREE) and predicted resting energy expenditure (PREE) as calculated with the Schofield formula for weight, age and sex, but Bland-Altman analysis showed lack of agreement between individual MREE and PREE. We concluded that standard prediction equations are not appropriate to calculate energy needs and that energy expenditure should be measured individually.

In **Chapter 3** we determined the value of indirect calorimetry combined with nitrogen balance in 36 mechanically ventilated children. The ratio of caloric intake/MREE in children with a positive nitrogen balance was significantly higher than that in children with a negative nitrogen balance. In the children with a positive nitrogen balance, the caloric intake exceeded MREE by 40%. Obviously, caloric intake should equal measured energy expenditure in the acute phase of disease. Then, after the acute catabolic phase, caloric intake should be stepped up to account for tissue repair and growth. In the recovery phase of severe disease, the energy intake should be close to or even above recommended dietary reference intakes for healthy children. We recommend daily assessment of energy intake to tailor carbohydrate, protein and fat intake. Excessive carbohydrate intake should be monitored by serial RQ measurements and blood glucose levels. Protein and fat intake should be monitored by urea and triglyceride levels.

In **chapter 4 e**nergy expenditure was measured in 94 mechanically ventilated children with mixed diagnoses. The Schofield formula for weight, height, age and sex showed the highest accuracy by predicting energy expenditure within 10% of the MREE in 40% of the children. The equations developed by White et al. for mechanically ventilated children yielded the lowest accuracies (16% and 19%, respectively). We have elaborated on the most plausible reasons why the prediction equations fail to accurately predict REE.

Part II of this thesis covers pathophysiological mechanisms leading to hyperglycemia.

The study presented in **Chapter 5** describes pathophysiological aspects of the occurrence of hyperglycemia in 78 children, aged 1 month to 16 years, with meningococcal sepsis and septic shock. Insulin sensitivity and ß-cell function on admission were investigated by relating blood glucose levels to insulin levels and C-peptide levels and by using homeostasis model assessment (HOMA). One third of the children proved hyperglycemic on admission (glucose level >8.3 mmol/L). Blood glucose levels spontaneously normalized within 48 hours in most of the children, without insulin treatment. In general, the acute metabolic stress response lasted only shortly. After admission, pro-inflammatory cytokines and cortisol levels went up temporarily and both dropped rapidly after the first day of illness. The hyperglycemic children predominantly had insulin resistance, although ß-cell insufficiency or a combination of insulin resistance and ß-cell insufficiency was also seen. Insulin resistance may be caused by high levels of counter-regulatory hormones and cytokines, and by therapeutic interventions. Regarding therapeutic interventions, there was a trend towards higher cortisol and glucose levels in the children treated with glucocorticoids versus those without glucocorticoids. The administration of glucocorticoids is often indispensable in children with refractory shock and/or hypoglycemia. On the other hand, it may induce hyperglycemia, which will sustain with prolonged glucocorticoid use.

In **Chapter 6** we evaluated the time course of peri-operative blood glucose levels in 49 children, aged 2 months to 18 years, undergoing cardiac surgery for congenital heart disease. Hyperglycemia was present in 52% of the children at the end of surgery and associated with normal or (relatively) decreased insulin/glucose ratio in almost all of them. In all but three of the children blood glucose levels spontaneously normalized within 24 hours, without the use of insulin and without significantly longer duration of ventilation, ICU or hospital stay. The administration of glucocorticoids (in 65% of the children) during surgery was the main factor associated with hyperglycemia at the end of surgery. Since postoperative morbidity in our study was low, we concluded that the positive effects of glucocorticoids seemed to have outweighed the adverse effects of iatrogenic hyperglycemia.

Part III addresses the clinical use of a glucose control protocol in critically ill children. The main questions to be answered were the following: Which children should be treated with insulin therapy and how should they be treated?

Chapter 7 explores the relationship between insulin response to hyperglycemia and clinical outcome in critically ill hyperglycemic children treated with insulin. Sixty-four children with hyperglycemia, aged 2 weeks to 18 years with mixed diagnosis and meeting the criteria for insulin treatment (discussed in **chapter 8**) were included. Blood samples for stress hormonal, metabolic and immunological parameters were drawn just before start of insulin infusion. A hyperinsulinemic response was associated with a greater likelihood of mechanical ventilation, and with longer duration of insulin therapy, mechanical ventilation and PICU stay as compared with a hypoinsulinemic response. Duration of glucocorticoid use was strongly correlated with duration of insulin therapy, which might reflect the depressing effect of glucocorticoids on insulin sensitivity.

On the other hand, over three quarters (78%) of the children without respiratory failure showed a hypoinsulinemic response in combination with a short duration of insulin therapy. Therefore, the value of insulin therapy in these children is questionable. Their hyperglycemia would probably also have normalized within a day without insulin therapy and without negative effects on morbidity. This suggests that critically ill children without respiratory failure and without overt insulin "resistance" would not benefit much from insulin therapy.

In **chapter 8** we describe our experiences with the implementation of a glucose control protocol for the treatment of hyperglycemia in critically ill children on our PICU. This study included 50 critically ill hyperglycemic children, aged 1 month to 15 years with mixed diagnoses. The stepwise, nurse-driven protocol enabled to achieve normoglycemia (target glucose 4-8 mmol/L) within 12 hours after initiation of insulin therapy in 94% of the children. There were many protocol violations, but these were mostly of minor importance and severe hypoglycemia <2.2 mmol/L did not occur. Three quarters of the children were treated with insulin for shorter than 3 days. The question is whether these children will benefit from insulin therapy. In **chapter 9** suggestions how to minimize the risk of hypoglycemia are postulated. Main measures include the determination of safe target ranges for plasma glucose concentrations, provide adequate continuous glucose intake and the use of a detailed algorithm to adjust insulin therapy.

In **chapter 10** we discuss our findings in the context of the literature.

On the basis of our experiences, a review of the literature, and the results of our data analysis, we propose a guideline for nutritional assessment and nutritional support in clinical daily practice. Additionally, we designed a decision tree for the treatment of hyperglycemia with insulin. In general, a target range for blood glucose levels of 4 to 8 mmol/L is proposed.

We recommend a cautious use of insulin therapy aiming at a more liberal target for systemic glucose control (6-10 mmol/L) in brain-injured children.

The main **conclusions** obtained from the studies described in this thesis are the following:

- Prediction equations are not appropriate to determine energy requirements for ventilated, critically ill children.
- Indirect calorimetry should be used to measure energy expenditure and RQ to accurately assess energy needs of the individual child and to guide nutritional therapy.
- Hyperglycemia is frequent, but spontaneously normalizes within 24 hours in the majority of critically ill children with or without insulin therapy.
- Exogenous factors such as glucose intake and glucocorticoid administration significantly influence blood glucose levels.
- Both insulin resistance and (relative) β-cell dysfunction play a role in the occurrence of hyperglycemia in critically ill children.
- Children with a hyperinsulinemic response have a longer duration of insulin therapy, mechanical ventilation and PICU length of stay compared to those with a hypoinsulinemic response.
- The use of a nurse-driven glucose control protocol is safe and effective in treating hyperglycemia in critically ill children.

SAMENVATTING

In Nederland worden elk jaar zo'n 5000 kinderen met verschillende medische en chirurgische aandoeningen opgenomen op de 8 Kinder Intensive Care afdelingen. Een gedeelte van deze kinderen is ernstig ziek, wat betekent dat ze kunstmatig beademd worden of medicatie nodig hebben om vitale organen te ondersteunen. Deze kinderen hebben een verhoogde kans op ondervoeding. Ernstige ziekte gaat gepaard met metabole ontregelingen van de koolhydraat-, vet- en eiwitstofwisseling. Er ontstaat een toestand waarbij het lichaam zichzelf afbreekt, ook wel katabole toestand genoemd. Deze katabole toestand, samen met verminderde voedselinname, -opname, -benutting of toegenomen verliezen aan voedingsstoffen, zorgen ervoor dat deze kinderen een verhoogd risico hebben op ondervoeding. Kinderen zijn in vergelijking met volwassenen extra gevoelig voor het ontstaan van ondervoeding tijdens ziekte doordat hun reserves aan voedingsstoffen in het lichaam relatief kleiner zijn. Ondervoede kinderen hebben meer kans op complicaties die kunnen leiden tot langere opname duur en verhoogde mortaliteit. Daarnaast is een te hoog glucosegehalte in het bloed (hyperglycemie) tijdens PICU opname, geassocieerd met een slechtere prognose. Er is veel discussie over het feit of deze hyperglycemie behandeld moet worden en indien er behandeld wordt hoe strikt dit moet gebeuren met behulp van continue intraveneuze toediening van insuline. In **hoofdstuk 1** worden de achtergronden en doelstellingen van de studies in dit proefschrift beschreven. Dit proefschrift richt zich met name op het bepalen van de energie behoefte van ernstig zieke kinderen in de acute fase van hun ziekte, alsmede op de oorzaken en gevolgen van het optreden van hyperglycemie. De resultaten kunnen gebruikt worden om het voedingsbeleid en maatregelen voor glucose controle te optimaliseren.

In Deel I wordt de energie behoefte van ernstig zieke kinderen geëvalueerd. Het energie verbruik van beademde kinderen wordt gemeten met behulp van een apparaat, ook wel indirecte calorimetrie genaamd.

In **hoofdstuk 2** worden de resultaten beschreven van de metingen van het energie verbruik van 50 beademde kinderen met verschillende diagnoses. Er was een sterke correlatie tussen het gemeten rustmetabolisme (MREE) en het voorspelde rustmetabolisme (PREE) berekend met behulp van de Schofield formule voor gewicht, leeftijd en geslacht. Bland-Altman analyse toonde echter weinig overeenstemming tussen het individueel gemeten MREE en PREE. Wij concludeerden daarom dat standaard formules voor het berekenen van rustmetabolisme niet geschikt zijn om energie behoefte van ernstig zieke kinderen te bepalen. Het energie verbruik van deze kinderen moet dus worden gemeten met behulp van indirecte calorimetrie.

De waarde van indirecte calorimetrie in combinatie met stikstof balans wordt beschreven in **hoofdstuk 3**. Zesendertig kinderen werden geïncludeerd. Kinderen met een positieve

stikstof balans hadden een significant hogere ratio van calorie inname/gemeten rustmetabolisme ten opzichte van diegenen met een negatieve stikstof balans. De calorie inname van de kinderen met een positieve stikstofbalans was 40% hoger dan het gemeten rustmetabolisme. Het is duidelijk dat de calorie inname minstens gelijk moet zijn aan het gemeten rustmetabolisme in de acute fase van ziekte. Na de acute, katabole fase moet de energie inname worden verhoogd zodat weefsel herstel en groei kunnen plaatsvinden. De energie behoefte van ernstig zieke kinderen tijdens de herstel fase van hun ziekte ligt dichtbij of zelfs boven de aanbevolen "Dietary Reference Intakes" voor gezonde kinderen. Het voedingsbeleid moet dagelijks geëvalueerd worden zodat koolhydraat-, eiwit- en vetinname kunnen worden geoptimaliseerd. Overmatige koolhydraat toediening kan voorkomen worden door dagelijkse berekening van daadwerkelijke glucose intake, seriële meting van het respiratoire quotiënt (RQ) en bloed glucose waarden. Eiwit- en vetinname kunnen aangepast worden op basis van ureum en triglyceride bepalingen.

In **hoofdstuk 4** worden de resultaten beschreven van de metingen van het energie verbruik van 94 beademde kinderen met verschillende diagnoses. De Schofield formule voor gewicht, lengte, leeftijd en geslacht was het meest nauwkeurig in het voorspellen van het gemeten rustmetabolisme; 40% van de kinderen had een voorspelde waarde binnen een range van plus of min 10% van het gemeten rustmetabolisme. Hoewel de White formules speciaal ontwikkeld werden voor beademde kinderen, waren deze het minst nauwkeurig. Mogelijke oorzaken hiervoor staan in dit hoofdstuk beschreven.

Deel II van dit proefschrift beschrijft pathofysiologische mechanismen die hyperglycemie kunnen veroorzaken of onderhouden.

De studie beschreven in **hoofdstuk 5** kijkt naar oorzaken van hyperglycemie bij 78 kinderen (leeftijd van 1 maand tot 16 jaar) met meningococcensepsis of septische shock. Bloed glucose waarden werden gerelateerd aan insuline en C-peptide metingen middels "homeostasis model assessment (HOMA). Hiermee werd inzicht verkregen in de insuline gevoeligheid en ß-cel functie van de pancreas. Een derde van de kinderen was hyperglycemisch (gedefinieerd als bloed glucose >8.3 mmol/L) bij opname op de Kinder Intensive Care. Voor verreweg de meeste kinderen gold dat bloed glucose waarden spontaan normaliseerden binnen 48 uur na opname zonder insuline toediening. Ook de pro-inflammatoire cytokines en cortisol concentraties waren slechts tijdelijk verhoogd en daalden snel na de eerste ziektedag. De meeste kinderen met hyperglycemie waren insuline resistent, maar ook verminderde ß-cel functie of een combinatie van insuline resistentie en verminderde ß-cel functie werden gezien. Insuline resistentie kan veroorzaakt worden door contraregulerende hormonen en cytokines en door therapeutische interventies. Zo zagen we dat kinderen die werden behandeld met glucocorticoïden hogere cortisol en glucose concentraties hadden ten opzichte van kinderen die geen glucocorticoïden kregen. De toediening van glucocorticoïden aan

kinderen met persisterende shock en/of hypoglycemie op basis van bijnierinsufficiëntie lijkt vaak onvermijdelijk. Het is van belang om toediening van glucocorticoïden af te wegen tegen de potentieel nadelige effecten zoals het induceren en onderhouden van hyperglycemie wanneer glucocorticoïden meerdere dagen achter elkaar gebruikt worden.

In **hoofdstuk 6** wordt het peri-operatieve beloop van bloed glucose concentraties geëvalueerd van 49 kinderen (leeftijd van 2 maanden tot 18 jaar) die een hart operatie ondergingen in verband met een aangeboren hartafwijking. Ruim de helft van de kinderen was hyperglycemisch aan het eind van de operatie. Bijna al deze kinderen hadden een normale of (relatief) lage insuline/glucose ratio. Bloed glucose concentraties normaliseerden spontaan, zonder insuline toediening, binnen 24 uur bij bijna alle kinderen (94%). Er was geen verschil in beademingsduur en IC- en/of ziekenhuis opnameduur in vergelijking met de kinderen die geen hyperglycemie hadden. De toediening van glucocorticoïden tijdens de operatie (aan 65% van de kinderen) was de belangrijkste factor voor het optreden van hyperglycemie aan het eind van de operatie. Aangezien de postoperatieve morbiditeit in onze studie populatie laag was, kunnen we concluderen dat de beschreven positieve effecten van glucocorticoïd toediening groter waren dan de potentieel nadelige effecten van glucocorticoïd geïnduceerde hyperglycemie.

In Deel III wordt ingegaan op de klinische aspecten ten aanzien van het gebruik van een protocol voor glucose controle. De belangrijkste vragen die aan bod komen zijn welke kinderen behandeld zouden moeten worden met insuline en hoe zij behandeld moeten worden.

In **hoofdstuk 7** wordt gekeken naar de relatie tussen insuline respons op hyperglycemie en klinische uitkomst van ernstig zieke kinderen die behandeld werden met insuline. Vierenzestig kinderen (leeftijd van 2 weken tot 18 jaar) met hyperglycemie met verschillende diagnoses, die in aanmerking kwamen voor insuline therapie (zoals beschreven in **hoofdstuk 8**) werden geïncludeerd. Net voor start van insuline toediening werd bloed afgenomen voor de bepaling van hormonale, metabole en immunologische parameters. Het bleek dat kinderen met een hyperinsulinemische respons vaker en langduriger beademd werden, langduriger behandeld werden met insuline, en langduriger opgenomen bleven op de PICU ten opzichte van kinderen met een hypoinsulinemische respons. De duur van glucocorticoïd gebruik was sterk gecorreleerd met duur van insuline behandeling en is een aanwijzing voor het negatieve effect van glucocorticoïden op de insuline gevoeligheid.

Aan de andere kant hadden de niet beademde kinderen meestal een hypoinsulinemische respons (in 78% van de gevallen) en werden zij slechts kortdurend behandeld met insuline. Het is de vraag wat de waarde is van insuline behandeling bij deze kinderen zonder aantoonbare insuline resistentie. Het is zeer aannemelijk dat de hoge bloed glucose waarden van deze kinderen ook spontaan zouden zijn genormaliseerd zonder toename van de morbiditeit.

In **hoofdstuk 8** worden ervaringen met de implementatie van een glucose controle protocol voor de behandeling van hyperglycemie bij ernstig zieke kinderen opgenomen op de PICU beschreven. Vijftig ernstig zieke kinderen (leeftijd van 1 maand tot 15 jaar) met verschillende diagnoses werden geïncludeerd. Met het door verpleegkundigen uitgevoerde protocol bleek het mogelijk om in 94% van de kinderen normoglycemie (gedefinieerd als bloed glucose waarden tussen de 4 en 8 mmol/L) te bereiken binnen 12 uur na start van insuline infusie. Ernstige hypoglycemie (glucose <2.2 mmol/L) trad niet op tijdens de behandeling met insuline. Drie kwart van de kinderen werd minder dan 3 dagen behandeld met insuline. Het is maar zeer de vraag of je de prognose van deze kinderen kunt verbeteren met insuline therapie. In **hoofdstuk 9** worden voorwaarden beschreven waaraan een glucose protocol zou moeten voldoen om de kans op het optreden van hypoglycemieën zo klein mogelijk te maken.

In **hoofdstuk 10** worden de voornaamste bevindingen van onze studies besproken in relatie met eerdere publicaties. Op basis van onze ervaringen, literatuur gegevens en data analyses, doen we een voorstel voor routinematige "nutritional assessment" en "nutritional support" op de Kinder Intensive Care. Hierop aansluitend hebben we twee algoritmes gemaakt voor glucose controle met insuline; een voor neonaten jonger dan 28 dagen oud en een voor oudere kinderen van 1 maand tot 18 jaar. In het algemeen wordt gestreefd naar bloed glucose waarden tussen de 4 en 8 mmol/L, echter voor kinderen met ernstig traumatisch hersenletsel adviseren we bloed glucose waarden tussen de 6 en 10 mmol/L aan te houden.

De belangrijkste **conclusies** resulterend uit dit proefschrift zijn de volgende:

- De energie behoefte van ernstig zieke kinderen kan niet nauwkeurig voorspeld worden met predictie formules.
- Indirecte calorimetrie moet gebruikt worden om het energie verbruik en respiratoir quotiënt te meten zodat de energie behoefte en het voedingsbeleid per kind kan worden vastgesteld.
- Hyperglycemie komt vaak voor bij ernstig zieke kinderen en herstelt meestal met of zonder behandeling met insuline binnen 24 uur.
- Exogene factoren zoals toediening van glucose en glucocorticoïden hebben een belangrijke invloed op bloed glucose waarden.
- Zowel insuline resistentie als relatieve β-cel dysfunctie spelen een rol bij het optreden van hyperglycemie bij ernstig zieke kinderen.
- Kinderen met een hyperinsulinemische respons worden langer behandeld met insuline, langer beademd en hebben een langere verblijfsduur op de PICU in vergelijking met kinderen met een hypoinsulinemische respons.
- De behandeling van hyperglycemie met insuline volgens een strict glucose protocol uitgevoerd door verpleegkundigen is veilig en effectief.

LIST OF ABBREVIATIONS

ACTH, adenocorticotrope hormone
ALT, alanine aminotransferase
APC, activated protein C concentrate
AST, aspartate aminotransferase
CC, calf circumference
CHO, carbohydrate
CPB, cardiopulmonary bypass
CRP, C-reactive protein
DM, diabetes mellitus
DRI, dietary reference intakes
ECLS, extracorporeal life support
EN, enteral nutrition
ESPGHAN, European society for paediatric gastroenterology, hepatology and nutrition
FFA, Free Fatty Acids
GLP-1, glucagon-like-peptide-1
GLUT, glucose transporter
HOMA, homeostasis model assessment
HOMA-%B, ß-cell function
HOMA-%S, insulin sensitivity
ICU, intensive care unit
IL, interleukin
LOS, length of stay
MREE, measured energy expenditure
mTEE, measured total energy expenditure
MUAC, mid upper arm circumference
N-balance, nitrogen balance
pBMR, predicted basal metabolic rate
PELOD-score, pediatric logistic organ dysfunction score
PEPCK, phosphoenolpyruvate carboxy kinase
PICU, pediatric intensive care unit
PREE, predicted resting energy expenditure
PRISM, pediatric risk of mortality
PT, prothrombin time
RACHS, risk adjustment for congenital heart surgery
RDA, recommended daily allowences
REE, resting energy expenditure
RQ, respiratory quotient

1. RQmacr, RQ of macronutrients administered
2. TDEE, total daily energy expenditure
3. TG, triglycerides
4. TISS, Therapeutic Intervention Scoring System
5. TMEE, total measured energy expenditure
6. TNF-α, tumor necrosis factor-α
7. TPN, total parenteral nutrition
8. TUN, total urinary nitrogen excretion
9. VAS, vasopressor score
10. WI-score, weighted inotropic score
11. WHO, world health organization
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Jennifer

ABOUT THE AUTHOR

Jennifer Jogien Verhoeven was born on November 28th, 1972 in Oss, The Netherlands. She obtained her Gymnasium diploma at the Van Maerlantlyceum in Eindhoven in 1991. In the same year she started medical school at the Erasmus University Rotterdam and received her medical doctor degree in 1998. During her study period, she started her research into energy requirements and glucose control in critically ill children under the guidance of Dr. K.F.M. Joosten resulting in this thesis. Furthermore, she participated in a study among racing cyclists in 1994 and 1995 at the Rijksuniversiteit Limburg, Maastricht (prof. dr. H. Kuipers). In 1995, she worked for 2 months at the Rumah Sakit Polisi Hospital in Jakarta (Indonesia). In 1996, she stayed for 3 months in Sengerema (Tanzania) to perform a study on joint hypermobility among African schoolgirls and medical students (Dr. P.W.J. van Dongen). From 2000 to 2004 she was a resident in Pediatrics in the Sophia Children's Hospital Rotterdam (Prof. Dr. H.J. Neijens and Prof. Dr. A.J. van der Heijden) and in the Medical Centre Rijnmond Zuid in Rotterdam (Prof. Dr. A.M. Oudesluys-Murphy). Following her registration as a Pediatrician in 2004 she started her fellowship Pediatric Intensive Care at the Sophia Children's Hospital (Dr. J.A. Hazelzet). She finished her fellowship in 2008 and is currently working as a staff member Pediatrics in the Maasstad Hospital in Rotterdam. She is married to Arjen Brouwers, Internist-intensivist in the Sint Franciscus Gasthuis Rotterdam, and together they have two children; Anniek (2003) and Juliet (2006).

LIST OF PUBLICATIONS

Disturbance of glucose homeostasis after pediatric cardiac surgery
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Pediatric Cardiology (2010) in press

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Nutrition, provisionally accepted for publication

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PhD Portfolio

Summary of PhD training and teaching

Name PhD student:J.J. Verhoeven	PhD period: 2005-2010
Erasmus MC Department: Pediatrics	Promotor: Prof.dr. D. Tibboel
Research School: Erasmus MC	Supervisor: Dr. K.F.M. Joosten

1. PhD training

	Year	Workload (Hours)
Specific courses		
• Postgraduate course on neonatal and pediatric intensive care (WFPICCS, Genève)	2007	16
• Grenzen aan de toekomst (SICK)	2007	3
• Postgraduate course on pediatric intensive care (ESICM, San Francisco)	2006	16
• Fellow-onderwijs intensive care (GIC)		
• Fellow-onderwijs kinder intensive care (SICK)	2005-2008	120
• Postgraduate course on practical cardiology for neonatal and paediatric intensive care practitioners, (ESPNIC, Londen)	2005-2008 2004	48 16
Seminars and workshops		
• Scholing Berlin Heart (ErasmusMC Rotterdam)	2008	3
• Hands on cursus: Echocardiografie voor de kinderarts en de neonatoloog (PAOG, VUmc, Amsterdam)	2007	12
• Kunstmatige beademing (Postgrade, ErasmusMC, Rotterdam)	2005	10
• Crew Resource Management (ErasmusMC-Sophia, Rotterdam)	2005	6
Presentations		
• Remarkable differences between critically ill children treated with insulin for hyperglycemia with and without insulin resistance. (20th ESPNIC Medical & Nursing Annual Congress, Verona)	2009	60
• Should we treat children with hyperglycemia with insulin after cardiac surgery? (Poster) (20th ESPNIC Medical & Nursing Annual Congress, Verona)	2009	30
• Insulin treatment for hyperglycemia in the pediatric intensive care; better glucose control with a nurse driven protocol? (European Academy of Pediatrics, Nice, France)	2008	60
• The influence of corticosteroid use on insulin therapy for hyperglycemia in critically ill children. (Poster) (NVIC dagen, Ede)	2008	30
• ABCdef Glucose (Research meeting, ErasmusMC-Sophia)	2007	50
• Guidelines for glucocorticoid use in the pediatric intensive care unit (PICU): where are we? (Poster) (5th World Congress on pediatric critical care, Genève, Zwitserland)	2007	30
• The influence of corticosteroid use on insulin therapy for hyperglycemia in critically ill children. (Poster) (5th World Congress on pediatric critical care, Genève, Zwitserland)	2007	30
• Insulin resistance in children with meningococcal sepsis: does it occur? (NVIC dagen, Ede)	2006	60
• Insulin resistance in children with meningococcal sepsis: does it occur? (Poster) (Europaediatrics, Barcelona)	2006	30
• Sedatie en pijnstilling bij kinderen. (Refereeravond ICK, ErasmusMC-Sophia, Rotterdam)	2005	40
• Indirect calorimetry in mechanically ventilated infants and children. (2nd World Congress on Pediatric Intensive Care, Rotterdam)	1996	60

(Inter)national conferences		
• 20th ESPNIC Medical & Nursing Annual Congress, Verona, Italy	2009	24
• 21st ESICM Annual Congress, Lisbon, Portugal	2008	24
• 2nd Congress of the European Academiy of Paediatrics, Nice, France	2008	24
• 5th World Congress on Pediatric Critical Care, WFPICCS, Genève, Switzerland	2007	24
• 8th European Postgraduate Course on Neonatal and Pediatric Intensive Care, Genève, Switzerland	2007	24
• Nederlandse Intensivisten Dagen, Ede	2007	16
• 35th Critical Care Congress, ESICM, San Francisco, USA	2006	30
• NVIC Circulatiecursus, Ede	2005	12
• 15th ESPNIC Medical and Nursing Annual Congress, Londen, UK	2004	24
• Beademingsdagen NVIC, Arnhem	2004	16
2. Teaching		
Introduction training Internship pediatrics	2005-2008	150
APLS training residents	2005-2008	6
PICU/NICU nurses education	2005-2008	15
Medical training Pediatric residents	2005-2008	40
Total		**1159 hours**