Metabolic, endocrine and nutritional aspects of critically ill children

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METABOLIC, ENDOCRINE AND NUTRITIONAL ASPECTS OF CRITICALLY ILL CHILDREN

METABOLE, HORMONALE EN VOEDINGDASPECTEN VAN HET ERNSTIG ZIEKE KIND

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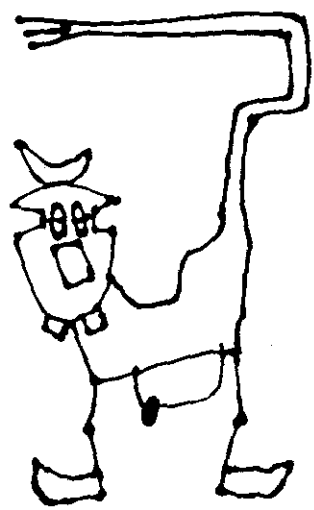

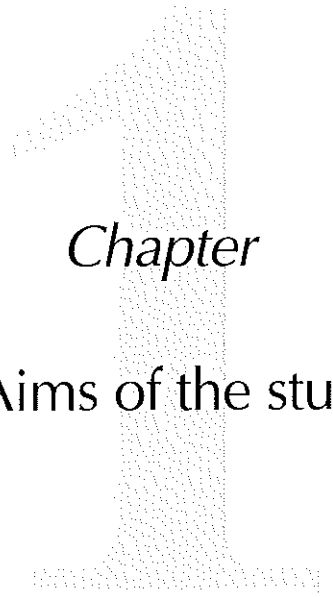

Chapter

Aims of the studies

Aims of the studies

Part 1 provides the aims of the studies (*chapter 1*) and a general overview and discussion of the current literature of metabolic, endocrine and nutritional aspects in critically ill children (*chapter 2*).

In **Part 2** the clinical use of an indirect calorimeter is tested and validated for use in critically ill mechanically ventilated children.
In *chapter 3* a new indirect calorimeter is tested in a laboratory setting using a ventilated lung model and a butane burner system to determine the accuracy of the calorimeter for use in young infants and children. The influence of low tidal volumes and low levels of oxygen consumption and carbon dioxide production with different levels of inspired oxygen concentrations is investigated.
In *chapter 4* it is questioned how accurately total daily energy expenditure of mechanically ventilated pediatric patients can be estimated from measurement periods of less than 24 hours. In addition, the influence of tube leakage on energy expenditure measurements is determined.

In **Part 3** the clinical use of the indirect calorimeter is tested in mechanically ventilated children.
In *chapter 5* using indirect calorimetry the following issues were studied:

1. What are the actual energy needs are for critically ill mechanically ventilated children?
2. What is the relation between the measured energy needs and equations predicting energy expenditure based on age and weight used for healthy children?
3. What is the relation between the ratio energy intake/measured energy and the nitrogen balance as a measure for underfeeding?

In *chapter 6* indirect calorimetry is used to get answer on the questions:

1. How are substrates administered with nutritional support utilized in a critically ill child?

2 Does the amount of nutritional support influences the nitrogen balance?
3 Can the difference between the measured respiratory quotient and the respiratory quotient calculated from the administered nutrients be used as a predictor of over- or underfeeding?

In **Part 4** the time course and variability of endocrine and metabolic parameters are studied in children with meningococcal sepsis (*chapter 7*). The purpose of this study is to evaluate the time course of the endocrine and metabolic responses of children during the first 48 hours of admission on the pediatric intensive care. Furthermore, we try to identify parameters that can be used to predict return to anabolic metabolism as an important prerequisite to tailor and improve nutritional support.

Part 5 is the final part with discussions of the results from the previous studies (*chapter 8*. It provides recommendations for metabolic, endocrine and nutritional assessment of the critically ill child, while future perspective studies are suggested.

Chapter

Metabolic, endrocine and nutritional aspects of critically ill children: a review

Contents

1 Introduction

Nutritional support is an essential aspect of the clinical management of pediatric intensive care patients because the diversity in clinical presentation and the various age groups dictates a patient tailored approach. The mean length of stay of a child in a Dutch intensive care unit is 4.7 days, and the median stay 2 days (1). During this brief stay, attention is mostly focused on the primary medical problem. There is usually little attention for the child's nutritional status. Therefore, if the child stays in the intensive care for longer than 5-7 days, the likelihood of developing serious nutritional deficiencies increases significantly (2). Protein-energy malnutrition is present in approximately 15-20% of children admitted to the pediatric intensive care unit (3, 4). From several studies of adult patients it is known that protein-malnutrition is associated with impaired wound healing, impaired immune response to infections, reduced gut function, decreased function of respiratory muscles and an increase in morbidity and mortality (5). Malnutrition and nutrient store depletion may be particularly important in children under 2 years of age because this is the most critical period of brain growth. Studies have associated malnutrition in infancy to decreased intelligence and neurological function (6). Although a critical duration of nutritional deprivation has not been established, even infants undergoing relatively short periods of nutritional deprivation may have poorer learning abilities (7). Pollack emphasized the relationship of critical illness to malnutrition (8) (see fig. 1) and demonstrated that critically ill children receiving better nutritional support showed significant improvement in physiologic stability and outcome (9). There is also evidence for the importance of providing adequate nutritional support in conditions such as prematurity (10) and pediatric burn injury (11).

Nutritional requirements in patients who are stressed due to critical illness may be significantly different from those of healthy individuals or other patients who are less ill. The determination of nutritional needs depends on a number of factors like the cause and phase of the disease. The classic approach for the assessment of nutritional needs and support is based on ideal growth rates from normal healthy children and consequently cannot be used in patients being severely ill. The optimal nutritional and metabolic support of the individual critically ill child has to be determined.

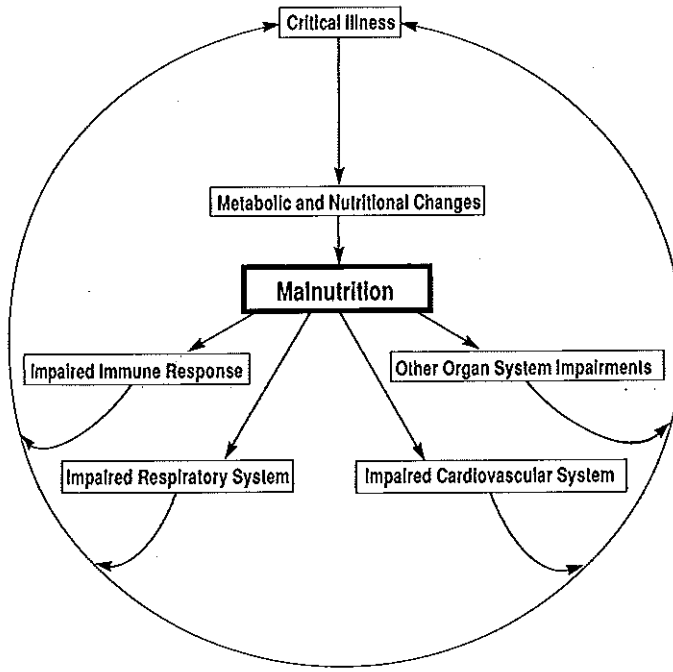

Figure 1 Relationship of critical illness to malnutrition (adapted from Pollack (8))

There is an individual maximum capacity to utilize the administered glucose, proteins and lipids. But the protein-energy malnutrition that occurs in the face of catabolism is more than the repletion of energy with glucose, protein and lipids. Some nutrients adequately synthesized endogenously under normal conditions are lost during the catabolic state (mainly with urine) and become essential.

The concept of requirements has changed from the traditional nutritional standpoint (i.e., growth or weight maintenance) to a broader functional outcome. Nutrients not only posses nutritional and metabolic functions but they also actively affect in physiologic and pathophysiologic events (12). Specific metabolic, endocrine and nutritional assessment have to be determined as an important prerequisite to tailor these nutritional requirements.

2 Metabolic aspects of nutritional assessment: energy expenditure and substrate utilization

2.1 MEASUREMENT OF ENERGY EXPENDITURE

The human body is able to take in chemical energy and converting it, by controlled oxidation of fuels, into other forms of chemical energy (e.g. by the synthesis of storage compounds), into mechanical work and heat. The measurement of metabolic rate (energy expenditure (EE)) has a long history and probably Antoine Lavoisier (1743-1794) was the first to study the metabolic rate of a human. The discovery of oxygen during the 18th century as an elementary gas which generates carbonic gas and heat during combustion of organic substances, produced the scientific basis for the development of calorimetry. The theory of combustion coupled to metabolism was developed by Lavoisier who showed that in vitro (fire) and in vivo combustion (life) produced the same amount of heat per quantum of O_2 consumed and CO_2 produced (13). From these discoveries two basic approaches to measure EE were developed. First, a technique of direct measurement of heat liberated by the body (known as direct calorimetry) and second a technique whereby EE is assessed from measurement of the oxidation of fuels, assessed in turn from the whole-body consumption of oxygen (VO_2) and production of carbon dioxide (VCO_2) (known as indirect calorimetry).

Direct calorimetry can be performed in a special insulated chamber whose walls contain some device for measurement of heat liberated but it is impractical for clinical use. Indirect calorimetry is performed by measurements of the differences of O_2 and CO_2 during gas exchange. This can be done in a closed circuit method or in an open circuit method. In the closed circuit method the subject breathes through a closed system, originally containing pure oxygen and oxygen consumption is determined by the volumetric change from the reservoir. A great disadvantage of this system is

that it does not allow the determination of VCO_2. In the open circuit method the subject is permitted to breath air from the outside, while the expired air is either collected for later analysis or immediately and continuously analyzed by an automatic metabolic monitor (14).

Recently another technique has been introduced to measure EE, the so-called double-labeled water technique ($^2H_2{}^{18}O$). This technique estimates CO_2 production over a period of 2-3 weeks by determining the difference in the turnover of deuterium ^2H and ^{18}O (15). The advantage of this method is that it allows measurement of EE outside the hospital. EE can also be determined by a method based on the Fick principle, relating the arterio-venous oxygen and carbon dioxide gas-content difference and cardiac output (called circulatory indirect calorimetry). Studies have shown a significant correlation between circulatory and standard respiratory indirect calorimetry (16).

There are also some none-calorimetric methods that rely on the relationship between EE and various physiological parameters of an individual, such as heart rate, minute ventilation or electromyography. Similar approaches have tried to correlate EE with indexes of physical activity (i.e. pedometer) (17-20).

2.2 PHYSIOLOGY

2.2.1 Energy expenditure

In an individual the energy generated by oxidative metabolism is subsequently expended in 3 major bodily processes (13):

1 basal metabolism; this represents energy for the basic requirements for staying alive: i.e. at the cellular level, pumping ions across membranes to maintain normal gradients, turnover of proteins and other cellular constituents; at the organ level, pumping blood around the body, respiration and many others;
2 the energy cost of physical activity and the energy for growth;
3 the increase in rate of EE after meals referred to diet-induced thermogenesis; it represents the energy cost of gastrointestinal tract activity, digestion, absorption and the metabolic cost of storing fuels.

All the energy intake of humans is derived from the potential chemical energy contained in the nutrients that are absorbed from the diet. Carbohydrate, fat and protein provide substrate for the continuous synthesis of adenosine triphosphate (ATP) which provide the fuel requirements of cellular processes. All the chemical reactions release heat, which is therefore the end-point of energy utilization by the cells in

resting condition. This is not true during exercise, where a part of energy is transformed into external work. In other words except for urinary and fecal losses, all the energy is transformed into heat and external work. As a rough approximation, the human body is about 25% efficient, that is to say that of the energy it uses from its fuel stores, about 25% is converted to external work, and 75% into heat. The rate of using fuel stores is measured as EE (13).

The quantity of energy that is liberated per liter of oxygen is roughly equal in the combustion of carbohydrates, fats and proteins. On the other hand, per liter of carbon dioxide produced the amount of liberated energy varies considerably. Therefore, measurement of VO_2 alone allows the calculation of EE to a reasonable accuracy. However, the estimate can be improved by measuring VCO_2 and urinary urea (or total nitrogen) excretion, to allow the appropriate energy values. The most important principle to calculate EE was described by Weir (21):

Calculation of EE (Weir (21))

$EE = 4184(5.5 \times VO_2 + 1.76 \times VCO_2 - 1.99 \times N)$

EE in kJoules/day, VO_2 in l/min, VCO_2 in l/min

N as urinary nitrogen excretion in g/min.

Because nitrogen excretion values hardly influence EE results, the abbreviated Weir formula is used mostly only using VO_2 and VCO_2 in the equation. Bursztein demonstrated in adult patients that differences in calculated values of EE, including or neglecting N, varies on average < 2% and rarely exceed 3% (22).

2.2.2 Respiratory quotient

The respiratory quotient (RQ) is the ratio of VCO_2 to VO_2. In comparing the metabolism of the three substrates, glucose oxidation is associated with the highest RQ at 1.0, fat oxidation the lowest at 0.7, and protein metabolism in between with an RQ of 0.8. Hyperventilation, metabolic acidosis (with buffering of acid generating carbon dioxide), and overfeeding (leading to lipogenesis) may all increase RQ. Hypoventilation, ketoacidosis, gluconeogenesis and alcohol metabolism may all decrease RQ. By excluding protein, which represents only 15% of the total calories in the fuel mixture of the average diet, the nonprotein respiratory quotient (npRQ) provides a range of substrate utilization from 0.70 at the bottom (indicating 100% fat utilization and 0% carbohydrate utilization) to 1.0 at the top (indicating the opposite). A npRQ of 0.85 at midpoint in this range would indicate 50% glucose and 50% fat oxidation. The npRQ can be calculated by the formula:

Calculation of npRQ

$NpRQ = (VCO_2 - 4.84N)/(VO_2 - 6.04N)$

VO_2 in l/min, VCO_2 in l/min

N as urinary nitrogen excretion in g/min.

When the RQ is close to 0,80, the npRQ and RQ are essentially identical, and a correct estimate of protein utilization is not crucial to calculate the relative utilization rates of carbohydrate and lipid. Conversely, as the RQ deviated from 0.80, the difference between the RQ and the npRQ becomes progressively larger.

2.2.3 Substrate utilization

The method of indirect calorimetry allows one to calculate the overall amount of substrate that is oxidized in the body. It is important to point out that indirect calorimetry does not measure true oxidation rates of carbohydrates, lipids and proteins but only their overall disappearance rates and therefore does not provide information on the intermediate metabolic processes. There are situations in which substrate is not only oxidized but also converted or utilized for other purposes. This is the case for lipogenesis (conversion of carbohydrate to lipids) and neoglucogenesis (conversion of amino acids to glucose) (15). Net substrate utilization for fat and carbohydrate can be calculated from the measured values of VO_2, VCO_2 and nitrogen excretion according to the following formula (23):

Calculation of fat and glucose utilization

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:

$1.34(VCO_2 - 4.88\ N)$

VO_2 in l/min, VCO_2 in l/min

N as urinary nitrogen excretion in g/min.

The assessment of substrate utilization is strongly dependent on the accuracy and precision of both VO_2 and VCO_2 measurements. A 0.01 error on RQ induces a 3% error on the proportion of substrate utilized; this produces an even larger error in the absolute value of substrate utilization (15). Generally the nitrogen excretion value

will only have a small contribution in the formulas. However when substrate utilization results are derived from npRQ values of pre-calculated tables it has been shown that failure to use nitrogen excretion in the calculation of a npRQ can result in errors in substrate utilization in the range of 50% to 100% (22).

Because the nitrogen that is liberated during protein utilization is ultimately excreted in the urine, a reasonable estimate of protein oxidation can be obtained from measurement of the urinary nitrogen excretion rate (24). Because the nitrogen content of mixed protein is ±16% it is generally assumed that each gram of urinary nitrogen is stoichiometrically derived from the oxidation of 6.25 g of mixed protein.

Calculation of protein utilization

Protein utilization (g/min) = 6.25 x urinary urea nitrogen (g/min)

Isotopic labeling techniques can give a better understanding of the changes in substrate flows. Using these techniques the methods used to study protein and glucose metabolism are basically the same. In a metabolic pool with glucose and amino acids there is a continuous appearance of endogenous and exogenous glucose and amino acids. By infusing labeled glucose or amino acids into the metabolic pool, measurement of the isotopic labeling pattern in the plasma pool can be performed. This gives information on the total rates of appearance and disposal of the substrate. Alternatively, measurement of the appearance of label in metabolic products gives information on the specific rates of disposal into these individual products. In case of labeled glucose it can be either oxidized to CO_2, stored as glycogen, transformed into fat by lipogenesis or be used for non-essential amino acid synthesis.

Glucose turnover studies can be performed with labeled H or C atoms. The tracer usually chosen for measuring whole body protein turnover is ^{13}leucine. The rate of lipolysis can be measured by studying the systemic rate of appearance of labeled glycerol and ^{13}C labeled fatty acids, e.g. palmitic and linoleic acid. Further studies should be performed to combine substrate utilization data obtained by indirect calorimetry with data of substrate fluxes obtained by isotope studies to get a better insight of the endogenous substrate handling in the critically ill child.

2.3 INDIRECT CALORIMETRY

Indirect calorimetry provides unique information, is noninvasive and can be combined with other measurements techniques to investigate numerous aspects of nutrient metabolism, heat production, energy requirements of physical activity, and the altered energy metabolism of disease and injury (22). Recent technological

developments and a broader knowledge of the intermediate metabolic processes have offered the possibility of measuring EE in critically ill patients. Knowledge of the methodological pitfalls using indirect calorimetry is important when applying this technique. It is important to recognize those factors that affect the measurement of resting EE (REE) and RQ, to recognize and avoid the potential sources of error that may occur when performing indirect calorimetry and to describe the conditions necessary to obtain optimal results when performing metabolic tests. We will give a summary of the most important factors influencing indirect calorimetry.

2.3.1 Technical considerations

In the open circuit system, VO_2 is calculated by the difference between inspiratory and expiratory oxygen concentration. For the open circuit calorimeters, the method of gas collection involves either the mixing chamber, a dilution system or the breath by breath technique. A commercially manufactured monitor with a unique gas dilution system to determine expired volume is the Deltatrac from Datex. Measurements are performed with the aid of a fast differential paramagnetic O_2 analyzer, an infrared CO_2 sensor, a mixing chamber, and a build-in microprocessor. The instrument allows for real time graphics of VO_2, VCO_2 and expiratory tidal volume on an integral screen.

The best clinical feature of the closed circuit system is that patients on ventilators on any level of inspired oxygen fraction (FiO_2) can be measured because this technique does not need to use the Haldane transformation (see below). Fluctuations in the delivered FiO_2 of the ventilator are not a problem because oxygen analyzers are not required (14).

Inspired oxygen

FiO_2 is a critical factor for both the accuracy and precision of VO_2 measurement. This is essentially due to the fact that VO_2 is calculated in the open circuit method from the RQ as $VO_2 = VCO_2/RQ$. RQ is calculated with the Haldane transformation from the gas fractions:

$$RQ = \frac{1 - FiO_2}{\frac{FiO_2 - FeO_2}{FeCO_2} - FiO_2}$$

The inspiratory oxygen fraction FiO_2 is measured from inspiratory limb of the ventilator. The expiratory oxygen fraction (FeO_2) and the expiratory carbon dioxide fraction ($FeCO_2$) are measured from the mixing chamber which collect the mixed air from the outlet port of the ventilator.

A mathematical analysis of error of VO_2 determination as function of VO_2 has been developed (22, 25). In vitro studies mimicking VO_2 in the adult range have shown that the error on VO_2 measurements increases significantly with FiO_2, particularly for FiO_2 exceeding 0.60-0.80. VO_2 can be measured with a 5% accuracy, provided a maximum level of 0.60 for FiO_2. It is important to maintain a stable FiO_2 and to avoid fluctuations during the inspiratory and expiratory phases of mechanical ventilation (26).

Application of indirect calorimetry: additional conditions to fulfill

Additional conditions which have to be fulfilled using indirect calorimetry in critically ill adults and children on mechanical ventilation are (15, 27):

- no gas leaks in the ventilator patient circuit or endotracheal tube leakage;
- ventilation must be stable (i.e. no hyperventilation), to provide stable body CO_2 stores;
- steady haemodynamic, respiratory and metabolic states must be present to insure that respiratory gas exchange is equivalent to tissue gas exchange;
- a stable bicarbonate pool must be ascertained, in particular no renal or digestive losses and no alkali therapy must occur. Changing metabolic acid-basis status (i.e. developing or resolving lactic or ketonic acidosis) must be excluded. In case of ketone body metabolism or lactate metabolism oxygen utilization can be increased and compensatory shifts of CO_2 can occur. One may correct for the contribution of these substances to overall substrate utilization and energy production by knowing the change in the plasma concentration, space of distribution, urinary excretion rate, and heat of combustion (24);
- urea pools must be constant ;
- anaerobic metabolism must be excluded since in this condition, there is an EE that is not related to VO_2;
- gas exchange measurements must be avoided in critically ill patients during and shortly after procedures have been performed with inhalation anesthetics;
- no extra-corporeal CO_2 removal or oxygenation device may be used;
- the calorimeter must be correctly calibrated, particularly the gas analyzers and the flow measurement system. At regular intervals, the instrument must be tested in vitro, using a gas infusion system or a combustion system;

- validation of any metabolic monitoring device should be performed by simulating gas exchange in a similar rate to the clinical ranges of VCO_2 and VO_2. To accomplish validation of metabolic monitoring devices, several methods have been described like gas injection, combustion of Fe and combustion of carbohydrate fuels like ethanol and butane. Calibrating the oxygen and carbon dioxide analyzers by test burning agents with a known RQ of 0.67, such as methanol (28), ethanol (29) and butane, indicates a high level of absolute accuracy for the indirect calorimetric technique.

2.3.2 Duration of measurements

There is a difference between studies of critically ill adult patients and studies of premature infants regarding the accuracy of shorter measurement periods than 24 hours to accurately estimate the total daily energy expenditure (TDEE). A study in critically ill adult patients showed that multiple short measurement periods (i.e. twice 15 min) were more accurate in approximating TDEE than longer measurement periods (30). On the other hand Gudinchet et al concluded from measurements made during 1.30-3 hour in 3 non-ventilated children that it provides a reliable estimation of TDEE. The coefficients of variation of VO_2 of these 3 children were low, 3.5%, 6.6% and 6.5% respectively (31). Abdulrazzaq et al concluded in a study of preterm infants that short periods of measurements under carefully controlled conditions can certainly provide information about maintenance requirements, but if data are required on which to base decisions about the thermal environment, or to calculate energy balance, then it seems that periods of at least 6 hours are essential. With a period of 3 hours they found a significant difference (13%) in the highest and lowest values of VO_2 (32). Bell et al also performed a study in non-ventilated premature infants and found that the mean EE during the first 6 hours was within 6.5% of the mean for the entire 24 hours period in all but one case. The mean error in estimating TDEE from 6 hour measurements was 0.9%. The mean coefficient of variation in EE among the 2 hours periods was 11.0%. Bell et al concluded that TDEE of small premature infants can be estimated from measurements as short as 6 hour with sufficient accuracy for most purposes (33). From the studies mentioned above it can be stated that there is a significant difference between studies in adults and studies in infants in the duration of EE measurements to accurately estimate TDEE. This difference can probably be explained by the fact that the premature infants were on an intermittent feeding regimen and not sedated whereas adult patients were sedated, ventilated and on a continuous feeding regimen. Studies in mechanically ventilated children beyond infancy were not performed so far.

2.3.3 Serial measurements

There are multiple factors which influence the REE in critically ill adult patients and due to these factors there is a significant variability in the daily REE ranging from 4 to 56%. Furthermore, the variability of REE in adult patients increases from one day to the next if the patient is more critically ill (34, 35). An example of the usefulness of serial daily EE measurements are those adult patients with acute respiratory failure who mostly have shown a condition of hypermetabolism, which is the major determinant of ventilatory demand. The degree of hypermetabolism is not predictable. It seems appropriate to perform multiple indirect calorimetric measurements (maintaining a RQ between 0.8 and 0.9), with the purpose of administering a caloric load equal to the measured EE, limiting diet-induced thermogenesis and reducing the risk of carbon dioxide overload (27).

Marks et al performed a study on the day-to-day variability of EE in low birth weight neonates. Their analysis showed variations of some 10% within a measurement of VO_2 lasting 2 hours, whereas VO_2 measured in the same infant repeated on another day may have been 12% below or 10% above the best estimate of the true mean value (36). These results seem to contradict those obtained by Rutter et al who measured the resting rate of VO_2 of small babies over a period of 3 to 15 minutes and found small variations in serial VO_2 measurements repeated over 24 hours and from day to day. However, the longer sampling interval, the more likely it was that behavioral state, periods of wakefulness, or body movements were included in the sample and thus affected the results (37). Studies of serial measurements of EE have hardly been performed in mechanically ventilated children. Gebara et al showed in a study concerning children after cardiac surgery no significant alteration of REE during the first 3 days after surgery (38). Philips et al performed a study in children with neurotrauma and measured these patients at non-regular intervals but the patients included in this study were too small to draw conclusions about the value of repeated measurements (39). In our experience the variability of EE from day to day is within 10% when measured for 2-4 hours. Increased temperature is one of the most important factors, which increase EE. Serial indirect calorimetric measurements are more useful for determining the RQ as a guide for underfeeding or overfeeding (see below).

2.3.4 Clinical use of indirect calorimetry

The potential use of indirect calorimetry in critically ill adult patients is well established (27) and can also be applied in critically ill children:

- assessment of EE for patients who fail to respond adequately to estimated nutritional needs;

- assessment of EE for patients with single- or multiple-organ dysfunction who need prolonged ICU care and artificial nutritional support;
- assessment of the effects induced by artificial nutrition on the cadiocirculatory and respiratory systems in mechanically ventilated patients with acute respiratory failure;
- monitoring of VO_2 during weaning from mechanical ventilation.

Furthermore the method can be used in (preterm) infants:

- to get a better understanding of the metabolic response to illness and to make recommendations for specific nutritional requirements (40);
- to determine the metabolic costs of growth (31).

Theoretically the greatest advantage for the use of indirect calorimetry is to design total parenteral nutrition/total enteral nutrition that exactly meets the patient energy requirements and avoids the complications of overfeeding. Overfeeding can lead to hepatic dysfunction, hyperglycemia, elevations of blood urea nitrogen, cholesterol and triglycerides, delayed weaning from the ventilators, fluid overload, hyperosmolar states, and increased secretion of norepinephrine and urinary catecholamines (34).

Only a few studies in adults have been performed which describe the influence of different feeding protocols on outcome. Bartlett et al reported a direct relation between cumulative caloric balance and mortality rate in critically adult surgical patients with an average ICU stay of 18 days, fed with regimens based on the estimation of caloric and nitrogen requirements (41). Vo et al evaluated the effect of caloric overfeeding with high carbohydrate intake (based on RQ values measured by indirect calorimetry) on morbidity and mortality. Septic episodes and mortality were greater in the overfed group versus the group receiving calories equal to the measured EE (42). Identifying a hypometabolic response from the more characteristic hypermetabolic response may be a predictor and an important factor of the clinical outcome, differentiating the pattern of survival from nonsurvival (27).

However most of the studies in adults and children performed using indirect calorimetry are descriptive or deal with different feeding protocols to determine the appropriate mixture of substrates to be administered. McClave stated that the advantage of tailored feeding protocols by exactly measuring energy requirements with indirect calorimetry has not yet been demonstrated convincingly (34).

Resting and total energy expenditure

In adults the REE accounts for 75% to 90% of the TDEE, the remainder of which is accounted for by thermogenesis resulting from nutrient intake (diet-induced thermogenesis), environment (shivering/nonshivering thermogenesis), and physical activity (34). In children TDEE is made up of REE, diet induced thermogenesis, activity and growth. REE is 65% to 70% of TDEE. Diet-induced thermogenesis constitutes 5% to 10% of TDEE, physical activity is 25% to 30% TDEE, and growth on a daily basis is too small to measure except in rapidly growing infants.

Early after admission of adults to an intensive care unit, interaction with nursing personnel and health care givers, frequent procedures and therapeutic interventions result in a little difference between TDEE and REE which may be less than 5%. Later in the course of hospitalization this difference between REE and TDEE can increase up to 15% (35). Furthermore there seems to be a ceiling effect or physiologic plateau in this response of EE to injury that correlates to approximately two times the baseline REE (43, 44). With other words there can be significant differences between REE and TDEE in the time course of critical illness necessitating frequent evaluation of these values.

Studies in non-ventilated children

Studies of non-ventilated children with a variety of diseases showed a wide variation of REE measured with indirect calorimetry. It was recommended in these studies that measurement of REE should be performed in individual patients instead of using a prediction equation for ensuring adequate nutrition (45, 46). However there are a number of studies of specific patient groups measuring REE. Groner et al measured REE in 12 children (8-19 yr) following major elective surgery and found contrary to adults no significant increase in REE (compared with the predicted values of Harris-Benedict) (47). Jones et al found a modest short-lived increase in REE in postoperative infants (48). Studies in infants with pulmonary hypertension and congestive cardiac failure showed that failure to thrive was associated with high resting metabolic rates or TDEE mainly due to an increased VO_2 (49, 50). Greatly increased VO_2 values were observed before surgery in a group of infants with a large left-to-right intracardiac shunt and heart failure. Postoperatively a decrease up to 43% (mean 15%) of VO_2 was observed in these infants (51). A study in infants with bronchopulmonary dysplasia showed that REE or TDEE were elevated (52). An increased EE has been described patients suffering from cystic fibrosis as a result of a primary defect in the gene product, in relation with a detoriating pulmonary function (53) or in relation with severe malnourishment (54). A study in burned children showed that the EE was 1.3 times the predicted value (55). Furthermore no increased REE were in children with

acute lymphoblastic leukemia receiving chemotherapy (56), in children during growth-hormone treatment (57) and in children with Crohn's disease (58). Increased rate of REE were measured in children in sleep suffering from obstructive sleep apnea syndrome (30%) (59), children with extrahepatic biliary atresia (29%) (60), children with Gaucher's disease type I (44%) (61) and in children with asthma (15%) (62). In a study of non-obese children with Duchenne muscular dystrophy REE was 13% lower than in controls (63). Table 1 gives an overview from the cited literature concerning effects on (R)EE or VO_2 measurements with indirect calorimetry in children with these different clinical diagnoses. From all these studies it can be concluded that for patient groups the mean value of REE can be normal, increased or decreased but that the wide individual variability should be taken into account (64).

Other factors in the intensive care influencing REE are diet-induced thermogenesis, body weight, catecholamines, narcotics, muscle relaxants and increased body temperature. Most of these data are derived from adult studies. Only a few studies in children describe the influence of these factors on EE such as the study of Matthews et al who found a positive relationship between rectal temperature and EE; EE increased by a mean of 7.4% per grade Celsius (65). Further studies in critically ill children should be performed to investigate these factors.

Studies in ventilated children

Only a few studies of mechanically ventilated children report results of EE measurements using indirect calorimetry (table 1) (38, 39, 66-70). In 6 of these 7 studies REE was measured and only one study performed prolonged measurements of EE. In 2 of these studies posttraumatic head injured children were measured and the ratio measured EE to predicted EE was 1.5 and 1.3 respectively, indicating hypermetabolism in these children (39, 67). However all the 7 studies showed a wide variation in individual actual energy requirements in different diseases and a wide range in the ratio of measured TDEE or REE to predicted basal metabolic rate. Coss-Bu et al, who performed a study on a group of 55 mechanically ventilated children, concluded that standard prediction equations are not appropriate to calculate the energy needs of critically ill mechanically ventilated children and they advocate to measure EE by means of indirect calorimetry (70).

Vent	Clinical diagnosis	Effect on (R)EE or VO_2	Ref
No	Surgery pre/postoperative	No increase REE	(47)
No	Surgery postoperative	14-26% increase REE 2-4 h after surgery	(47)
Yes	Trauma and different clinical diagnosis	48% increase REE	(67)
Yes	Head injury	19% increase REE	(39)
No	Burning	30% increase REE	(55)
No	Congenital heart disease pre/postoperative	15% decrease VO_2 postoperative	(51)
Yes	Heart surgery postoperative	No increase REE	(38)
Yes	Different clinical diagnosis	No increase REE	(66)
Yes	Different clinical diagnosis	No increase REE	(68)
Yes	Different clinical diagnosis	53% increase REE	(70)
No	Congenital heart disease	Increased REE	(49, 50)
No	Bronchopulmonary dysplasia	30% increase EE	(52)
No	Cystic fibrosis F508/F508	25% increase REE	(53)
No	Cystic fibrosis malnourished	33% increase REE	(54)
No	Acute lymphoblastic leukemia with chemotherapy	No increase REE	(56)
No	Growth hormone treatment	No increase REE	(57)
No	Crohn' s disease	No increase REE	(58)
No	Obstructive sleep apnea	30% increase REE	(59)
No	Extrahepatic biliary atresia	29% increase REE	(60)
No	Gaucher' s disease	44% increase REE	(61)
No	Asthma	15% increase REE	(62)
No	Non-obese Duchenne	13% decrease REE	(63)

Table 1 Effects on (R)EE or VO_2 measured with indirect calorimetry in children with different clinical diagnosis and with or without mechanical ventilation (Vent)

Respiratory quotient and substrate utilization

The respiratory quotient (RQ) is a helpful element of indirect calorimetry determination. Attention for the RQ has been considered important by some in evaluating substrate utilization and/or nutritional support and to determine overfeeding and underfeeding. Most data regarding RQ and substrate utilization in injury and sepsis come from studies in critically ill adult patients and from studies in minimally stressed infants and children. Only a few studies were performed in critically ill children

RQ and substrate utilization in injury and sepsis in adult studies

Askanazi et al compared the effect of total parenteral nutrition consisting of a hypertonic glucose/amino-acid solution between nutritionally depleted adult patients and septic or injured patients. They found a rise in RQ in the depleted group from 0.83 to 1.05 (a 32% rise in CO_2 production and a 3% rise in O_2 consumption) and a rise from 0.76 to 0.90 in the septic group (56% rise CO_2 and 29% rise O_2). They concluded that administration of a large glucose load to hypermetabolic patients does not totally suppress the net fat oxidation as it does in depleted patients. Rather there is an increase in VO_2, continued oxidation of fat and apparently an increase in the conversion of glucose to glycogen (71). Other studies in septic and injured adult patients confirmed these finding namely that the response to glucose loading is very different in the injured patient compared to normal fasted adults (72, 73). Burke et al who studied burn injured adult patients concluded that there appears to be a maximal rate of glucose infusion, beyond which physiologically significant increases in protein synthesis and direct oxidation of glucose cannot be expected. Furthermore he stated that there appears to be a physiologic cost of exceeding the optimal glucose infusion rate, as indicated by increased rates of CO_2 production during infusions as well as large fat deposits in the liver at autopsy in patients infused with large amounts of glucose (74).

RQ and substrate utilization with different feeding regimens in minimally stressed infants and children

Studies which were performed in healthy or minimally stressed newborn babies compared the influence of varying feeding protocols with different amounts of glucose, fat and protein on RQ and substrate utilization (75-78). These studies showed a significant increased RQ (in 2 of these studies > 1.0) when glucose was the predominate substrate in the solution and a lower RQ when a substantial amount of fat was added to the solution. Studies with small numbers of infants and children also showed in comparing different feeding regimens that with a RQ > 1.0 glucose was the predominant fuel (79, 80).

RQ and substrate utilization studies in critically ill children

No studies in septic or injured children were performed to investigate the influence of different feeding protocols on RQ and substrate utilization. Some observational studies with children only receiving a glucose infusion were performed.

Letton et al described a study in postoperative children and found that during the early postoperative stress lipogenesis due to carbohydrate overfeeding (with increased CO_2 production and RQ > 1.0) was substantial, even at reduced caloric delivery

rates that exceeded measured EE by only 50% (81). Powis et al observed in 10 children who had undergone a major operation a decrease in RQ from a preoperative value of 0.92 to 0.89 postoperatively and concluded that this reflected mobilization of endogenous fat (82). Only in a few studies concerning mechanically ventilated children indirect calorimetric measurements were performed. In 2 of these studies children who were receiving only glucose infusion showed that the relative energy contribution of fat was 53% and 78% respectively which reflected a fat utilization rate of 2.7 g/kg/day (67) and 4.8 g/kg/day respectively (38). 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 (83).

From all the studies mentioned above it can be concluded that substrate utilization patterns differ markedly from patient to patient depending on the phase of disease, the amount of glucose and fat administered. Furthermore there seems to be a maximum rate of glucose and fat oxidation at least in adults which probably occurs also in critically ill children. Again, one must recognize that the fundamental measurement provided by indirect calorimetry is the net disappearance rate of a substrate regardless of the metabolic interconversions that the substrate may undergo before its disappearance from its metabolic pool. Under most circumstances, direct oxidation represents the major route by which a substrate disappears from its metabolic pool, and the two terms oxidation and disappearance rate are often used interchangeably. However, under conditions when rates of gluconeogenesis, ketogenesis, or lipogenesis are elevated, the presumed equivalence between oxidation and disappearance may no longer apply, even though actual measurements derived from indirect calorimetry remain valid (see fig. 2). Measurement of a RQ showed to be helpful in determining underfeeding and overfeeding in the time course of critical illness.

A combination of indirect calorimetry and isotope labeling can probably give a better understanding in substrate flows. Van Aerde et al performed a study to investigate the effect on the energy metabolism of newborn infants of replacing glucose with lipid. They used the (U-^{13}C) glucose technique to measure glucose oxidation and indirect calorimetry to measure glucose utilization (75). They found in both the glucose only and the lipid supplemented group the values of glucose utilization obtained by indirect calorimetry to be higher than those of glucose oxidation determined by the tracer technique. However, the amount of glucose carbon stored as fat, calculated from the difference between glucose utilization and glucose oxidation, and the lipogenesis, calculated as the difference between fat utilization and fat oxidation rate, both decreased markedly when one-quarter of the non-protein energy was

administered as intravenous fat. They stated that one of the unresolved problems in using indirect calorimetry in neonates is that it does not fully account for where all the glucose ingested or infused is used for. They postulated that glucose carbon atoms enter a tissue carbon pool and are used for the synthesis of various elements that do not affect RQ, such as non-essential amino acids, bone bicarbonate, mucopolysaccharides, phospholipids and cholesterol. Further research is required to resolve these issues.

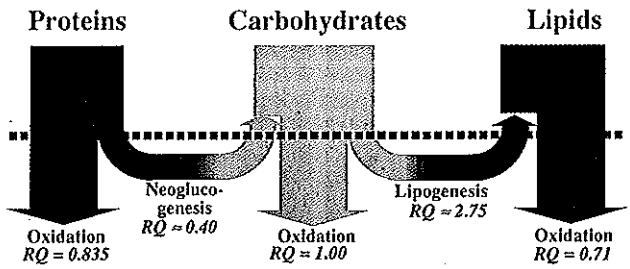

Figure 2 Substrate flows assessment by the indirect calorimetry method. (adapted from Chioléro (15))

Indirect calorimetry measures only the overall disappearance rate (broken line) and not the true oxidation rate. For protein, the disappearance rate consists of the true oxidation rate plus the rate of neoglucogenesis. The same is true for carbohydrates (oxidation + lipogenesis – neoglucogenesis) and lipids (oxidation – lipogenesis)

3 Endocrine and biochemical aspects of nutritional assessment

3.1 CHARACTERISTICS OF THE ENERGY RESPONSE TO INJURY AND STRESS

The pattern of energy response to injury has been well worked out in adult patients, and compromises an ebb and flow phase (84). The initial ebb phase is characterized by intravascular volume depletion and hypotension, and lasts for 8 to 12 hours. Although catecholamines, cortisol, and other counterregulatory hormones are all released during this period, a latency period exists before their effects are seen in peripheral tissues. As a result, initial EE may remain unchanged or even decreased, accompanied by a decrease in body temperature. Both effects are thought to be related to changes in thermoregulation by the hypothalamus. Progression from the ebb to the flow phase of injury is associated with dramatic increases in EE, the height of which is related to the type, severity, and extent of injury. A plateau or maximum physiologic response occurs at a level corresponding to a 200% increase above REE, where respiratory and circulatory capacities are maximized and where further insults to the system (e.g., fever, sepsis) do not produce further increases in EE (43, 44). The duration of the flow phase and return of EE to normal is 7 to 10 days, unless concomitant organ failure or ensuing sepsis complicates the clinical picture. The height of the energy response represents the sum of many physiologic processes initiated by the injury (85). As a result, a sequence of metabolic events is initiated. This includes the utilization of endogenous stores of protein, carbohydrate and fat to provide essential substrate intermediates (primarily amino acids) and energy necessary to fuel the ongoing response. Amino acids from degraded proteins flow to the liver, where they provide substrate for the synthesis of acute-phase proteins and glucose (gluconeogenesis). The acute metabolic stress response then, represents a

hypermetabolic, hypercatabolic state that results in the loss of endogenous tissue and can lead to a poor clinical outcome in the absence of appropriate exogenous support (see fig 3). As the acute response resolves, adaptive anabolic metabolism ensues to restore catabolic losses. In children, this phase is characterized by the resumption of somatic growth.

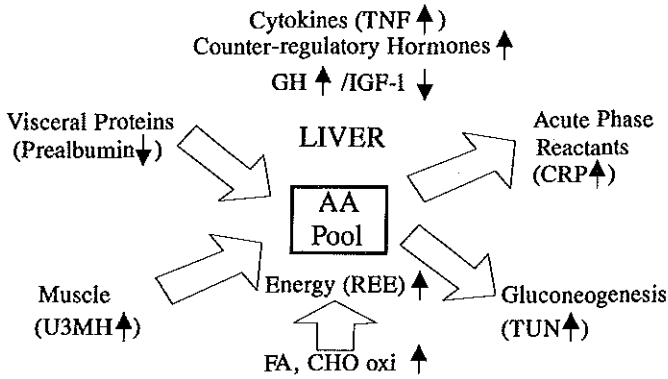

Figure 3 Metabolic response to acute injury (adapted from Chwals (86))
TNF=tumor necrosis factor; GH=growth hormone; IGF-1=insulinlike growth factor I; AA=amino acid; CRP=C-reactive protein; TUN=total urinary nitrogen; FA, CHO oxi=fatty acid and carbohydrate oxidation; U3MH=urinary 3-methylhistidine; REE=resting energy expenditure

It is not clear if the pattern of ebb and flow phase that has a characteristic pattern in the time course of injured and septic adult patients is also present in critically ill children. Therefore we will give an overview of what is known from the metabolic and hormonal alterations described in critically ill children. We will also focus on established and on new parameters which can be used to predict the early restoration of anabolic function.

3.2 ENDOCRINE CHANGES: GENERAL

The endocrine response during the acute, catabolic phase of injury is enacted by hormones primarily under the control of hypothalamic-pituitary axis and the autonomic nervous system (see table 2). In general, injury and operation cause increased release of all hypothalamic-pituitary axis hormones with the exception of thyroid hormones and the gonadotropines. Hormones primarily controlled by the autonomic system are also increased in the early phase following injury, with the

exception of insulin and the insulin-like growth factors (87). In contrast, prolonged critical illness is characterized by reduced neuro-endocrine stimulation. These changes have consistently been viewed as adaptive or beneficial, as they may reduce and redirect energy consumption, postpone anabolism and, at the same time, activate the immune response while protecting the host against deleterious biological effects of the latter. It is still unclear to which extent some of these defense mechanisms may hyperrespond and, as a consequence, be harmful.

Hypothalamic-pituitary axis	Autonomic nervous system
Corticotropin-Releasing factor (CRF) ↑	Catecholamines ↑
Adrenocorticotropic Hormone (ACTH) ↑	Renin ↑
Cortisol ↑	Angiotensin ↑
Arginine Vasopressin (AVP) ↑	Aldosteron ↑
Growth Hormone ↑	Atrial Nutriuretic Peptides (ANP) ↑
Thyroid Hormones ↓	Insulin ↓
Gonadotropines ↓	Glucagon ↑
Prolactin ↑	Somatostatin (?)
Opoid peptide ↑	Insulin-like Growth Factors ↓
	Parathyroid Hormones ↑

Table 2 Hormonal control during acute stress in adults: the hypothalamic-pituitary axis and autonomic nervous system

3.2.1 The pituitary-adrenal axis

Plasma cortisol concentrations increase with the development of the sepsis syndrome in adults (88-90), children (91) and neonates (92). Sepsis-induced hypercortisolism is partially due to decreased rate of cortisol extraction from the blood, and decreased binding of cortisol to transcortin, resulting in an increase in the circulating free cortisol concentration. The increased cortisol concentrations induce shifts in carbohydrate and protein metabolism resulting in instantly available energy and postponement of anabolism. Furthermore, the hypercortisolism elicited by disease or trauma can be interpreted as an attempt by the organism to mute its own inflammatory cascade, thus protecting itself against possible endogenous overresponses (93). Animal studies suggested that normal adrenal gland function is vital for survival from septic insults, and that the increased levels of plasma cortisol in septic shock may be a protective homeostatic response (90). In adult studies cortisol

levels appeared to be highest in patients with the highest illness-severity scores and in those with the highest mortality (94, 95). Studies in children with meningococcal sepsis showed that non-survivors had lower cortisol levels on admission compared with survivors. At autopsy a majority of these patients showed adrenal hemorrhagic necrosis suggesting that adrenal insufficiency may complicate the initial stage of disease (91, 96). Adrenal function in severely ill adult patients is often evaluated by a corticotropin-stimulation test and it is advocated that the adrenal hyporesponse of this test can be of predictive value for outcome (97, 98). Inappropriately low serum cortisol responses to corticotropin also suggest the presence of relative adrenal insufficiency. It is important to recognize this condition, because therapy with corticosteroids can improve the clinical conditions of these patients, making their outcome dependent only on the underlying disease (95). The value of high-dose corticosteroid therapy in critically adult patients with an intact hypothalamic-adrenal axis is controversial, however there have been some beneficial reports in some patients (95). Recently a study in adult patients suffering from septic shock showed that low dose of hydrocortisone was associated with an improvement of duration and severity of shock (99). Clinical symptoms and signs that might raise suspicion of the existence of relative adrenal insufficiency are shown in table 3. Furthermore in adult studies the circadian rhythm was shown to be disrupted in proportion to the length of operation and to the magnitude of injury and persistent elevations of serum cortisol levels were associated with reduced survival (87).

Symptoms and signs of hypoadrenalism
• Unexplained circulatory instability
• Discrepancy between the anticipated severity of the disease and the present state of the patient, including nausea, vomiting, orthostatic hypotension, dehydration, abdominal or flank pain (indicating acute adrenal hemorrhage), fatigue, and weight loss
• High fever without apparent cause (negative cultures), not responding to antibiotic therapy
• Unexplained mental changes; apathy or depression without a specific psychiatric disturbance
• Vitiligo, altered pigmentation, loss of axillary or pubic hair, hypothyroidism, hypogonadism
• Hypoglycemia, hyponatremia, hyperkalemia, neutropenia, eosinophilia

Table 3 Symptoms ands signs that raise the suspicion of hypoadrenalism in critically ill patients

The widespread metabolic effects of cortisol are extensively described (87). There is however little data regarding adult studies which relate serial cortisol levels in critically ill patients to nutritional outcome parameters. Frayn et al performed a study in injured adult patients and found that cortisol concentrations were subsiding as the nitrogen excretion raised to its maximum. They stated that although cortisol itself has been proposed as a contributory cause of the catabolic response, the time course of these results were not in accordance with this previous statement (100). Bernier et al performed a study in burned adult patients and found a positive relationship between urinary free cortisol and nitrogen balance but not between plasma cortisol and nitrogen balance (101).

The time course effects of hypercortisolism or hypocortisolism in relation with the metabolic alterations of the critically ill child has never been assessed.

3.2.2 Growth hormone

Growth hormone (GH) has direct and indirect anabolic actions. The principal mediator of the indirect anabolic actions is IGF-1. Adult studies have shown that basal GH secretion is increased in critical illness, although the pulse amplitude is usually reduced (102). Critically ill patients appear relatively resistant to endogenous growth hormone and circulating levels of IGF-I and IGF-II are invariably low despite the increased basal GH secretion (100, 103). Importantly, pharmacological agents commonly used to support the critically ill, such as dopamine chloride, have been shown to decrease GH secretion in adults (104). Through its action on growth hormone secretion, prolonged dopamine administration in critical illness presumably contributes to the maintenance of fat depots and to the failure to induce protein anabolism despite optimal feeding (105). This decrease in GH secretion was also seen in newborns but not in older infants and children probably due to age-dependent differences in the characteristics of dopamine receptors (106). In addition, changes in metabolic and nutritional status influence the GH/IGF-I axis. In normal adults circulating levels of IGF-1 are low after starving (107) and in the malnourished, whilst production is stimulated by high protein and carbohydrate intake (108). A close relationship between circulating levels of IGF-I (with a half- life of 2 to 6 hours) and nitrogen balance in the critically ill was found, and it has been suggested that IGF-I may be an useful index of nutritional status in such patients (109).
No studies in children were performed to investigate the relation between IGF-1 and nutritional parameters.

3.2.3 Insulin

Synthesis and secretion of insulin is controlled by the concentration of circulating substrate (glucose, amino acids, and free fatty acids), the activity of autonomic nervous system, and the direct and indirect effects of several hormones. In any study of recently injured adult patients an extremely wide range of insulin concentrations is a prominent feature. It seems that the plasma insulin concentration after injury reflects the opposing effects of the stimulus of hyperglycemia and the inhibitory effect of adrenaline (110). Insulin concentration rises over the first few days after injury and peaks at about the time of the maximal catabolic response (110, 111). However the elevation of insulin concentrations fail to exert the expected anabolic effects and the effect of glucose is blunted by neural and humoral mechanisms. This insulin resistance has been broadly defined as "a state (of a cell, tissue, or organism) in which a greater than normal amount of insulin is required to elicit a quantitatively normal response" (112). Only a few studies described the insulin response in critically ill children. A study in head injured children showed highly variable insulin levels, however the most severely injured children had the highest insulin levels (113). Studies in septic preterm infants showed that increased glucose needs were not associated with hyperinsulinemia (114). This is in contrast to the hyperinsulinaemic response found in adults. If this altered glucoregulation in preterm infants is also present in critically ill children is not known.

Several clinical studies in adult patients investigated the degree of insulin response to different infused calorie and amino acids solutions. The nutrient mix that resulted in the most efficient increase in insulin production rate (and probably other anabolic factors) is constituted by amino acids and more than 80% of the calories of glucose (115). Other studies showed that with this prevalent glucose system yielding the overall measured or expected energy requirement, coupled with insulin supply to maintain normoglycemia, reaches an "optimal" anabolic insulin level, that with protein supply, seems to be the most efficient tool to optimize protein metabolism. The use of extra insulin as an anabolic drive has only been studied in burned children. Herndon et al used insulin to treat the hyperglycemia that occurred during treatment of severely burned children with growth hormone (116). Gore et al performed a study in burned children and compared the effects of infused growth hormone and insulin and they concluded that both appeared to be equally effective in stimulating protein synthesis (117). Gilpin et al compared in a study of burned children those who only received growth hormone and those who received a combination of growth hormone and insulin. There were no significant differences in initial skin donor site healing times (118).

3.2.4 Thyroid hormones

Multiple alterations in the thyroid axis in critical illness have been recognized, the most prominent being the combination of low serum thyroxine (T_4), triiodothyronine (T_3), and thyrotropin (TSH) concentrations and frequently with increased reverse T_3 (rT_3) concentrations. It is forming an entity called the "low T_3 syndrome" or "euthyroid sick syndrome" or "non thyroidal illness" (119). It has generally been thought that this syndrome does not produce hypothyroidism but rather is an adaptation in patients who are euthyroid. Furthermore it has been suggested that the low T_3 values and increased production of rT_3 may be the expression of an adaptive mechanism aimed at preventing protein catabolism and lowering energy requirements (120-123). Dopamine infusion induces or aggravates this syndrome in critical illness. Glucocorticoids and somatostatin may also suppress pituitary TSH release and glucocorticoids may inhibit T_4 to T_3 conversion. The cytokines TNF-alpha, IL-1 and IL-6 have been investigated as putative mediators of the "low T_3 syndrome" (124). Richmand et al showed that a large component of the alteration in thyroid hormone levels in critically adult patients was due to the caloric deprivation associated with such severe illness (123). The degree of T_3 suppression with concomitantly low TSH correlates positively with disease severity and duration, and correlates negatively with outcome (125, 126). The magnitude of the T_3 drop within 24 hour reflects the severity of illness (127). Accordingly, an increase of serum TSH is a hallmark of recovery from severe illness (128).

Alterations in the thyroid axis during the prolonged phase of critical illness appear to be different and the reduced production of thyroid hormones may have a neuroendocrine pathogenesis (central hypothyroidism). As normal levels of T_3 are required for protein synthesis, lipolysis, fuel utilization by muscle, and GH secretion and responsiveness, central hypothyroidism has been hypothesized to contribute to the feeding-resistant catabolic state of prolonged critical illness (124). The neuroendocrine pathogenesis of the low T_3 syndrome of prolonged critical illness is unknown (124).

As mentioned above the "euthyroid sick syndrome" has a similar clinical picture in studies which were performed in infants and children after cardiac surgery (106, 129), in critically ill infants and children with infections (130, 131), in children after head trauma (113) and in preterm and newborn infants (132-135). Some authors related thyroid function tests with survival or degree of illness. Uzel et al found significantly lower initial and subsequent T_4 values in non-survivors and an increase of T_3 values in the group who recovered, whereas in non-survivors there was a

further decrease in T_3 levels, accompanied by a decrease in rT3 levels in the terminal stage (130). Allen et al found that changes in rT_3 levels parallel changes in of therapeutic interventions after a delay of 12 to 24 hours and clinical indicators of illness severity did correlate (inversely) with serum T_3 levels (129).

The most striking feature of the "euthyroid sick syndrome" is the suppressive influence of dopamine on TSH secretion that was found in infants and children after cardiac surgery (106). The question is whether the so-called "euthyroid sick syndrome" does not reflect an adaptive mechanism, but may represent at least in part a condition of iatrogenic hypothyroidism. The analogy with congenital hypothyroidism suggests that impaired thyroid function during infancy increase the risk for irreversible neurologic damage (93) that deserves further investigation (134).

In summary we can conclude from studies in adults and children:

- the "euthyroid sick syndrome" might be an adaptive mechanism in the early course of critical illness that does not warrant intervention;
- thyroid function tests can be used to predict the severity of disease;
- in prolonged illness iatrogenic central hypothyroidism can develop which may participate in associated neurological and clinical alterations in adults and impaired neurological development in children.

Taken together acute and prolonged critical illness seems to result in different neuroendocrine paradigms and should perhaps be approached with different therapeutic strategies. The initial endocrine response evoked by severe illness or trauma and by starvation consists primarily of a peripheral inactivation of anabolic pathways (low IGF-1, T_3), whereas pituitary activity is essentially maintained or amplified. Substrates for survival are provided, anabolism is postponed, and the immune response is activated while the host is protected against deleterious systemic effects of the latter. In the chronic phase of critical illness, reduced pulsatile secretion of anterior pituitary hormones correlate positively with activity of target tissues; cortisol secretion is a notable exception, being maintained through a peripheral drive (see fig. 4).

3.2.5 The protein hormone leptin

Leptin is a protein hormone that is expressed in adipocytes and the physiological significance of is just beginning to unfold. Leptin has central effects, playing a role in appetite control and in the regulation of EE (136). Because leptin levels parallel changes in nutritional status and energy storage across a broad range

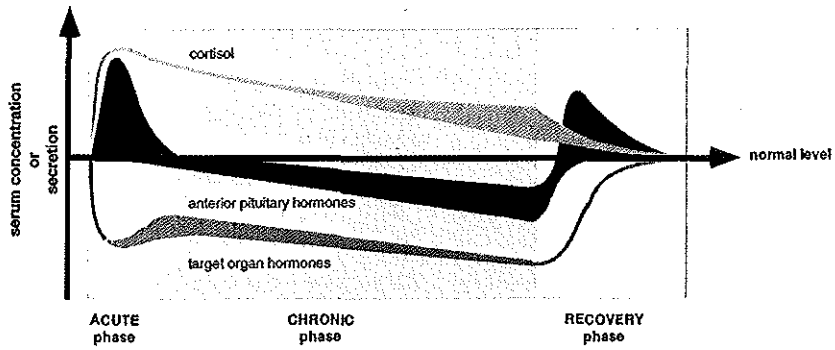

Figure 4 Simplified concept of the pituitary-dependent changes during the course of critical illness (adapted from van den Berghe (124)).

In the acute phase of illness (first hours to a few days after onset), the secretory activity of the anterior pituitary is essentially maintained or amplified, whereas anabolic target organ hormones are inactivated. Cortisol levels are elevated in concert wit ACTH. In the chronic phase of protracted critical illness (intensive care dependent for weeks), the secretory activity of the anterior pituitary appears uniformly suppressed in relation to reduced levels of target organ hormones. Impaired anterior pituitary hormone secretion allows the respective target hormones to decrease proportionately over time, with cortisol being a notable exception, the circulating levels of which remain elevated through a peripheral drive, a mechanism that ultimately may also fail. The onset of recovery is characterized by restored sensitivity of the anterior pituitary to reduced feedback control.

from starvation to obesity, leptin is well positioned to signal energy insufficiency or energy excess, causing responses that could counter the adverse consequences of either starvation or obesity. Recently serum leptin concentrations were studied in critically adult patients. Leptin levels were related to the suppressed growth hormone/IGF-I axis (137). Reactivating the growth hormone/IGF-I axis with growth hormone secretagogues for 2 days concomitantly increased leptin levels within 12 hours. Whether this findings reflected a direct leptin-releasing effect of growth hormone secretagogues or, rather, points towards a role of growth hormone in the physiological regulation of leptin secretion remains to be determined. The authors stated that increasing levels of leptin, together with growth hormone, IGF-1, and insulin, might switch substrate use from protein to fat, enabling protein anabolism to restore, which is crucial for the onset of recovery from prolonged critical illness. In another study of adult patients with sepsis leptin was found to be a stress related hormone, which

might be important for survival. In this study plasma leptin levels were increased in survivors (138). Studies in children however showed no relation between serum leptin levels and EE in healthy children but also there was no difference in serum leptin levels in young patients with inflammatory bowel disease compared to healthy controls (139, 140) . The role of leptin in critically ill children has to be determined.

3.3 CYTOKINES

In response to a variety of local or systemic stimuli such as trauma, sepsis, and acute inflammatory conditions, a series of metabolic changes occur that characterize the acute stress state (86). In large part, this response is stereotypical and does not depend so much on the nature of the insult and on its degree. Among the early features of injury response are the releases of cytokines followed rapidly by important alterations in the metabolic, immune and hormonal environment (86). Several prominent cytokines are tumor necrosis factor (TNF), interleukine-1 (IL-1), interleukine-2 (IL-2), interleukine-6 (IL-6) and interferon gamma. These cytokines have short half-lives. Whereas TNF-alpha and IL-1 can exert activity as cell associated or secreted a form, IL-6 exists only in a secreted form and serves a more classic endocrine function. Bernier et al investigated in adult burned patients the relationship of IL-6 with cortisol and protein metabolism. They found that high IL-6 concentrations were predictors of low plasma concentrations of cortisol binding globuline and high cortisol free fractions but there was no relationship between IL-6, nitrogen balance, and 3-methylhistidine excretion. They hypothesized that the decrease in circulating cortisol binding globuline has important consequences on the amount of cortisol available to the tissues in the days after injury and, thus, may influence protein metabolism, the immune system and wound repair (101). In children with meningococcal sepsis levels of cytokines are significantly increased at the onset of disease and these levels are associated with outcome and severity of disease (141). No studies in children were performed to relate interleukines with nitrogen balance studies and nutritional support.

3.4 ACUTE PHASE PROTEINS

One of the key features of the acute metabolic stress response is that the liver switches to synthesis of acute phase proteins such as C-reactive protein (CRP), caeruloplasmin, fibrinogen and alpha1 glycoprotein, which carry out a number of important immunologic and repair functions during the acute stress period. Amino acids from catabolized proteins flow to the liver, where they are substrate for the synthesis of these acute-phase proteins. This process is mediated by cytokines. The

serum concentration of CRP is often used in the initial screening of patients suspected of an acute infection and the magnitude of the CRP concentrations will help to differentiate between infections of bacterial or viral origin. The magnitude of the rise in acute phase proteins depends on the severity of the injury and can be used as an indicator of severity of illness. A study of infants who underwent major surgery examined pre- and postoperatively showed that peak levels of CRP were significantly higher in children who did not survive (142). While, in contrast in studies of children with severe meningococcal sepsis the magnitude of the CRP concentration was negatively correlated with outcome (143, 144). CRP levels can not only be used as an indicator of severity of illness but serial measurements can also be used as indicator for resolution of the acute stress and in advance used to stratify nutritional support. Furthermore the changes in the serum concentrations of acute phase proteins appeared to coincide with nitrogen excretion (86). Because CRP concentrations can be measured easily and accurately it is suggested that CRP is the preferred acute phase protein to be used not only for diagnoses and treatment of infections, but also as a follow-up indicator for anabolic restoration.

3.5 VISCERAL PROTEIN STATUS

In the acute phase of trauma and sepsis synthesis of the visceral proteins such as albumin, pre-albumin, transferrin and retinol-binding protein is inhibited. In the recovery phase the liver will return to produce visceral proteins which are needed for repair of injured tissue and in children for somatic growth. Proteins with a short biologic half-life such as pre-albumin (transthyretin) ($t_{1/2}$ = 2 days) and retinol-binding protein ($t_{1/2}$ = 10 hours) can better be used to predict changes in acute nutritional status than albumin ($t_{1/2}$ = 20 days) and transferrin ($t_{1/2}$ = 8 days) which have a longer half-life. Clinical studies of critically ill infants showed that pre-albumin and retinol-binding protein were the most suitable proteins to evaluate protein nutritional status (145, 146). Georgieff et al studied growing premature infants and found that changes in pre-albumin occurred 1 week before changes in anthropometric measurements and they concluded that changes in pre-albumin levels are more predictive than changes in protein intake alone for monitoring growth velocity in preterm infants (147). Thomas et al concluded that pre-albumin offer a rapid, accurate, and moderately inexpensive way to monitor protein-energy adequacy in preterm and sick infants (148). It can be concluded from the studies cited above that pre-albumin and retinol-binding protein are the most suitable proteins in assessing changes for somatic growth and recovery of catabolism. Because changes will be evaluated in days or weeks pre-albumin with a sort half-life of 2 days is the preferred protein.

A combination of acute phase proteins and visceral proteins was used to develop a prognostic inflammatory nutritional index (PINI). It consisted of a combination of two markers each of infection (CRP and alpha1-acid glycoprotein) and of malnutrition (albumin and pre-albumin) (149). It was concluded that the PINI scoring system provides the clinician with a sensitive tool assessing the severity of inflammatory events and taking into consideration of the aggravating effect of associated protein-calorie malnutrition. The formula would be of particular help in pediatric practice to recognize early subclinical complications and efficacy of specific therapeutic strategies. Chwals et al used the levels of pre-albumin and CRP in combination with the total urinary nitrogen excretion and values obtained with indirect calorimetry as guidelines for infant metabolic monitoring during acute stress (see table 4). When serial measurements of the metabolic indicators mentioned above demonstrate resolution of the acute stress phase, nutritional supplements are increased (86).

Parameter	Stress Characteristic Evaluated
Pre-albumin	Visceral protein catabolism
	Hepatic synthesis
Total urinary nitrogen (TUN)	Protein and fat catabolism
	Gluconeogenesis
	NB= N_i – (TUN + 75 mg/kg N_2)
C-reactive protein (CRP)	Acute-phase response
Indirect calorimetry	Energy expenditure and RQ
	RQ = VCO_2/VO_2
	EB = E_i – MEE
	RQ = VCO_2/VO_2

NB=nitrogen balance, N_i=24-hour nitrogen intake, EB=energy balance, Ei=energy intake, MEE=measured energy intake

Table 4 Infant metabolic monitoring during acute stress (adapted from Chwals(86))

3.6 TOTAL URINARY NITROGEN AND NITROGEN BALANCE

Protein metabolism during acute metabolic stress results in increased protein breakdown and a greater urinary nitrogen loss. In studies of adult patients the magnitude of urea nitrogen excretion has been used as an index of the degree of hypermetabolism. Supplementation of carbohydrates, protein and fats will influence

protein breakdown and thus nitrogen loss in the urine. Daily assessment of nitrogen intake and nitrogen excretion (nitrogen balance) is a very useful index of the capacity to synthesize protein and is sensitive to changes in nutrient intake. In practice, urinary excretion is by far the predominant (> 90%) mechanism of nitrogen removal in normal subjects. Patients with uremia and/or renal failure may not have adequate urinary nitrogen output and gastrointestinal and skin losses become important in these patients. Lesions such as wounds, fistulae and rapidly accumulating effusions may cause nitrogen losses that cannot be quantified. Total urinary nitrogen can be measured by the Kjeldahl method however extrapolation from urinary urea to total N excretion is probably accurate enough for clinical purposes (150). An adjustment can be made for the 10% to 20% of other urinary nitrogen loss such as ammonia, creatinine, and uric and amino acids. A 24 hours urinary collection is preferred but in clinical practice it is not always easy to collect it. Mickell determined the magnitude and time course of urinary urea nitrogen excretion to establish a preliminary database for future nutritional studies in critically ill children admitted to a pediatric intensive care unit. The daily urinary urea nitrogen excretion was 171 ± 89 mg/kg, range 28 to 584 mg/kg. There was an individual variability in average daily urinary urea nitrogen excretion that was independent of diagnoses or therapy (151).

Urinary nitrogen excretion data are used for different purposes in studies of critically ill children:

- *to correlate with severity of disease:* Steinhorn et al evaluated the correlations between severity of illness scoring systems and biochemical markers of physiologic stress. They found significant correlations between daily total urinary nitrogen excretion and pediatric risk of mortality scores (PRISM scores), therapeutic intervention scoring system scores (TISS scores) and levels of oxygen consumption (69). Winthrop et al studied children after blunt trauma but did not found a correlation between the injury severity score (ISS) and urinary nitrogen excretion data. They concluded that the ISS does not always indicate the magnitude of the physiologic effects of injury (152).
- *descriptive:* Phillips et al described the magnitude of urinary nitrogen excretion in different age groups of children and showed a markedly increased excretion in adolescents compared with younger children but they gave no explanation for this observation (39).
- *in relation with different feeding protocols:* in several studies of newborn infants, infants after surgical procedures and critically ill children different feeding protocols were tested to show the benefit of the different feedings on nitrogen retention (77, 79, 80, 153-155).
- *to calculate substrate utilization:* Gebara et al and Tilden et al used urinary excretion data in combination with results from indirect calorimetry in

mechanically ventilated children to calculate the contribution of substrate utilization expressed as percent of kilocalories (38, 67).

- *to estimate daily protein intake for nitrogen equilibration:* some authors used the nitrogen excretion data to calculate the protein intake necessary for approaching nitrogen equilibrium for the critically ill child (39, 67).

3.7 OTHER PARAMETERS USED IN NUTRITIONAL ASSESSMENT

Products of muscle catabolism can also be measured by urinary excretion of creatinine and 3-methylhistidine (3-MH). A decrease in urinary excretion of creatinine should suggest a reduction in muscle mass. The creatinine-height index is another indirect reflection of muscle mass but changes in muscle mass occur relatively slowly during nutritional repletion. Furthermore several factors influence the levels of creatinine excretion in the intensive care patient which makes this test cumbersome to use (156).

3-MH is an amino acid found in actin and myosin, is not further metabolized and is quantitatively excreted following muscle degradation. Urinary 3-MH excretion is therefore a good marker of protein breakdown but it often shows wide fluctuations in acutely ill patients (157). Seashore et al performed a study in healthy or stressed premature infants and found that the 3-MH/creatinine ratio might be a sensitive indicator of metabolic status and might be useful clinically, especially in infants receiving total parenteral nutrition (158). Maldonado et al compared the effects of two isocaloric parenteral nutrition infusions, differing in the amino acid composition on the nitrogen balance and urinary 3-MH excretion in children after trauma and on children with an infection (159). In this study no differences related to amino acid composition were found but nitrogen balance and 3-MH were correlated in the study groups.

Immune function tests as a simple lymphocyte count and a cutaneous hypersensitivity test are used to assess the severity of malnutrition. These tests however may be difficult to interpret because the variable response of an immature system in children.

3.8 SEVERITY OF ILLNESS

The value of establishing injury severity lies in the implications for the metabolic response to such injury and the ability to predict outcome based on that response. When injury response is stratified, severity related therapeutic strategies

can be developed to supplement or enhance the response and improve the outcome. There are different injury severity scoring systems which are used in children for different purposes:

- mortality scoring systems;
  the standard mortality model for pediatric intensive care is PRISM (pediatric risk of mortality) which score is calculated from the most abnormal values in the first 24 hours of physiological variables and the patient's age and operative status (160). Recently a simplified pediatric index of mortality (PIM) score was introduced which is based on 8 explanatory variables collected at the time of admission to the intensive care (161).
- therapeutic intervention scoring system;
  the therapeutic intervention scoring system (TISS) assumes that critically ill patients receive specific, identifiable interventions that are consistently applied by the physician and that the approach to patients with a comparable degree of illness is similar between intensive cares (162).
- trauma scoring systems;
  the injury severity score (ISS) is a method for describing patients with multiple injuries and evaluating emergency care (163). Winthrop et al performed a study in children after trauma to quantify the changes in energy expenditure and protein turnover and to correlate them with the injury severity score. The glascow coma scale (GCS) is based on scoring of neurologic functions. Matthews et al studied head-injured children and correlated the GCS with EE and hormonal mediators (113).
- metabolic monitoring;
  Chwals et al showed in a study of surgical infants that serial postoperative measurements of EE can be used to stratify injury severity and may be useful to monitor the return to normal growth metabolism. The serial measurements of acute changes in metabolic parameters are likely a more accurate reflection of injury severity than are disease category criteria (164). In another study of 41 infants Chwals et al evaluated the responses to acute metabolic stress following major surgery. Tumor necrosis factor (TNF), CRP and pre-albumin were evaluated preoperatively and on postoperative days 1 through 7. Infants were retrospectively grouped according to whether they survived or died within 30 days of surgery. The most significant difference was observed in persistently depressed late (post operative day 4 to 7) pre-albumin levels in non-survivors relative to survivors, suggesting an increased risk of poor outcome if acute metabolic stress had not abated by this time (142). Steinhorn et al performed a study in critically ill pediatric patients and correlated PRISM and TISS scores with VO_2 measurements and nitrogen balance (69). The PRISM score correlated with VO_2 and the PRISM and

TISS score correlated with daily total nitrogen excretion. These correlations were independent of diagnostic category. They concluded that the strong correlation of illness scoring systems and biochemical markers of stress provides a method for making plans for nutritional support that are independent of the diagnosis and relate only to the degree of illness. The limitation of this study was that the data collected reflected only information obtained on the first day.

- endocrine monitoring;
  an alternative approach to the physiologic stress of critical illness is to measure endocrine parameters. Rothwell et al performed a study in adult intensive care patients to evaluate the discriminating ability of thyroid hormones and hormones of the adrenocortical axes on patient outcome from intensive care. Thyroxine, thyrotropin and cortisol were independent predictors for outcome and an equation using these parameters predicted outcome with 82% accuracy (127).

Taken together, the studies cited allow us to conclude that several scoring systems are used in critically ill children to stratify injury and to relate these scores with survival and with nutritional parameters. Because of the diversity of the scoring systems used it is difficult to compare these data. Table 5 gives an overview of the nutritional parameters cited in the literature. References are given for studies in children or for adult studies (a) if no data for children are present.

Parameters to distinguish survivors and non-survivors	Parameters for follow-up survivors	Reference
Endocrine	*Endocrine*	
– cortisol	– cortisol (urine)	(91) (96) (101a)
– thyroid: T_3, T_4, TSH, rT_3	– thyroid: T_3, TSH, rT_3	(129) (130)
	– IGF-1	(107a) (108a) (109a)
– leptin	– leptin	(137a) (138a)
Metabolic	*Metabolic*	
– cytokines	– IL-6	(101a) (141)
– CRP	– CRP	(86) (142) (143) (144)
– nitrogen balance	– nitrogen balance	(77) (80) (153) (154) (155)
	– urinary nitrogen excretion	(69) (151)
	– pre-albumin	(145) (146) (147) (148) (165)
	– retinol binding protein	(145) (146) (165)
	– urinary 3-methylhistidine	(157a) (158)
	– creatinine	
Scoring systems	*Scoring systems*	
– therapeutic: TISS	– therapeutic: TISS	(69)
– trauma: ISS/GCS	– trauma: ISS	(152)
– physiologic: PRISM/PIM		(160) (161)
Other	*Other*	
– oxygen consumption	– energy expenditure	(69) (86) (161)
	Parameter combinations:	
	– TNF, CRP, pre-albumin	(142)
	– prognostic inflammatory nutritional index (PINI): albumin, pre-albumin, orosomucoid, CRP	(149)

(a) studies performed in adults

Table 5 Nutritional assessment: Parameters used to distinguish survivors from non-survivors and parameters used for follow-up in survivors.

4 Nutritional support

4.1 INTRODUCTION

Nutritional support of the critically ill patients has significantly changed over the past years. It is now evident that the host response to critical illness, including shock, is key to the survival or demise of these patients and that nutrients are capable of modifying the inflammatory host response (12). Current standards of care regarding nutritional support for critically ill pediatric patients are largely based on recommended dietary intakes for healthy children, despite the fact that critically ill patients have significant physiologic and metabolic differences that may affect nutrient requirement and utilization. In addition one has to account for the normal physiologic differences in children such as the low energy reserves in the young child, the differences in body size and composition in different age groups and the energy necessary for growth. With the emerging knowledge of properties of some nutrients, the concept of requirement has changed from the traditional nutritional standpoint (i.e., growth or weight maintenance) to a broader functional outcome that affect physiologic and pathophysiologic events (12). Based on this knowledge about non-nutritional functions of some nutrients, a key question regarding nutritional adequacy is what objective is to be achieved? The nutritional support of critically ill children should be tailored according to their particular needs. However it is not known when and how to start optimal nutrition in the critical ill pediatric patient. Questions to be answered are:

- how to determine the "turning point" after the acute catabolic state;
- when is it "safe" to maximize nutrient administration without the risk of over-feeding or underfeeding;
- what is the influence of sedation, the thermoneutral intensive care environment and the diminished growth rate on total caloric needs;
- how should caloric intake be divided among carbohydrate, fat and protein;
- which conditionally essential nutrients should be added to maintain non-nutritional functions.

Furthermore guidelines for nutritional support will be different in the acute process of disease, in the chronic phase of disease or in the child with an acute exacerbation of an ongoing critical illness (i.e. bronchopulmonary dysplasia or cardiac disease).

4.2 BODY COMPOSITION IN CRITICALLY ILL CHILDREN

The body's components can be divided into lean body mass or fat free mass and fat mass. The assumptions about lean body mass are that is contains all the water in the body, all the nitrogen and all the potassium (fat or adipose tissue is anhydrous). Body water, body potassium and body nitrogen are all indices of lean body. Methods of measuring fat and lean tissue are indirect and use the assumption outlined above. Several techniques were developed for the assessment of human body composition, which can be divided in traditional and new methods.

Traditional methods include anthropometry, measurement of total body potassium and measurement of total body water with isotopes:

- anthropometry;
  the golden standard for assessing nutritional status in pediatric patients is weight gain and growth. Malnutrition in the non-stressed pediatric population can be determined more accurately by weight-for-height and height-for-age assessment. Weight is more likely to be affected by acute changes, while deviation from height curve perhaps reflects a more insidious change. To diagnose children as underweight or wasted, different cutoffs have been proposed for weight-for age (WFA) and weight-for-height (WFH) (166). These cutoffs are traditionally proposed as fixed percentages of a reference median. Diagnostic levels frequently used are 75% of median WFA for underweight and 80% of median WFH for wasting. Nowadays standard deviation scores (= (measured value – mean value)/standard deviation) are more appropriate. Van den Broeck et al compared in a cross-sectional study in Zairian children a clinical assessment of nutritional status with WFA and WFH SDS-scores (167). They showed that the diagnostic validity of weight-for-height could be improved by using a cutoff for wasting at a SDS of –0.75 instead of –2. Waterlow has classified acute and chronic protein-energy malnutrition into four stages, based on the actual weight to the 50th percentile of weight for height for acute malnutrition and the actual height to the 50th percentile for height for chronic malnutrition. Pollack et al have used this index for the initial assessment of children admitted on a pediatric intensive care (3). However for some congenital syndromes (such as Down's syndrome) and other health conditions (such as the low birth-weight infant) associated with growth abnormalities, disease-specific growth references would be more appropriate for

more accurately assessing nutritional status and understanding the limitations of a treatment regimen (168). Head circumference is another important aspect of nutritional assessment in young children but this parameter is hardly used in the pediatric intensive care. For newborn infants and children up to 24 months old, the lower-leg-length measure consists of a heel-to-knee measurement (knenometry), a promising method for measurement of growth (169). However, the main problem in the pediatric intensive care setting is that the critically ill child tends to gain large amounts of weight due to third spacing of fluid during the time of acute metabolic stress. Consequently, inaccurate anthropometric measurements and inaccurate assumptions of true weight versus water weight gain can result (170). In addition fat mass can be assessed from measurements of triceps and subscapular skinfold thickness and lean body mass can be assessed from measurements of arm circumference and triceps skinfold.

- total body potassium;
  the body contains a certain amount of the naturally occurring gamma ray emitting isotope potassium-40. The energy emitted over a period can be measured in a total body counter and, assuming a constant relationship between the potassium-40 content and lean body mass, lean body mass can be calculated (157). Vaisman et al used this technique to investigate changes in body composition in short children on growth hormone treatment (171).
- isotope dilution methods;
  total body water can be measured from an ingested or infused amount of radioactive or stable isotope of water that equilibrates with the body water pool. The amount of isotope lost in urine is measured, and total body water can be calculated from the dose and dilution (172).

New methods include neutron activation analysis for nitrogen and calcium, muscle metabolites measurements such as total plasma creatinine and endogenous urinary 3-methylhistidine excretion, absorptiometry techniques (DPA, DXA), electrical conductance techniques (BIA, TOBEC), computerized tomography, ultrasound, infrared interactance and magnetic resonance imaging (157). All these methods have been developed with the assumption of the chemical maturity of a human body. It is estimated that chemical maturity is reached in children at the age of 3-4 years. The usefulness of one of these methods has not been tested so far on the pediatric intensive care. Most promising are the bioelectrical and absorptiometry methods.

- bioelectrical methods:
  a measuring total body electrical conductivity (e.g. TOBEC). The subject passes through a low-energy electromagnetic coil, causing alterations in the coil, the measured change in the electrical signal can be converted to body composition estimates. TOBEC has been validated for young infants (173).
  b measuring bioelectrical impedance (BIA). This technique consists of passing a tiny sensationless alternating current between electrodes on the hands and on the feet to obtain total body resistance, or impedance. The result is converted with an equation to estimate body composition. BIA has been validated for healthy children above 3 years of age (174). However, recently changes in total body water was studied with BIA in children < 3 year post-cardiac surgery (175, 176). Maehara et al found BIA to be a valuable tool in researching the major water fluxes associated with cardiopulmonary bypass techniques (176). Smith et al found a reduce in total body water with BIA in children after cardiac surgery on a continuous air pulsation bed compared to a standard bed (175).
- absorptiometry methods:
  dual photon absorptiometry (DPA) and dual X-ray absorptiometry (DXA) are techniques that measure three compartments of the body: bone mass, lean body mass, and fat mass. Because of the varying densities, bone, lean tissue and fat attenuate the energy beams differentially. By using dual energy beams, it is possible to assess separately three compartments (168). The radiation exposure of DXA is extremely low (0,3 mrad) and results of body composition in infants and children are obtained in a few minutes. The DXA has a wide application for assessing bone mineral content in patients with cystic fibrosis, Crohn's disease, anorexia nervosa, severe neuromuscular disease and chronic liver, cardiac, and renal disease (156). The accuracy and precision of such measurements in intensive care patients are being investigated at the moment in several institutions (170).

4.3 CURRENT DATA ON NUTRITONAL SUPPORT FOR CRITICALLY ILL CHILDREN

4.3.1 Carbohydrate, fat and protein metabolism: general

The glucose blood concentration is controlled by regulatory factors governing both uptake from exogenous sources and endogenous production. Following the ingestion of a meal or during a glucose infusion, the exogenous glucose is the major

fuel of the body but a significant portion of glucose ends up stored as glycogen in the liver. The rate of glucose metabolism is closely linked to the rate of uptake. There are two components of endogenous glucose production: glycogenolysis and gluconeogenesis. Glycogenolysis is under hormonal control; glucagon is the primary stimulator but other hormones, for example epinephrine, are stimulators as well. Gluconeogenesis is the formation of glucose from non-carbohydrate precursors and lactate is the single most important precursor under most conditions. Alanine is the major amino acid precursor for gluconeogenesis (177). In critical illness an elevated glucose production is central to the disruption of normal glucoregulation but the magnitude of glucose production may vary. Furthermore, it was shown in patients with burns that the normal suppressive action of exogenous glucose intake on endogenous production was either diminished or completely lost (178). From studies in adults and children with burns it was suggested that nonprotein energy should be largely in the form of carbohydrate to stimulate protein anabolism.

Catecholamines are the predominant stimulator of the breakdown of stored triacylglycerols to free fatty acids (FFA) and glycerol (lipolysis) mediated by the enzyme hormone sensitive lipase. FFA will be released into the general circulation and albumin will transport FFA. Local vasoconstriction limits the availability of albumin to transport FFA out of adipose tissue, and local hypoxia, together with any rise in the systemic lactate concentration, act to stimulate reesterification of FFA (see fig. 5) (110). Because of increasing reesterification of fatty acids in severely stressed patients there is little metabolic rationale for the provision of exogenous fat as an energy substrate. This rationale does not take into account the requirement for enough linolate to avoid essential fatty acid deficiency, but the amount required for this purpose (2-3% of energy intake) is trivial in terms of substrate energy metabolism (179).

Net protein breakdown is the result of the absolute rates of protein synthesis and breakdown. Net balance of body proteins is measured from the difference between nitrogen intake and total nitrogen loss, whereas the absolute rates of protein synthesis and breakdown can be measured directly in vivo using isotopically labeled amino acids. Loss of lean body mass in acute stress conditions results mainly from a sustained increase of the rate of protein breakdown in the muscle. It may be hypothesized that increased availability of intracellular amino acids derived from proteolysis may stimulate protein synthesis directly. Irreversible catabolism of free amino acids derived from proteolysis is accelerated (i.e., increased urea synthesis in the liver and oxidation of the branched-chain amino acids, leucine, valine, and isoleucine) (see fig. 6) (5).

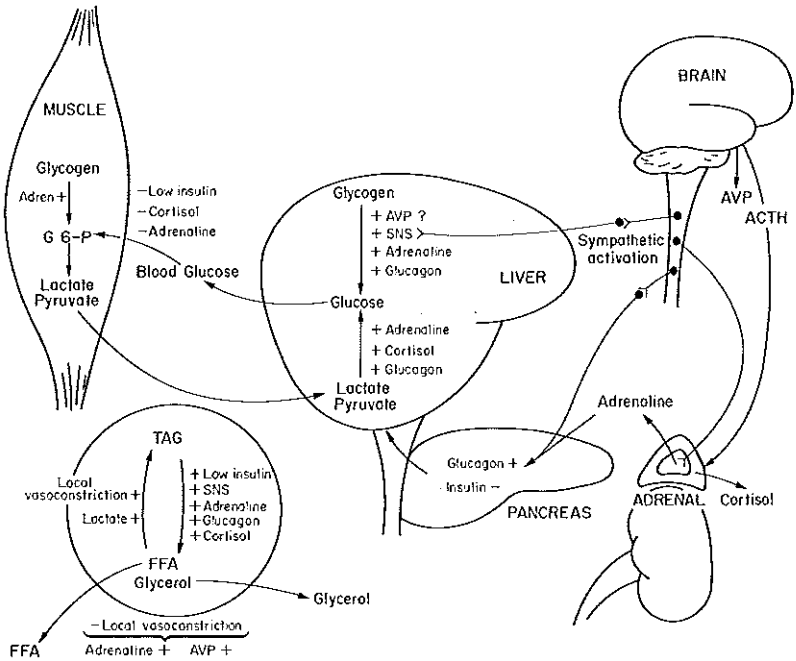

Figure 5 Central nervous control of metabolism in the ebb phase of the response to injury (adapted from Frayn (110)).

Primary events are the activation of the sympathetic nervous system (SNS) and release of adrenaline from the adrenal medulla, with pituitary secretion of vasopressin (AVP) and corticotrophin (ACTH). The metabolic changes can all be viewed as stemming, directly or indirectly from these central responses. Secondarily, the sympathoadrenal activation acts on the pancreas to stimulate secretion of glucagon and inhibit that of insulin, and ACTH promotes cortisol release from the adrenal cortex (+, stimulation of a process, -, inhibition). These changes result in stimulation of liver and muscle glycogenolysis; release of lactate and pyruvate from muscle, together with the hormonal changes, act to promote hepatic gluconeogenesis. Liver glucose release is thus massively stimulated. Glucose uptake by muscle is not, however, increased as it would normally be in hyperglycemia because inhibition by adrenaline and cortisol, and because of the failure of insulin to respond to the hyperglycemia ('low insulin'). In adipose tissue several factors act to stimulate lipolysis, i.e. the breakdown of triaglycerol (TAG) to free fatty acids (FFA) and glycerol; impaired insulin secretion ('low insulin') allows to proceed unchecked. Release of FFA into the general circulation is not, however, as great as expected after severe injury. Local vasoconstriction -brought about by adrenaline and AVP- limits the availability of albumin to transport FFA out of adipose tissue, and local hypoxia, together with any rise in the systemic lactate concentration, act to stimulate reesterification of FFA (through increased provision of glycerol 1-phosphate).

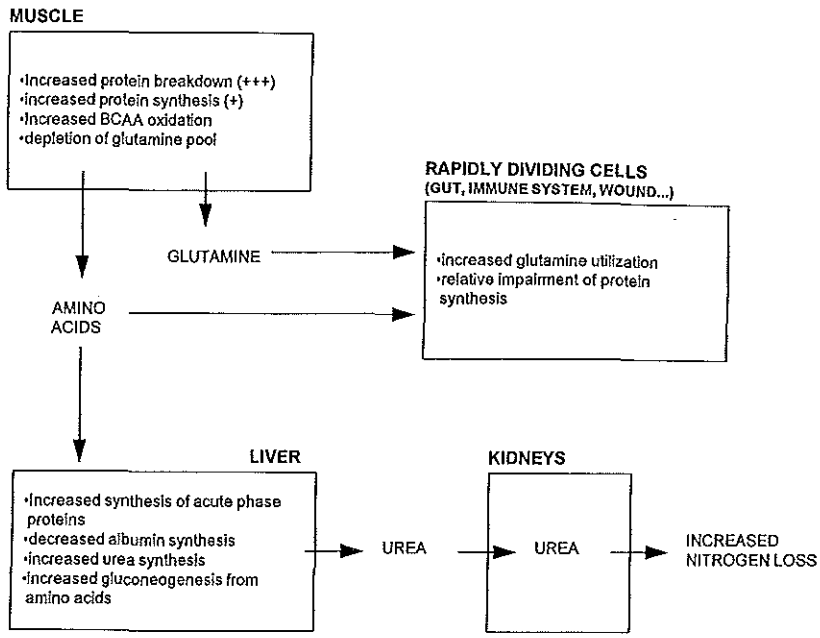

Figure 6 Protein and amino acid metabolism in trauma and sepsis (adapted from Biolo (5)). BCAA, branched-chain amino acids.

What can be learned from adult studies?

From adult studies it is known that the accelerated net breakdown of body protein can be slowed by the administration of adequate quantities of energy, protein and other essential nutrients. However, serial measurements of body composition and substrate-flux studies indicate that it is extremely difficult to maintain or replenish body protein during catabolism. Aggressive nutritional support does not prevent substantial body protein loss during severe catabolic illness (105). Failure to feed for some days cannot be compensated by subsequent overfeeding, and will result in progressive wasting until convalescence starts (180).

4.3.2 Energy requirements

Metabolic support starts with a calculation or an estimation of energy requirements. Several prediction equations have been developed to estimate REE or basal metabolic rate. At the moment the equations according to Schofield for weight appears the most appropriate (see table 6) (181). One has to take into account the inaccuracy of these predictions in critically ill children because of the wide variation

in individual actual energy requirements in different diseases (70). The best way is to measure TDEE or REE with indirect calorimetry. When REE is predicted or measured it has to be modified to metabolic status, activity level, energy for growth and need to catch up growth to calculate TDEE. For healthy children in the first year of life 30-35% extra energy for growth is needed but in the stressed patient this energy is less because growth will be diminished or even halted (182). Furthermore when enteral feeding is supplied the loss of energy with stools (10-20% of the total caloric intake (50)) has to be taken into account if total energy intake is calculated. One should realize that the values of predicted REE are approximately 50% of the recommended TDEE allowances of healthy children. Because current standards of care regarding nutritional support for critically ill pediatric patients are largely based on the recommendations for healthy children there is also an important risk for overfeeding e.g. if the measured EE is 50% of the normal energy intake in health (see table 7).

Age (yr)	Boys	Girls
0-3	(60.9 x kg) – 54	(61.0 x kg) – 51
3-10	(22.7 x kg) + 495	(22.5 x kg) + 499
10-18	(17.5 x kg) + 651	(12.2 x kg) + 746

Table 6 Prediction equations for resting energy expenditure according to Schofield for weight (181)

Age (yr)		Recommended TDEE (kcal/kg/day)(range)	Predicted REE (kcal/kg/day)
Infants:	0-0.5	115 (95-145)	53
	0.5-1.0	105 (80-135)	55
Children:	1-3	100 (70-140)	57
	4-6	85 (65-115)	47
	7-10	86 (60-120)	40
Males:	11-14	60 (44-78)	32
	15-18	42 (32-59)	28
Females:	11-14	48 (32-65)	29
	15-18	38 (22-55)	26

[a] Food and Nutrition Board, National Academy of Science. National research Council, 9th Edition, Washington, DC, 1980

Table 7 Recommended total daily energy allowances[a] vs predicted resting energy expenditure according to Schofield for weight (181)

4.3.3 Carbohydrate intake

In healthy children a carbohydrate intake of 40-55% of the total energy intake is recommended. In critically ill children most studies focus on the maximum amount of glucose which can be administered because of the risk of overfeeding. Some of these studies also compared different glucose-fat solutions to establish the best nitrogen sparing solution. Most of the studies on carbohydrate metabolism were performed either on not critically ill newborn infants or on infants postoperatively. A maximum oxidative capacity for glucose of 12 –14 mg/kg/min was described for newborn infants (80, 183). Letton et al found in the early postoperative period at a carbohydrate infusion rate of 6.9 mg/kg/min a maximum oxidative capacity whereas Jones et al found in the late postoperative phase a maximum oxidative capacity of glucose of 10-13 mg/kg/min (78). Nose et al described in a group of non-septic infants and children that the maximum glucose rate was 15 mg/kg/min. In all these studies the (np)RQ increased to > 1.0 indicating lipogenesis (81). Other side effects of a high carbohydrate intake were an increased EE (75, 79) and an increased alveolar minute ventilation (76, 183). No studies in critically ill children were performed to determine the maximum amount of glucose that can be supplied. From the data cited above it can be concluded that the most appropriate way to determine the amount of glucose supply is to increase the amount of glucose in combination with measurement of the RQ.

4.3.4 Fat intake

The recommended normal fat intake for healthy children consists of 50% of the total energy intake in children 0-6 months (5-6 g/kg/day), 35-40% children 6 months-3 years and 30-35% for children above 3 years of age. There are no reference values available for the net fat oxidation rate for normal fasting children.

A few studies were performed in critically ill children who only received a glucose infusion to investigate the extent of fat oxidation in the beginning of their disease. These studies showed a variation of fat oxidation from 2.3 to 4.8 g/kg/day (38, 67, 83). Different studies reported on the maximum amount of fat that can be supplied. Salas et al showed in not sick newborn infants that the maximum fat oxidation capacity was approximately 2 g/kg/day at a fat infusion rate of 3.5 g/kg/day (183). Pierro et al showed in surgical treated newborns who only received intralipid that with an infusion rate of 4 g/kg/day, 83% of the exogenous fat was oxidized (154). A fat intake exceeding these values did not increase fat oxidation but enhanced fat deposition.

Care must be taken to ensure that the infused lipid is cleared, otherwise the lipid overload syndrome may ensue (184). The lipid may deposit in pulmonary capillaries or engulfed by macrophages and platelets. In turn, these processes interfere with gas exchange across the lung, impair the action of the reticulo-endothelial system and inhibit platelet function (75). In two studies of newborn infants receiving a solution with a high fat content a significant drop in $tcPO_2$ was seen compared with infants receiving a low fat solution (76, 183). Studies of severely burned adult patients showed an increase of fatty acids that were reesterified because lipolysis was stimulated to a greater extent than fat oxidation (185). Consequently, there was a fivefold increase in triaglycerol-fat acid recycling. This indicates that there are more endogenous fatty acids available as energy substrates than are required to meet energy demands. Consequently these fatty acids will serve to maintain peripheral lipid stores and fatty infiltration of the liver.

Taken together, in critically ill children there might be a maximum oxidative capacity for fat. Therefore intravenous fat administration should be supplied with monitoring the complications of fat overload.

4.3.5 Protein intake

The recommended protein intake for healthy children should constitute 7% to 10% of a child's total energy intake, or approximately 2 to 3 g per kg of body weight per day.
There are limited data with regard to specific amino acid requirements and total protein intake in critically ill children. Most knowledge in this area can be derived from measurements of urinary nitrogen excretion in critically ill children.

Mickel investigated a group of critically ill children and showed that the variability in average daily urinary urea nitrogen excretion was independent of diagnostic or therapeutic subgroups and ranged from 28 to 584 mg/kg/day. This means that a provision of 0.2 to 3.7 g protein/kg/day would equilibrate the excretion (151). Alexander et al advocated the beneficial effect of a protein intake of more than 4 g/kg/day in children with burns (11). Patterson et al compared in children with burns the effect of a high protein diet (mean intake 1.84 g/kg/day) with a very high protein diet (mean intake 2.92 g/kg/day). They found that the rate of appearance of plasma urea, plasma urea concentration, and rate of urinary urea excretion increased linearly with dietary protein intakes of 1 to 3.6 g/kg/day. This suggests that excess of amino acids were oxidized with a concomitant increase in urea production. They concluded that excessively high protein intake was not useful in minimizing the muscle and

whole-body protein catabolic response in burn patients. However, they found a possible beneficial effect on wound healing which may justify a higher than normal protein intake when plasma urea and ammonia concentration are not markedly elevated (186). From these studies it can be concluded that protein needs will be individually different and depends not only on the nature of disease. With increasing nitrogen intake nitrogen balance will improve, this effect will plateau at some point and extra protein will, in some way, be excreted. Over administration of protein in the face of severe catabolism may lead to a prerenal azotemia due to the nitrogen generated by deamination. In the adult depleted or hypercatabolic patient protein is administered until blood urea nitrogen increases to about 100 mg/dl (187).

Furthermore it has been suggested that nitrogen intake can be maximized by providing calorie/nitrogen ratios of approximately 100:1 for severely stressed patients and about 150:1 for non-critically stressed patients (8). As far as we know only one study in adult patients evaluated and confirmed this statement. Maximal N retention was obtained by patients receiving a calorie/N ratio of 97:1. In addition, a strong inverse correlation was observed between nitrogen retention and an increasing calorie/N ratio. A study in surgical treated infants showed that for each level of protein intake an increase of 40 kcal/kg/day in nonprotein energy intake enhanced protein retention by 0.4 g/kg/day. Protein retention was almost 90% when 2g protein/kg/day and 75 non-protein calories/kg/day were administered (154).

Taken together, an estimation of protein needs in critically ill children can be obtained by measuring urinary nitrogen excretion. Nitrogen retention can be optimized by adding an appropriate amount of non-calories. No data in critically ill children are available for the optimal ratio protein intake/non-protein calories. Protein intake might safely be increased by monitoring blood urea nitrogen.

Energy, carbohydrate, fat and protein requirements: conclusion

The question remains how caloric intake should be divided among carbohydrate, fat, and protein in the critically ill child in different disease states. Different glucose-fat solutions were tested in children not only to evaluate the effect of glucose and fat metabolism but also to evaluate the maximum protein sparing effect. In most of these studies optimal nitrogen retention was obtained when fat was added to one of the solutions. The contribution of total energy for fat varied between 29% and 50% (79, 80, 183). Only in the study of Rubesz et al no additional effect was seen when lipid was added to a glucose/amino acid solution (155). In table 8 some recommendations of feeding protocols during the acute metabolic stress period are given. From the cited literature the following conclusions can be drawn:

- if it is possible EE should be measured;
- glucose is the major energy source in critical illness and the caloric content of glucose infusion should at least equal the EE. In practice this will be a glucose infusion of 4-8 mg/kg/min;
- administration of fat might be limited in the acute phase except for the administration of essential fatty acids;
- during recovery non-protein calories from carbohydrates and fat can be equal;
- proteins should be given to equal nitrogen losses, protein intake can be increased in the recovery phase to 4 g/kg/day.

	Chwals Ref (86)	Pollack Ref (8)	Curly Ref (12)	Velasco Ref (188)
Energy	65-70 kcal/kg/day	150% BMR		
Glucose	10 g/kg/day	25 En%	55-65 En% of non-protein calories	
Fat	2 g/kg/day		35-45 En% of non-protein calories	30-50% of total energy
Protein	2-2.5 g/kg/day	2-3 g/kg/day infants 1.5-3 g/kg/day children		<1 yr: 1-2.5 g/kg/day 1-3 yr: 0.6-1 g/kg/day
Remarks	Increase kcal with a RQ<1.0	Calorie/nitrogen ratio; 100:1 severe stress 150:1 mild stress		Non-protein energy/ nitrogen ratio; 150-200:1 kcal/g N

En = Energy BMR = Basal metabolic rate

Table 8 Feeding protocols during the acute metabolic stress period

4.3.6 Minerals, trace elements and vitamins

Minerals play an important role in the human metabolism. The human body accounts for a few minerals in relative big amounts such as sodium, potassium, chloride, calcium, phosphor and magnesium. In the critically ill child it is important to ensure an adequate intake of these minerals by measuring daily plasma levels and to correct low serum levels if necessary.

Trace elements are defined as those elements whose individual total body quantity accounts for less than 0.01% of dry bodyweight. Some are non-essential, like lead, and others are essential for normal health, function and development. Both essential and non-essential elements can be toxic in case of high concentrations in tissues and fluids. Zinc (Zn) is one of the most important of at least ten essential trace elements in man (Fe, Zn, Se, Mo, Mn, Cr, Co, I, F). Zinc is important for the function of more than 200 enzymes. The activation of receptors by hormones like insulin, growth hormone and steroids is zinc dependent. In children deficiency of trace elements can lead to a spectrum of deficiency syndromes (189), the importance of these deficiencies in critically ill children has to be determined. There has been documentation in critically adult patients for increased mineral requirements during stress (190).

Vitamin deficiencies are thought to be of importance for the optimal activity of the immune system and to serve as antioxidants in acute inflammatory state (191). Vitamin supplementation to the acute catabolic patient during the first days of acute illness has become an important issue. In a study of low birth weight infants the importance of early versus delayed vitamin A supplementation was shown by a significant reduced stay on the neonatal intensive care of the supplemented group (192). Seear et al investigated the vitamin B status of 80 infants and children admitted to a pediatric intensive care unit. Thiamin deficiency was detected in 10 of the 80 patients. The authors recommended an enteral thiamin dose of 0.5 mg/kg/day for high-risk children (193). Vitamins C and D have also been identified as being needed in higher requirements in critically ill children (2).

Mineral, vitamin and trace element requirements for the healthy growing infant and child are widely published. Concerning the few studies in critically ill children showing deficiencies, requirements should be established. Furthermore one should account for the deficiencies which can occur especially during prolonged parenteral nutrition.

4.4 ADJUNCTIVE THERAPIES IN NUTRITIONAL SUPPORT

There is an increasing interest to investigate new and adjunctive therapeutic approaches to improve the metabolic and clinical efficacy of nutritional therapy (194). These approaches are summarized in table 9.

Adjunctive therapies in nutritional support
Administration of recombinant growth factors and anabolic steroid hormones
– growth hormone, insulin-like growth factor-1, insulin, anabolic steroid hormones
Provision of conditionally essential amino acids
– glutamine, arginine, cysteine, methionine, taurine, tyrosine
Use of novel lipid products
– medium chain triglycerides, omega-3 polyunsaturated fatty acids
Administration of nutrient antioxidants
– vitamin C and E, selenium
Peptide growth factors

Table 9 Adjunctive therapies in nutritional support

4.4.1 Administration of recombinant growth factors and anabolic steroids

To enhance recovery of the critically ill patient several trials in adults and pediatric patients were performed to investigate the effect of growth hormone (GH). Studies which were performed in adults concerned patients with the following conditions; gastro-intestinal disease requiring parenteral nutrition, postoperative patients, chronic obstructive lung disease, end stage renal disease, patients with wasting associated with human immunodeficiency virus infection, trauma/burn patients and patients with sepsis. Clinical effects which were described in these studies were improved wound healing, shortened hospital stay, decreased infection rate, increased hand grip strength and variable effects on respiratory and peripheral muscle strength. Different dosage regimens and starting time during the course of disease for administration of GH are described (195-199). A few studies in children with burns were performed and showed increased wound healing and shortening of hospitalization (116-118). One study with GH treatment in intrauterine growth-retarded preterm infants did not result in increase in growth rate nor a change in body composition or EE during the early postnatal period (200).

Since the anabolic effects of GH, particularly as they relate to protein kinetics in liver and muscle tissue, appear to be mediated by insulin-like growth factor I (GF-1), IGF-1 administration might play a beneficial therapeutic role in severe injury states. The results of IGF-1 use in catabolic adult patients have recently been reported. IGF-1 therapy appeared to be less efficacious than GH in promoting protein-anabolism in catabolic patients. Side effects were reported such as hypoglycemia, arthralgias,

parotid gland swelling, and edema. These side effects may limit the clinical utility of this hormone in catabolic states (194). In children, IGF-1 has been administered in patients with Laron syndrome (GH receptor deficiency resulting in dwarfism) and resulted in promotion of skeletal growth (201). No studies were performed to investigate the effect of IGF-1 in critically ill children.

The use of insulin to maintain normoglycemia has been useful in adult patients combined with protein supply and a prevalent glucose system (> 80%) yielding the overall measured or expected energy requirement to optimize protein metabolism. Furthermore hyperglycemia is routinely treated with insulin in adult patients (194). Insulin therapy has only been studied in children with burns. The limitations of insulin therapy primarily related to the risk of hypoglycemia will restrict the use in the pediatric intensive care.

Surprisingly little data have been published concerning metabolic or clinical effects of anabolic steroid administration in catabolic patients. Several short-term studies in hospitalized patients demonstrated protein anabolic effects and improved nitrogen retention with steroids such as nandrolone (194). Because of the potential side effects of these hormones it is questionable if these hormones will have a place as an adjunctive therapy for critically ill children.

4.4.2 Provision of conditionally essential amino acids

The concept that certain nutrients, synthesized endogenously in adequate amounts under conditions of health, may become essential in conditions of catabolism (conditionally essential amino acids) is an important issue in the field of clinical nutrition. Such proteins are glutamine and arginine and cysteine (12, 86, 202). Glutamine is the most abundant amino acid in the body and it is a vehicle for nitrogen transport between tissues. Glutamine is a significant energy source for intestinal mucosa, a precursor for nucleotide synthesis as well as a substrate for hepatic gluconeogenesis and renal handling of ammonia. During catabolism, there is a significant efflux of glutamine from skeletal muscle, used presumably as a fuel source for the cellular system. Several clinical trials were performed in adult patients in which parenteral nutrition was supplemented with glutamine and were compared with standard parenteral nutrition. Improved nitrogen balance, reduced infections and length of hospital stay were reported beneficial effects (194). There are beneficial effects reported in premature infants such as a shorter duration of mechanical ventilation (203). In addition glutamine supplementations showed beneficial effects on mucosal atrophy. The role of glutamine supplementation in critically ill children has been less studied so far.

Arginine serves a number of important metabolic functions in addition to its well recognized role in the transport and excretion of nitrogen and as a substrate for protein synthesis. Currently, there are no data regarding arginine supplementation in children (12, 202).

Requirements for methionine, cysteine and taurine that are important amino acids in both protein synthesis and non-protein functions in the critically ill child remains to be established (12). Castillo et al performed a study on the phenylalanine and tyrosine kinetics in critically ill children with sepsis. They concluded that tyrosine becomes an essential amino acid in critical illness and they suggested that it would be desirable to establish the intake levels and ratio of phenylalanine to tyrosine (204).

4.4.3 Branched-chain amino acids

Branched-chain amino acids (leucine, isoleucine, and valine) are thought to undergo minimal hepatic degradation. Solutions used in adults enriched with branched-chain amino acids reduce skeletal muscle proteolysis, increase protein synthesis, and decrease the release of aromatic amino acids from muscle. A study in children with trauma or infection did not show a better effect of enrichment with a branched-chain amino acid solution used for parenteral nutrition compared with a non-enriched one in terms of muscle catabolism and nitrogen balance (159). Because clinical studies in metabolically stressed adults showed beneficial effects in terms of muscle-sparing effects and better nitrogen balance these studies in critically ill children have to be performed (86).

4.4.4 Use of novel lipid products

Alternative lipid sources are increasingly being investigated for use in enteral or parenteral nutritional support. Very important are the medium-chain triglycerides (MCT) and the omega-3 polyunsaturated fatty acids (PUFA).

MCT preparations are directly absorbed into the circulatory system from the gut and do not require bile for absorption. Studies with MCT enriched diets were performed in combination with other lipid substrates but not in critically ill children.

The relative importance of omega-3 polyunsaturated fatty acids appears to reduce the inflammatory and thrombotic responses, while protecting tissue microperfusion and immune defense (205). There is growing evidence that PUFAs are important for

development of the newborn infants. In critically ill adult patients, no prospective study of omega-3 PUFA alone has been reported. The influence on outcome or infection rate is still undetermined (see below). However these fatty acids also represent potential toxicities and for now use of these compounds should be limited to clinical trials (12, 206). No studies were performed in critically ill children.

4.4.5 Combination formula

An enteral formula with immunologic and nutritional properties has been the subject of several recent studies. This formula called Impact (Sandoz Nutrition, Minneapolis) is containing arginine, omega-3 fatty acids and RNA. The studies were performed in critically ill adult patients and showed significant less total complications, reduced acquired infections and reduced median hospital length of stay (207-209). However in the study of Bower et al the mortality of the group of patients receiving the Impact formula was increased; the implications of this study for pediatric patients at the moment is unknown (207).

4.4.4 Administration of nutrient antioxidants

In patients responding to infections and trauma cytokines are produced which lead to the generation of oxidant molecules which are potentially toxic to the patient. Studies were performed to investigate the influence of antioxidant therapy on the interaction of cytokines and free radicals during inflammation. N-acetylcysteine, vitamin E, and a cocktail of antioxidant nutrients have reduced inflammatory symptoms in inflammatory joint disease, acute and chronic pancreatitis, adult respiratory distress syndrome and slow progression of acquired immunodeficiency syndrome in adult patients (210). No studies in children were performed to test the use of these antioxidants.

4.4.5 Peptide growth factors

Peptide growth factors are naturally occurring substances that induce cell proliferation. In animal models investigators have tried to establish the role of peptide growth factors in the gastro-intestinal tract, especially its function and growth. They focused primarily on epidermal growth factor, transforming growth factor alpha, and IGF-1. These studies suggest a beneficial role for the adjunctive use of peptide growth factors during acute metabolic stress to enhance gastrointestinal function and support the gut mucosal barrier (86).

4.5 EARLY ENTERAL AND PARENTERAL FEEDING

Zaloga et al reviewed the results of early enteral nutrition in both animal and human adult studies. Animal studies showed that early enteral nutrition improves gut blood flow and gut mass, diminishes the invasiveness of gut bacteria, protects the liver and injury during shock, improves protein synthesis and rate of wound healing and survival after critical illness is increased. More importantly prospective, randomized trials in humans indicated that early enteral nutrition improves outcome during critical illness (211).

Studies in premature and low birth infants have found that the lack of enteral feeding may result in an absence of the natural stimulus for growth of the intestinal mucosa, as well as diminished production of intestinal mucins, which acts as barrier to bacterial translocation (212). Further proof of the efficacy and safety of early enteral feeds was given in the form of case reports and case series of burn patients (213, 214). Chellis et al performed a study in 42 critically ill children to evaluate the feasibility and safety of early enteral feedings. All patients were able to achieve caloric goals within 48 hours of beginning enteral feedings and there were no documented complications such as aspiration and abdominal distention (215). Limitation of this study was the use of retrospective chart review for data collection.
Taken together it can also be advocated to start enteral feeding in critically all children as soon as possible. If critically ill children are heamodynamically stabilized, even if high doses of inotropics are necessary, small amounts of enteral feeding can be started. Because critically ill children will suffer from gastric dysmotility and emptying difficulties duodenal tube feeding is the preferred route.

Total parenteral feeding is indicated when the gastro-intestinal tract is non-functional, when it is impossible to obtain enteral access or when enteral nutrition alone is not able to satisfy the child's energy requirements. The administered amount of glucose, lipid and protein will not be different when enteral or parenteral feeding is supplied. However parenteral nutrition differs from enteral nutrition in the sort of carbohydrates, proteins and lipids which can be supplied. Parenteral nutrition often has a deficiency of dipeptides and amino acid substances that are important for protein synthesis and the immune response. The energy content of parenteral feeding can be maximal 1 kcal/ml whereas the energy content of enteral feeding can be 2 kcal/ml. Compared to enteral nutrition there is an increased risk for septic complications when administering parenteral nutrition.

In conclusion, in the critically ill child enteral nutrition has several benefits compared to parenteral nutrition including preservation of gut function and morbidity.

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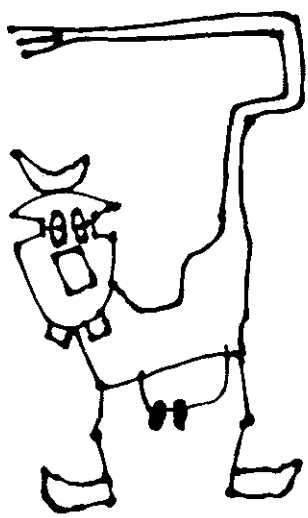
Part 2

Indirect calorimetry in mechanically ventilated children: validation studies



Chapter 3

Accuracy of an indirect calorimeter for mechanically ventilated infants and children: the influence of low rates of gas exchange and varying FiO_2

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ABSTRACT

Objective: To test the accuracy and validity of the Deltatrac™ II MBM-200 metabolic monitor for use in mechanically ventilated infants and children in the pediatric intensive care unit.

Design: Laboratory validation of an indirect calorimeter using a ventilated lung model. The influence of low tidal volumes and low levels of VO_2 and VCO_2 in combination with different levels of inspired oxygen concentrations (FiO_2) was investigated.

Setting: University research laboratory.

Subjects: Low tidal volumes were provided with two intermittent flow types of ventilators, a Servo 300 and a Servo 900C.

Interventions: A butane flame with a VO_2 approximating 20 and 40 ml/min was ventilated. To investigate the effect of oxygen concentration on the accuracy of VO_2, VCO_2 and RQ, measurements were performed at FiO_2 target values of 0.25, 0.40 and 0.60.

Measurements and Main Results: No significant differences were found between both ventilators regarding VO_2, VCO_2 and RQ measurements. The mean deviation of VO_2 increased significantly with increasing FiO_2 to –7.98% with a VO_2 of 21.0 ml/min and to –8.46% with a VO_2 of 38.9 ml/min (FiO_2 =0.558) with a variability (2SD) of ± 4.6% and ± 6.8% respectively. The mean deviation and variability of VCO_2 in all tests remained within 8%. The mean deviation of RQ increased significantly with increasing FiO_2 to 5,5% with a VO_2 of 21.0 ml/min and to 5.7% with a VO_2 of 38.9 ml/min (FiO_2 =0.558) with a variability (2SD) of ± 5.6% and ± 5.8% respectively. The minute to minute delivered FiO_2 fluctuated significantly when increasing the level of FiO_2.

Conclusions: The Deltatrac™ II MBM-200 metabolic monitor appears accurate for low levels of VO_2 and VCO_2 during mechanical ventilation with FiO_2 levels up to 0.390. With increasing FiO_2 up to 0.558 the increase in deviation of VO_2 for single measurements can be of clinical relevance for mechanically ventilated infants and children. The increased fluctuation of delivered FiO_2 on higher levels of FiO_2 is likely the cause of the inaccuracy.

INTRODUCTION

In the past decades, indirect metabolic monitoring has gained popularity, especially since several automated devices became available for daily clinical practice. The technique for calculation of energy expenditure is based on non-invasive measurement of carbon dioxide production (VCO_2) and oxygen consumption (VO_2). Indirect calorimetry is widely used in adult critical care, but its use in pediatric and neonatal patients is limited by several factors, like leakage of in- and expiratory gasses around the (uncuffed) endotracheal tube, use of continuous flow ventilators (especially in neonatal intensive care) and high inspiratory oxygen concentrations. In 1989 the performance of a new gas exchange monitor, the Deltatrac^{TM} I MBM-100 (Datex Division Instrumentarium Corp, Helsinki, Finland) was validated for adults both in laboratory and in clinical setting for use in canopy mode and mechanical ventilation (1, 2). Datex incorporated a new pediatric option for the measurement of lower levels of VO_2 and VCO_2 by reducing the size of the mixing chamber and the constant dilution gas flow trough this mixing chamber. This option for ventilated children was validated in 1994 in a laboratory setting (3). The Deltatrac^{TM} II MBM-200 was developed to enable also measurements of neonates.

The purpose of our study was to test the accuracy and validity of this new monitor for low levels of VO_2 and VCO_2 and different levels of FiO_2 in conjunction with the two ventilators used in our pediatric intensive care. We used a laboratory set-up system with an inline ventilated lung model and used the combustion of butane as the calibration method (4,5). We designed a system to make use of the difference in weight before and after the combustion of butane.

MATERIALS AND METHODS

The Deltatrac^{TM} II MBM-200 metabolic monitor

The Deltatrac is an open system indirect calorimetry device and measures VO_2 and VCO_2 and calculates from these variables the respiratory quotient ($RQ= VCO_2/VO_2$) and energy expenditure. During mechanical ventilation the inspired oxygen fraction (FiO_2) is measured from the ventilator's limb. The expiratory gases from the ventilator are led to a 4 liter mixing chambre inside the monitor. The purpose of this chambre is to prevent cyclic concentration differences. From this chamber, mixed expiratory oxygen (FeO_2) and carbon dioxide ($FeCO_2$) are sampled and diluted with a constant flow (Q) of ambient air generated by the calorimeter (in "baby range" with 3 l/min, in "child range" with 12 l/min). While other metabolic monitors depend

on the measurement of expired gas volume, the Deltatrac™ II MBM-200 determines VCO_2 using this dilution method. VCO_2 is calculated as the product of the constant flow (Q) and the fraction of CO_2 in the diluted expiratory gas flow (Fe^*CO_2). The respiratory quotient (RQ) is calculated with the Haldane transformation from the gas fractions of the mixing chamber: $RQ = (1-FiO_2)/((FiO_2 - FeO_2)/FeCO_2-FiO_2))$. VO_2 is calculated from the RQ as $VO_2 = VCO_2/RQ$.

The difference between the inspired and expired oxygen fractions is measured with paramagnetic differential oxygen sensor (OM-101, Datex Instrumentation) (6). It has a response time of 150 msec and resolution of 0.01%. The expired CO_2 fraction is measured with an infrared CO_2 sensor. The CO_2 analyzer has a resolution of 0.01%. To eliminate the effect of humidity on gas analysis, special nafion tubing (Perma Pune Products, Kent, UK) equalizing the humidity of sample gas to the level of ambient air is used for all gas sampling lines. All gas values were corrected to STPD.

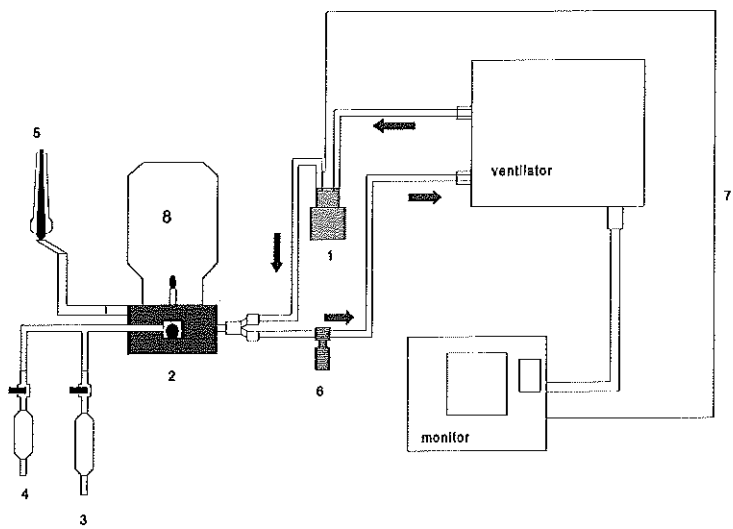
Laboratory setup: Butane burner unit

The butane burner unit modified from the ethanol burning unit (provided by Datex) modified to burn pure (99.9997%) butane (Air Liquide, France), was placed in a Pyrex glass jar of 1 liter. Two stainless steel butane tanks (containing 10 ml and 25 ml of liquid butane) each designed with a quick-release filler cap on one side and a ball valve on the other side were connected to the burner unit using stainless steel tubing and a needle valve. The burner based on the Venturi principle, was equipped with catalysts made of platinum wire, or stainless steel needles connected to the burner using silicone tubing. The butane burner unit was used in conjunction with a small gas jar for calibration of the constant flow (Q) generator and in conjunction with a Pyrex glass jar of 2 liter for ventilatory tests (fig 1). A test lung was connected to the burner unit to enhance the system compliance and to have a stable combustion. To reduce the influence of weighing errors, at least 1000 mg butane was burned in all experiments. Before and after each experiment butane was weighed on a precise scale with a standard resolution of measurement is 1 mg (Mettler PM 1200, Mettler Instruments, Greifensee, Switzerland). The values obtained by the monitor for the total CO_2 production and O_2 consumption were compared with the predicted values of CO_2 and O_2 based on the weight of butane used (1 mg butane will utilize 2.511801 ml O_2 and produce 1.545724 ml CO_2). The RQ value of combustion of butane is 0.615, as can bee seen from the burning formula of this fuel $C_4H_{10} + 6.5O_2 = 4CO_2 + 5H_2O$. Deviation is given as ((value measured – value predicted)/value predicted) * 100).

After allowing the monitor to warm up for at least 30 min the O_2 and CO_2 sensor were calibrated before the start of each experiment with a gas mixture of 95% O_2 and 5% CO_2 (Quick Cal, Datex IC, Helsinki, Finland).

Calibration of the constant flow generator

Calibration of the constant flow generator was performed before the start of all experiments and after three months for the "child range" and the "baby range". The monitor was set in canopy mode and attached to the butane burner unit. A flame producing approximately a VCO_2 of 35 ml/min and 15 ml/min (for "child range" and the "baby range" respectively) was created, and the system was allowed to stabilize. When no minute-to-minute deviation of VCO_2 larger than 5% was present, the calibration run was started. For both constant flow settings, three measurements of total produced VCO_2 were performed and with the average of these measurements a correction for the constant flow setting in the monitor was calculated as follows: New constant flow = set constant flow x (value VCO_2 measured/value VCO_2 calculated).



1=humidifier 2=burner unit 3=gas tank 25 ml (stabilization prior to experiment) 4=gas tank 10 ml (experiment) 5=test lung 6=water trap 7=inspiratory gas sampling line 8=Pyrex glass jar

Figure 1 Experimental setup: butane burner unit in conjunction with the ventilator and the metabolic monitor

Ventilator set up

We wanted to test two intermittent flow ventilators, a Servo 900C and a Servo 300 (Siemens-Elema, Solna, Sweden) because of the influence of two different specifications in these ventilators. 1: The Servo 900C has an internal bellow which is filled with air and oxygen to a preset working pressure of 60 cm H_2O. To fill this bellow an external air/oxygen mixer (Bird blender 10019A) was used. The Servo 300 does not have an internal bellow but uses separate modules for air and oxygen to deliver the set oxygen. 2: The Servo 300 has an expiratory bias flow used for patient triggering of the ventilator (1 l/min in pediatric mode), which is led through the patient circuit, but does not participate in the pulmonary gas exchange. This flow dilutes the expired gas fraction and might influence the measurements. The ventilators were connected to the butane burner unit using tubing exactly identical to the clinical setup, i.e. silicone rubber tubing (Siemens-Elema, Solna, Sweden), except for the tube leading from the humidifier to the patient, which has a heated wire tubing. Bacterial filters at the inspiratory and expiratory port of the ventilator were used. A standard humidifier was set to deliver humidified inspiratory gas at 37° C in the inspiratory limb of the ventilator (F&P MR 730, Fischer & Paykel, Panmure, Auckland, New Zealand) (fig 1)

Ventilator settings during butane burning

Both ventilators were set on a Volume Control mode because this ensured the most stable flame during butane burning. Because of the principle of measurement of expiratory flow led from the outlet port of the ventilator to the mixing chamber of the calorimeter it was not necessary to test different ventilatory settings (1). The ventilators were set on an inspiration time of 25%, a pause time of 10%, a PEEP of 5 cm H_2O and a trigger level of -20 cm H_2O below PEEP. The Servo 300 ventilator was set in "the pediatric mode". The ventilator frequency was set on 40 and 35/min with a tidal volume of 62 and 42 ml respectively to ventilate a butane flame with a VO_2 of ± 20 ml/min and ± 40 ml/min. The compliance of the system was 6 ml/cm H_2O and peak pressures of 6-8 cm H_2O were achieved. Measurements were done at a target level of FiO_2 of 0.25, 0.40 and 0.60. The FiO_2 level was set at the ventilator, the calorimeter stored every minute the delivered level of FiO_2. The mean level and standard deviation of FiO_2 was calculated from the total stored minutes of the experiment. Before the start of each experiment, the system was checked for any leakage by setting the PEEP to 20 cm H_2O, and keeping the breathing cycle of the ventilator in the expiratory phase. If airway pressure as indicated by the ventilator remained stable over 30 sec at the set pressure of 20 cm H_2O, this proved that no

significant leakage from the system was present. The constant flow generator was set on "baby range" and in "child range" for experiments with a VO_2 of ± 20 ml/min and ± 40 ml/min respectively.

Statistics

The effects of the factors of the two VO_2 experiments, FiO_2 and Servo ventilators were assessed using factorial Analysis of Variance (ANOVA). Both 2-way and 3-way interactions between the factors were investigated. Comparison of different levels of FiO_2 within VO_2 experiments was done using one-way ANOVA, with Bonferroni's adjustment for multiple comparisons. Mean standard deviations of FiO_2were compared with Mann-Whitney's test. P=0.01 (two-sided) was considered the limit of significance. Results are expressed as mean ± SD unless indicated otherwise.

RESULTS

Ventilated lung experiments

In total 60 measurements in 12 different settings were performed (table 1). ANOVA showed no significant three-way interactions regarding VO_2 and VCO_2. However, the effect of FiO_2 depended on the level of VO_2 (implicating also that the effect of the level of VO_2 depended on FiO_2), as shown by a significant two-way interaction. There were no significant differences between of the Servo 300 and Servo 900C for VO_2 and VCO_2 on different levels of FiO_2. Because the absence of ventilator effects, the results of Servo 300 and Servo 900C were combined.

The mean VO_2 in experiment 1 was 21.0 ± 2.1 ml/min and in experiment 2 was 38.9 ± 3.5 ml/min and the mean VCO_2 13.0 ± 1.3 ml/min and 24.5 ± 2.1 ml/min respectively.

The mean levels of each 20 measurements with a target level of a FiO_2 on 0.25, 0.40 and 0.60 were respectively 0.248, 0.390 and 0.558. The standard deviation of the delivered minute to minute FiO_2 was calculated for each of the 20 measurements separately. There was a significant increase of the mean standard deviation of the delivered minute to minute FiO_2 with an increasing FiO_2 of 0.248, 0.390 and 0.558, respectively 0.0005, 0.0011 and 0.0015.

The mean deviation (and standard deviation of the mean) of VO_2, VCO_2 and RQ on different FiO_2 levels are given in table 1.

			FiO_2 0.248	FiO_2 0.390	FiO_2 0.558
Experiment 1	VO_2	21.0 ml/min	1.14 ± 2.33	– 5.02 ± 2.59[a]	– 7.98 ± 2.43[b]
	VCO_2	13.0 ml/min	–2.81 ± 1.93	– 4.91 ± 1.33	– 3.36 ± 1.23
	RQ		–4.39 ± 2.14	0.65 ± 3.70[a]	5.53 ± 2.81[bc]
Experiment 2	VO_2	38.9 ml/min	–0.91 ± 2.21	– 2.12 ± 1.64	– 8.46 ± 3.41[bc]
	VCO_2	24.5 ml/min	0.05 ± 1.33	– 2.60 ± 1.42[a]	– 2.82 ± 1.49[b]
	RQ		0.81 ± 3.26	– 1.14 ± 2.85	5.69 ± 2.88b[c]

All values are mean values ± standard deviation (SD), each based on 10 measurements

(Servo 300 and Servo 900C combined)

[a]: p<0.01 compared between FiO_2 = 0.390 and 0.248

[b]: p<0.01 compared between FiO_2 = 0.558 and 0.248

[c]: p<0.01 compared between FiO_2 = 0.558 and 0.390

Table 1 Deviation (%) of VO_2 and VCO_2 and RQ measurements with increasing FiO_2

DISCUSSION

In this study we were able to simulate a pediatric clinical environment by ventilating a butane burning system with low tidal volumes. With this system it is possible to test the accuracy and validity of the Deltatrac™ II MBM-200 for low levels of VO_2 and VCO_2.

The most important result of our experiments was a significant increase in mean deviation up to ± 8% with low VO_2 (21.0 ml/min and 38.9 ml/min) with increasing FiO_2 (0.558). This deviation is acceptable for clinical purposes (below 10%). However, with a variability (2SD) up to 6.82% one should consider an error above 10% in individual measurements with a FiO_2 up to 0.558.

A possible explanation for the increased deviation of VO_2 with increasing FiO_2 is found in the instability of FiO_2 delivered by the ventilators (7). With increasing FiO_2 up to 0.558 a significant increase in mean standard deviation of the minute to minute delivered FiO_2 of both ventilators was experienced. For the calculation of the VO_2 by the calorimeter, the Haldane transformation is used and an increased fluctuation of

FiO_2 at higher levels of FiO_2 will result in an increased inaccuracy of VO_2. A mathematical analysis of this error of VO_2 determination as a function of FiO_2 has been developed (8). Whereas at a FiO_2 of 0.558 we found an increased inaccuracy of VO_2 measurement, in other studies in which higher tidal volumes and higher levels of VO_2 were used the measurement of VO_2 was accurate (deviation ± 5%) (1, 4, 9, 10). A FiO_2 above 0.60 resulted rapidly in a clinically significant deviation of VO_2 (1). The fluctuation of FiO_2 can be diminished by applying an internal bellow for mixing oxygen and air within the ventilator (11). Because the Servo 900C has an internal bellow and the Servo 300 did not we expected differences in the fluctuation of FiO_2 between both ventilators but there were no differences. Another way to reduce fluctuations in FiO_2 is sampling the inspired oxygen concentration after the humidifier (12). We applied this method standard in all our experiments but it could not prevent the marked fluctuations of FiO_2 described before.

Two studies tested the Deltatrac MBM 100 using a ventilated lung model and a gas injection technique with VO_2 levels below 50 ml/min and varying FiO_2 (3, 12). In these studies low deviations for VO_2 were found (-3.9% and –1.8%) but the variability (2SD) of the experiments was much higher (26% and 20%) than in our study, indicating an increased inaccuracy for single experiments. However, in these studies the influence of FiO_2 was not described in detail. Weyland et al showed that excluding all experiments with a difference between FiO_2 and FeO_2 below 0.03 could reduce the overall variability in VO_2 measurement. In these circumstances the low rates of gas exchange will influence the accuracy of the measurement. We expected to measure differences between the Servo 900C and the Servo 300 ventilator because the Servo 300 has a bias flow, which influences the low rate of gas exchange. From our results and the literature can be concluded that in general the fluctuation of FiO_2 remains one of the major problems applying indirect calorimetry with low tidal volumes and low VO_2 levels (13). Assuming a VO_2 of 7.5 ml/kg/min for critically ill young infants this would correspond in our study to an infants bodyweight of 2.8 and 5.2 kg. Therefore with the reasons outlined above the use of this indirect calorimeter is limited for these children with an increasing FiO_2. Furthermore we postulate that for mechanically ventilated infants with even a lower weight it will be difficult to perform accurate measurements of VO_2.

The mean deviation and variability (2SD) of VCO_2 for both experimental groups with increasing FiO_2 remained within 8%, which is acceptable for clinical purposes. The mean deviation of RQ increased significantly with an increasing FiO_2 up to

0.558. With a variability (2 SD) of 5.6% and 5.8% respectively the deviation of RQ can be above the 10% for single measurements. This increased deviation of RQ for single measurements is to be expected since the error of the RQ is due to the inaccuracy in either the VO_2 or VCO_2 measurement.

Conclusion: The Deltatrac™ II MBM-200 appears accurate in mechanically ventilation with low tidal volumes, for VO_2 at levels of 21.0 and 38.9 ml/min and with a FiO_2 up to 0.390. With increasing FiO_2 up to 0.558 the increase in deviation of VO_2 and the RQ for single measurements can be of clinical relevance. The increased fluctuation of delivered FiO_2 on higher levels of FiO_2 might be the cause of inaccurate measurements.

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Chapter 4

Indirect calorimetry in mechanically ventilated infants and children: Accuracy of total daily energy expenditure with 2 hour measurements

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ABSTRACT

Objective: To determine how accurately total daily energy expenditure can be estimated from measurement periods of less than 24 hours in mechanically ventilated infants and children.

Design: Prospective study to validate a method to determine energy expenditure

Setting: Pediatric intensive care unit (PICU) of an university hospital

Patients: Nineteen ventilated patients (age 3 weeks - 13 years) with a FiO_2 of less than 60% and tube leakage < 10% (the difference between inspiratory and expiratory tidal volume measured by the ventilator). Separately, in 5 patients with varying tube leakage (2-59%) the influence of tube leakage on measured energy expenditure was determined.

Measurements: Energy expenditure was measured by indirect calorimetry. Total daily energy expenditure measurements for 24 hours were compared with 2-hour energy expenditure measurements. The influence of body temperature on measured energy expenditure was determined.

Results: The mean coefficient of variation among 2-hour periods of measured energy expenditure was 6% (range 2-11%) compared with total daily energy expenditure measurements. The influence of body temperature revealed an increase of 6% of energy expenditure/°C. An increased tube leakage influenced the energy expenditure measurements significantly ($p<0.001$).

Conclusion: In a clinicial situation in patients with a tube leakage <10% total daily energy expenditure can be estimated from a 2-hour measurement period.

INTRODUCTION

Nutritional support is an essential part of treatment in mechanically ventilated pediatric patients. The classic approach for the assessment of nutritional status is based on ideal growth rates from normal healthy infants and children. Indirect calorimetric studies may help to establish these values. Studies in mechanically ventilated children showed a wide variation in individual actual energy requirements in different diseases and a wide range in the ratio of measured to predicted energy expenditure. The use of standard formula will not predict energy expenditure with acceptable precision for clinical use. Therefore individual measurements of energy expenditure by means of indirect calorimetry is necessary for matching adequate nutritional support (1,2).

Short periods of measurements of energy expenditure (MEE) in rest will be adequate to estimate resting energy expenditure. For a more precise approximation of total daily energy expenditure (TDEE) longer periods of measurements are essential. However, the optimal duration is not clear. In other studies in mechanically ventilated children the duration of MEE was chosen arbitrarily and varied in length from a few minutes to several hours (3,4,5,6). In studies of non-ventilated premature infants the duration of MEE approximating TDEE varied from 1.5 to 6 hours (7,8,9). Furthermore, the accuracy of MEE requires that there is no air leak around the endotracheal tube which can be a difficult problem in especially the younger age group children since these children are usually ventilated with uncuffed endotracheal tubes.

This study was performed in order to determine how accurately TDEE of mechanically ventilated pediatric patients can be estimated from measurement periods of less than 24 hours.

PATIENTS AND METHODS

Patient selection

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

- haemodynamic stable condition (within 2 SD of age related values to blood pressure and heart rate (10));
- mechanical ventilation with a Servo Ventilator 300 (Siemens-Elema, Solna, Sweden) either with pressure regulated control mode or with volume support mode;
- a FiO_2 of less than 0.60;
- continuous enteral or parenteral feeding;

- adequately sedated without muscle paralysis;
- a tube leakage of less than 10% (considered not to influence the measurement significantly (11)) Tube leakage was calculated as: (inspiratory tidal volume - expiratory tidal volume)/inspiratory tidal volume x 100%. Inspiratory and expiratory tidal volume were measured by the ventilator assuming that there were no leaks in the patient-ventilator circuit.

Patients showing variation in tube leakage of more than 10% were excluded for 24 hour measurement analysis. In these patients with a variation in tube leakage (<10% and >10%) the influence on energy expenditure was determined.
Severity of illness on the day of measurement was assessed by the Pediatric Risk of Mortality score (PRISM)(12) and Therapeutic Intervention Scoring System(TISS)(13).

Measurements

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)(14). 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 (15). The coefficient of variation of oxygen consumption, CO_2 production, and RQ did not exceed 4%. Each minute the computed VO_2 and VCO_2 values were recorded and downloaded to a personal computer. The aim was to measure 12 subsequent periods of 2 hours. The measurements were than analyzed for artifacts such as disconnection from the ventilator during suctioning and physiotherapy procedures; these time periods were not included in the final analysis. As a consequence it was not always possible to exactly measure an entire 2 hour period. If a measurement period lasted less than 60 minutes, the period was considered not-evaluable, and was not included in the analysis. Mean measured energy expenditure (MEE) values were calculated using the modified Weir formula (16): MEE = 4.184(5.5 VO_2 + 1.76 VCO_2); MEE in kJ/day; VO_2 in ml/min; VCO_2 in ml/min).

In patients with varying tube leakage the mean MEE of 15 min periods with more than 10% tube leakage were compared with the MEE of a 15 min period in which the tube leakage was less than 10%.
Rectal temperature was measured and recorded every two hours.

Statistical analysis

Results are expressed as mean ± SEM. MEE was calculated for each 2-hour period. The coefficient of variation (VC) among these 2-hour periods regarding MEE was calculated for each patient separately. VC's were compared between groups using Mann-Whitney's test. Spearman correlation was used for correlation between age and VC's. The relation between 2-hour assessment of MEE and body temperature and tube leakage allowing for between as well as within patient differences was evaluated using repeated measurements analysis of variance using the BMDP statistical software package(17). In this analysis MEE data were logarithmically transformed to obtain normal distributions. The same method was used to determine the relation between the change of MEE and tube leakage.

RESULTS

From the 40 patients who were admitted consecutively from April 1995 to October 1995 to our pediatric intensive care unit 21 patients were excluded because they did not fulfill the inclusion criteria. In 18 of the 21 patients the tube leakage was >10%, in 5 of these patients periods with varying tube leakage was determined.
The study group for 24 hour measurement analysis consisted of 19 patients (10 girls and 9 boys) with a wide range of clinical diagnosis (Table 1). Their median age was 7 months (3 days - 13 years). The median PRISM score was 7 (0-18) and median TISS score was 20 (11-32). All patients were sedated with midazolam (0.05-0.3 mg/kg/hr) and/or morphine (0.01-0.03 mg/kg/hr). Four patients received inotropical support. Ventilatory characteristics were: mean FiO_2 0.32 ± 0.03, mean tubeleakage 4 ± 1%, 11 patients were on pressure regulated volume control mode of ventilation, 7 patients were on volume support mode and one patient was on continuous positive airway pressure mode. Twelve patients received continuous enteral duodenal feeding, 6 patients received parenteral feeding and 1 patient received a combination of enteral and parenteral feeding.

The mean measurement period for a 2-hour period was 108 ± 2 min. In 1 patient 1 period was omitted. Figure 1 shows the variability in MEE among a 2-hour period for each patient. There was a great variability between patients, while the variation within patients is relatevely small. For each patient the coefficient of variation (VC) of the 2-hour assessments of MEE was calculated. For the whole group of patients the mean VC of the 2-hour periods was 6% (range: 2%-11%). The 2-hour estimates of TDEE showed a high degree of reproducibility: the intra-class correlation was calculated to be 0.98. Regression analysis showed that an increase of 1° C in body

temperature resulted on the average in a 6% (95% confidence limit:3%-9%) higher MEE. No significant influence of the amount of tube leakage was found in this group with less than 10% tube leakage. There was no significant difference between parenteral and enteral feeding and between pressure regulated volume contol and volume support mode of ventilation regarding the VC's. There was no correlation between age and VC's (r=0.09, ns, p=0.97).

In the 5 children with varying tubeleakage 13 periods of 15 minutes tube with leakage >10% were determined. There was a significant correlation between tube leakage and MEE (p<0.001)(figure 2). One percent higher tube leakage resulted in a decrease of 1.3% (95% confidence limit: 1.0%-1.6%) of MEE.

diagnosis	age	sex	PRISM	TDEE	VC	Feeding	MV
congenital heartdefect	0.10	m	10	179	4	en	prvc
congenital heartdefect	1	f	10	223	7	en	prvc
congenital heartdefect	1	f	7	231	6	en	cpap
congenital heartdefect	1	f	7	132	6	en	vs
congenital heartdefect	2	f	6	252	8	en	vs
convulsions	4	m	10	255	5	en	vs
sepsis	5	m	12	259	8	en	prvc
congential heartdefect	6	f	2	225	6	en/pn	vs
sepsis	7	m	9	237	4	pn	prvc
cardiac failure	7	m	3	208	5	en	vs
rs bronchiolitis	8	m	7	266	11	en	prvc
cardiac failure	18	f	11	218	9	pn	prvc
convulsions	26	f	18	126	4	en	prvc
laryngitis	30	m	2	187	7	pn	prvc
sepsis	36	f	7	246	6	en	prvc
sepsis	54	f	4	183	2	pn	vs
near drowning	60	f	0	205	6	pn	prvc
renal insufficiency	60	m	6	172	11	en	vs
pneumonia	155	m	9	149	5	en	prvc

age in months; m=male; f=female; PRISM=pediatric risk of mortality score;
TDEE=total daily energy expenditure in kJ/kg/day; VC=coefficient of variation; en=enteral nutrition;
pn=parenteral nutrition; MV=mechanical ventilation; prvc=pressure regulated volume control;
vs=volume support cpap=continuous positive airway pressure

Table 1 Clinical Characteristics of Study Patients

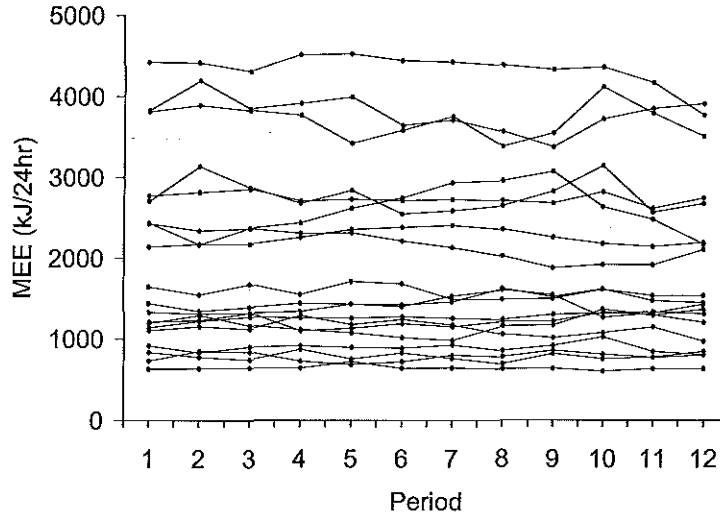

Figure 1 MEE among twelve 2-hour periods for individual patients (n=19)
MEE=measured energy expenditure in kJ/24 hour. Each symbol represents the MEE for a 2-hour period. Period 1 is the first 2-hour of measurement, etc.

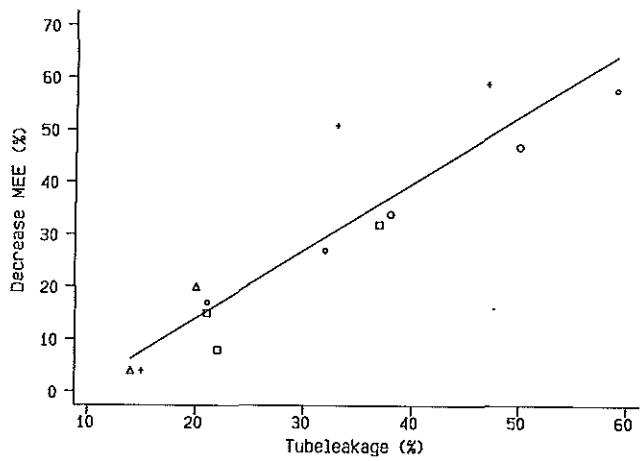

Figure 2 Influence of tube leakage on MEE
Different symbols represents measurements (n=13) in 5 patients. Decrease MEE=% decrease of measured energy expenditure in periods with a tube leakage of more than 10% compared with periods in which the tube leakage was less than 10%.

DISCUSSION

In critically ill patients the accurate measurement of the TDEE is important in establishing adequate energy intake, in order to maintain a positive energy balance, and to avoid complications of under and overfeeding (18). In the acute onset of illness it can be difficult to measure energy expenditure because of methodological problems as high FIO_2 and unstable haemodynamics. In our study we performed measurements in patients in the beginning of disease or recovering from a severe illness, as indicated by the low PRISM and TISS scores. In the mechanically ventilated child the normal overall physical activity will be markedly diminished due to sedation, the thermogenic effect of food is diminished by continuous feeding and the influence of cold is diminished because of a temperature-controlled environment. On the other hand bedside activities such as weighing, repositioning and suctioning will increase the energy expenditure (19). Increased body temperature will affect the MEE as shown in children with severe head injury (7,4%/ °C) and adult patients (13%/ °C) (20,21). In our study we showed an increase of 6% of MEE/ °C.

There is a difference between adult studies and studies of premature infants regarding the accuracy of shorter measurement periods to estimate accurately the TDEE. No studies in children were performed so far. Some studies in adults showed that multiple short measurement periods (2 x 15 min) were more accurate in approximating TDEE than longer measurements periods (22,23). In contrast, in two studies of non-ventilated premature infants a 6 hour measurement period was recommended to approximate 24 hour TDEE and in one study a period of 1.5-3 hours (7,8,9). Our results indicated that TDEE can be estimated from a measurement period of 2 hours. The mean coefficient of variation was 6% (range 2-11%) which is clinically acceptable. In our opinion the different measurement periods found in studies in adults and premature infants compared with our study can be explained by the fact that adult patients are probably less sedated and have more activities during the day and to the fact that the premature infants which were studied were on a intermittent feeding regimen and not sedated.

It is common clinical practice in children to use uncuffed endotracheal tubes which result in gas leakage leading to inaccurate measurements and therefore indirect calorimetry is of limited practical use. In our study 18 of the 40 patients were excluded for further 24 hour analysis because of too much tube leakage. However, recently the use of cuffed endotracheal tube in the pediatric intensive care unit was not found to be associated with an increased risk of postextubation stridor or significant long-term sequelae and therefore we advocate to use this tubes to overcome the problem

of tube leakage (24). Different methods have been used to determine expiratory tube leakage but most of these methods are difficult to perform in daily practice (11,25,26,27). We showed that the difference in inspiratory and expiratory tidal volume measurements with the Servo 300 can be used to estimate tube leakage less than 10% and above 10%. Furthermore we were able to show a significant correlation between tube leakage and MEE, a one percent higher tube leakage resulted in a decrease of 1,3% of MEE.

In conclusion total daily energy expenditure can be estimated from a 2 hour measurement period in case of documented tube leakage <10%.

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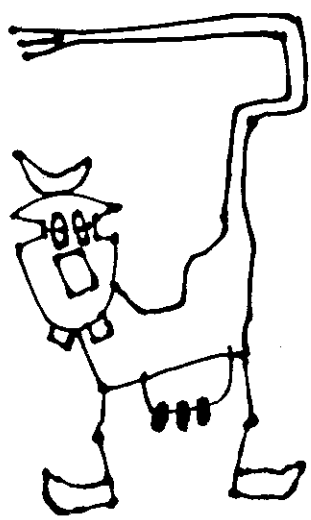
Part 3

Indirect calorimetry in mechanically ventilated children: clinical use



Chapter

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 daily energy expenditure (mTDEE) and the predicted basal metabolic rate (pBMR)($r=0.93$; $p<0.001$), Bland-Altman analysis showed lack of agreement between individual mTDEE and pBMR values. The ratio of caloric intake /mTDEE 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 daily energy expenditure (mTDEE) or mREE to predicted basal metabolic rate (pBMR).

Reference	Age-group	N	Diagnosis	mEE/pBMR	mEE (range)
[7]	5-17yr	9	Head injury	1.19 ± 0.07 [2]	-
[8]	5d-46mo	20	Wide range	1.02 ± 0.07 [1]	100-343 [1]
[2]	2-18yr	18	13 trauma; 5 other	1.48 ± 0.09 [2]	130-336 [2]
[9]	2d-120mo	12	Wide range	-	125-236 [2]
[10]	2mo-12yr	26	Open heart surgery	0.96 ± 0.03 [2]	126-289 [2]
[11]	3mo-10yr	18	Wide range	0.97 ± ? [2]	-
Present study	2d-13yr	50	Wide range	1.04 ± 0.03 [1]	85-270 [1]

mEE=measured energy expenditure (mTDEE [1] or mREE [2] in kJ/kg per day) pBMR=predicted basal metabolic rate

Table 1 Study population characteristics

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 TDEE (18, 19). Mean mTEE was calculated using the modified Weir formula [20]: mTDEE = 4184(5.5 VO_2 + 1.76 VCO_2); mTDEE 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 mTDEE 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 mTDEE and pBMR was r= 0.93 ($p<0.001$). A Bland-Altman plot for mTDEE 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/mTDEE 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/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.

Diagnosis	Number of patients
Congenital heartdefect	5
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 2 Clinical Diagnosis of study patients

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
mTDEE (kJ/day)	1987 ± 238	640-8678
mTDEE (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

Table 3 Patient characteristics and measurements results

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

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

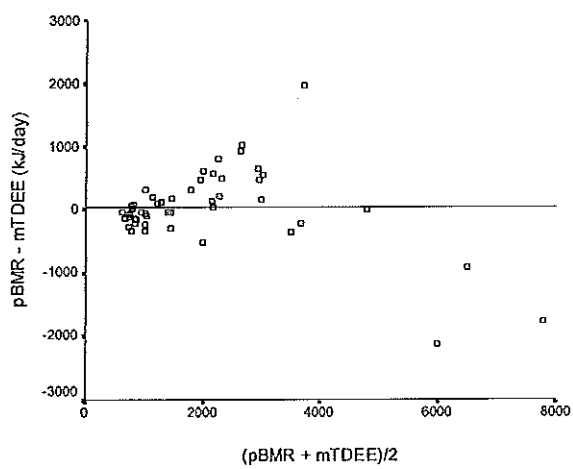

Figure 1 Bland-Altman plot for mTDEE and pBMR

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.

TDEE 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 mTDEE 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 mEE in our study 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 mEE 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 mTDEE and RQ. In our study, we showed that feeding according to the mTDEE could be a guideline because the ratio of caloric intake/mTDEE 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 mTDEE is necessary for growth and tissue repair. In our patients with a positive nitrogen balance, the caloric intake exceeded the mTDEE 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 mTDEE seemed to resemble pBMR, there was a wide range in the ratio of mTDEE 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

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;
- a FiO_2 of less than 0.60;
- 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;

- a 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 local Ethical Committee approved the study 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 liters 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

Thirty-six 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 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.
28 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 ($r=0.72$, $p<0.001$).

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).

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	F	385	7.6	7.7	231	1.02	150
Congenital heartdefect	1	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	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	F	472	8.8	8.6	266	0.98	244
Meningitis	3	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	M	283	7.1	6.0	208	0.85	229
RS bronchiolitis	8	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	M	298	7.6	7.0	228	0.92	232
Subglottic stenosis	10	M	368	7.0	6.7	212	0.95	255
Sepsis	11	M	242	6.4	5.4	188	0.85	493
Subglottic stenosis	11	M	465	9.2	7.4	252	0.81	116
Subglottic stenosis	13	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	F	68	7.6	5.9	218	0.77	198
Sepsis	18	M	220	8.9	7.2	253	0.81	323
Pneumonia	19	F	65	6.3	5.7	189	0.90	471
Sepsis	22	M	118	6.8	5.2	197	0.76	201
Subglottic stenosis	28	F	166	6.1	5.3	180	0.86	96
Upper airway obstruction	32	M	413	8.2	6.4	236	0.78	298
Upper airway obstruction	33	M	61	7.1	5.9	209	0.83	387
Sepsis	36	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	F	90	5.7	4.5	165	0.79	160
Sepsis	53	F	209	8.3	6.4	233	0.77	310
Sepsis	54	F	262	6.1	5.6	183	0.92	429
Sepsis	162	M	22	5.4	4.2	156	0.78	346

age in months; intake in kJ/kg/day; VO_2 in ml/kg/min; VCO_2 in ml/kg/min; TMEE in kJ/kg/day; TUN in mg/kg/day

Table 1 Clinical Characteristics of Study Patients

	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

Table 2 Substrate intake and utilization versus N-balance

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 endogeneous 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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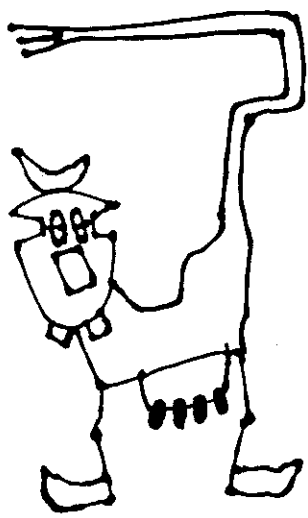
Part 4

Hormonal and metabolic status of children with meningococcal sepsis



Chapter 7

Time course and variability of the endocrine and metabolic response in children with meningococcal sepsis

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(submitted)

ABSTRACT

Sepsis may lead to pronounced neuro-endocrine and metabolic alterations. To get insight in the time course and variability of the endocrine and metabolic response in children with meningococcal sepsis serial measurements of cortisol, ACTH, thyroid hormones, insuline, glucose, C-reactive protein, lactate, non-esterified fatty acids and urinary urea excretion were performed during the first 48 hours of admission in 16 children, median age 24 months (range 5-185 months). On admission, one of the most striking alterations concerned the significant difference in cortisol/ ACTH response between non-survivors (n=5) and survivors (n=11). Non-survivors showed an inadequate cortisol response in combination to very high ACTH levels whereas survivors showed a normal stress response with significantly higher cortisol levels (0.55 vs 0.91 µmol/l) in combination with moderately increased ACTH levels (1469 vs 71 ng/l). Furthermore there was a significant difference between non-survivors and survivors regarding pediatric risk of mortality score (29 vs 15), TSH (1.12 vs 0.32 mE/l), T_3 (0.47 vs 0.33 nmol/l), reverseT_3 (rT_3) (0.95 vs 1.71 nmol/l), C-reactive protein (34 vs 81 mg/l), non-esterified fatty acids (0.44 vs 0.93 mmol/l) and lactate (7.4 vs 2.9 mmol/l). Levels of cortisol, ACTH, the ratio cortisol/ACTH, rT_3, the ratio T_3/rT_3 and non-esterified free fatty acids correlated significantly with the levels of established parameters to monitor the severity of disease such as the pediatric risk of mortality score, lactate and C-reactive protein. In those who survived cortisol and ACTH levels normalized within 48 hours after admission but a circadian rhythm was still absent; T_4 and T_3 remained unaltered, rT_3 decreased and the ratio T_3/rT_3 increased but all these levels remained abnormal; TSH and freeT_4 levels remained normal. The non-esterified free fatty acids levels decreased significantly and urinary nitrogen excretion remained high and unaltered. The question remains unanswered whether the hormonal abnormalities play a crucial role in the outcome of this disease or represent secondary affects of an impaired peripheral circulation comparable with other signs such as increased lactate levels. Understanding the metabolic and endocrine alterations is needed in order to design possible therapeutic approaches. Nevertheless the striking difference between non-survivors and survivors calls for reconsideration of steroid treatment in children with meningococcal sepsis.

INTRODUCTION

Septic shock with purpura is a life threatening clinical syndrome predominantly caused by *Neisseria meningitidis* and characterized by a sudden onset and rapid progression of disease. The physiological changes that constitute the process of sepsis are induced by microbial agents during bloodstream infection or by the toxic products of pathogens that are released from sites of focal infection. This process involves changes generated by the immune system in which hormones, cytokines and enzymes are involved.

In adult patients it has been shown, that sepsis may lead to pronounced neuro-endocrine and metabolic alterations including increased serum cortisol concentrations, low thyroid hormones, insulin resistance, elevations of plasma glucose, lactate and free fatty acid concentrations, and increased muscle protein breakdown (1-4). During the time course of sepsis an ebb and flow phase can be detected. Main features in the ebb phase are a decrease in metabolic rate and temperature and in the flow phase there is an increase in metabolic rate and urinary nitrogen excretion (5, 6). There are several differences between the host response of young children compared to adults during (meningococcal) sepsis (7). Little is known about the neuro-endocrine changes in critically ill infants and children. Previous studies in critically ill infants and children showed an altered thyroid function at the onset of acute diseases called "the euthyroid sick syndrome" (8-12). Dopamine infusion induces or aggravates partial hypopituitarism in newborn infants resulting in inhibited prolactin and growth hormone secretion (8).

The present study was undertaken to evaluate the time course of the endocrine and metabolic responses of children with meningococcal sepsis during the first 48 hours of admission in the pediatric intensive care unit.

MATERIAL AND METHODS

Study protocol

Children above 3 months and below 18 years of age with septic shock and petechiae/purpura requiring intensive care treatment were enrolled in this study. The group consisted children primary admitted or referred to the pediatric intensive care unit (PICU) of the Sophia Children's Hospital between October 1997 and October 1998.

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

1 presence of petechia/purpura;
2 presence of shock for less than 6 hours defined as persistent hypotension (systolic blood pressure <75 mm Hg for children between 3-12 months, <80 mm Hg for 1-5 years, <85 mm Hg for 6-12 years, <100 mm Hg for children older than 12 years), 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 mmHg, 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.

The patients participated in a randomized, double-blinded, dose-finding study of Protein C concentrate (Human), Immuno-Baxter. Because Protein C is assumed not to influence the endocrine and metabolic assays we did not account for it in further analysis. Informed consent was obtained from the parents or legal representatives. The Medical Ethics Committee of the Erasmus University Rotterdam approved the study protocol.

Clinical parameters

The pediatric risk of mortality (PRISM II) score was calculated based on the most abnormal values regarding 14 physiological variables during the first 6 hours of admission. A high score means a higher risk of mortality (13). The interval between appearance of petechiae and admission to the PICU, length of stay on the PICU and duration of inotropic support were recorded. In order to distinguish non-survivors from survivors established parameters to monitor the severity of disease such as PRISM, lactate and C-reactive protein were analyzed (14, 15).

Collection of blood

Arterial blood samples were collected within two hours after admission (T=0), after 24 hours (T=24) and 48 hours (T=48) for determination of thyroid hormones, insulin, glucose, pre-albumin, C-reactive protein (CRP), non-esterified free fatty acids (NEFA) and lactate. Bloodsamples for cortisol and ACTH were taken at T=0 and 12 hours (T=12) after admission. An ACTH test was not performed as all children had severe stress due to the life-threatening disease on admission. A diurnal rhythm for

cortisol and ACTH was estimated by sampling blood on the second day of admission at 8.00 am and subsequently at 14.00 pm and 20.00 pm.

Hormonal assays

Cortisol/ACTH

The plasma concentrations of cortisol were measured by competitive luminescence immunoassay (LIA). Detection limits: 0.03-1.38 µmol/l. The plasma concentrations of ACTH were measured by immunoradiometric assay (IRMA, ELSA-ACTH CIS bio international), using two monoclonal antibodies. The within-run coefficient of variation was 6.1% at 22 pg/ml, 2.9% at 59 pg/ml and 2.1% at 778 pg/ml. The between-run coefficient of variation was 5.3% at 40 pg/ml, 4.8% at 203 pg/ml and 1.3% at 1055 pg/ml. Reference values for cortisol: 8.00 h: 0.2-0.6 µmol/l, 14.00 h: 0.1-0.5 µmol/l, 20.00 h: 0.05-0.3 µmol/l. Reference values for ACTH: 20-100 ng/l. From the values of cortisol and ACTH the ratio cortisol/ACTH was calculated.

Thyroid hormones

Plasma T_4, T_3 and reverse T_3 (rT_3) were measured by established radioimmunoassay procedures as previously described (16,17). Reference values of the laboratory for T_4: 64-132 nmol/l, T_3: 1.1-2.6 nmol/l, rT_3: 0.15-0.43 nmol/l. From the values of T_3 and rT_3 the ratio T_3/rT_3 was calculated. The plasma concentrations of free T_4 (fT_4) were measured by a direct, labeled antibody, competitive immunoassay technique (Amerlite MAB fT_4 Assay). The within-assay coefficient of variation was 7.6% at 5.43 pmol/l, 4.3% at 16.1 pmol/l and 3.5% at 52.8 pmol/l. The between-assay coefficient of variation was 9.0% at 5.67 pmol/l, 5.6% at 17.4 pmol/l and 4.2% at 49.2 pmol/l. Reference value for fT_4: 11-25 pmol/l. The plasma concentrations of *TSH* were measured by an ultrasensitive immunometric assay (Amerlite TSH-30, Ortho-Clinical Diagnostics), using one monoclonal antibody. The within-assay coefficient of variation was 8.0% at 0.087 mIU/l, 4.2% at 4.22 mIU/l and 4.1% at 21.5mIU/l. The between-assay coefficient of variation was 11.7% at 0.077mIU/l, 6.6% at 4.25mIU/l and 5.1% at 21.4 mIU/l. Reference value for TSH: <4.5 mE/l.

Insulin/glucose

Insulin was measured in serum with an immunoradiometric assay (IRMA). Detection limits: 5-400 mU/l. Glucose measurements were determined on the routine clinical chemistry analyzers (Dimension ES, Dupont Medical Products, Wilmington, Delaware, USA)(reference values hypoglycemia < 2.6 mmol/l, hyperglycemia > 11 mmol/l). From the values of insulin and glucose the ratio insulin/glucose was calculated.

Metabolic assays

Lactate and NEFA

Lactate was measured by enzymatic endpoint determination (Hitachi 911, Boehringer Mannheim, Mannheim, Germany)(normal < 2.0 mmol/l). C-reactive protein was determined by an immuno-nephelometric assay (normal: < 5 mg/l) (18). Plasma NEFA concentrations were determined by enzymatic method (Nefac-kit, Wako, Instruchemie BV). Reference values for NEFA for children between 4 months - 10 year: 0.3 – 1.1 mmol/l, children > 10 year: 0.2 – 0.8 mmol/l.

Urinary nitrogen excretion

Urine was collected daily for 24 hours and analyzed for urinary nitrogen. Total urinary nitrogen excretion was defined as 1.25 x urinary urea nitrogen, in order to adjust for the urinary nitrogen loss as ammonia, creatinine, and uric and amino acids (19). No correction was made for nitrogen losses through stools, skin, wounds, nasogastric suction, or blood sampling.

Caloric intake

The patients were fed enteral and/or parenteral according to a standard feeding protocol. During stay on the PICU glucose was administered at a rate of approximately 4-6 mg/kg/min. If enteral feeding could not be started on the second day, parenteral feeding was started. Initial dose of proteins was 1.0 g/kg/day (Aminovenös N-paed 10%, Fresenius, Holland) and lipids (in case the body temperature was <38.5 °C) 1.0 g/kg/day (Intralipid 20%, Pharmacia, Upjohn, Holland). If clinically possible enteral and/or parenteral nutrition was adjusted on day 3 and 4 to normal needs for healthy children. The total caloric intake was recorded and calculated daily. The amount of caloric intake was corrected for extra protein calories such as plasma and/or albumin infusions. To estimate the adequacy of caloric intake the amount of energy intake was compared with calculated values for resting energy expenditure for healthy children according to the formula of Schofield for age, sex and weight (20).

Statistics

Statistical analysis was performed with a statistical analysis software program (SPSS 7.0 for Windows 95, SPSS Software, Chicago, IL). Results are expressed as medians (range) unless specified otherwise. The Mann-Whitney U-test was used for comparison of clinical and laboratory tests between survivors and non-survivors. For survivors the Wilcoxson signed rank test was used for comparison on different

time points of different laboratory tests. Spearman's correlation coefficient (r) was used to evaluate the relationship between different parameters. Two-tailed p-values of 0.05 or less were considered statistically significant.

RESULTS

Demographics

Sixteen patients admitted to the PICU fulfilled the inclusion criteria and were included in the study: 6 males and 10 females (table 1). The median age was 24 months (range 5-185 months). Cultures of blood revealed *Neisseria meningitidis* in all 16 patients.

Age (months)	Sex	Duration of petechiae Before admission (hours)	PRISM score	Survival
5	M	3.5	30	No
7	F	4	32	No
9	F	3.5	19	No
10	F	9	16	Yes
12	F	9	18	Yes
18	M	5.5	27	Yes
21	M	15	18	Yes
21	M	8	29	No
27	F	10	14	Yes
32	F	6	10	Yes
52	F	9	20	Yes
77	M	7	15	Yes
81	F	11	7	Yes
113	M	3.5	29	No
128	M	4	9	Yes
185	F	4	14	Yes

M = male, F = female, PRISM score = pediatric risk of mortality score

Table 1 Endocrine and metabolic parameters on admission

Clinical parameters

Five children died after a median stay in the PICU for 9 hours (range 2-40), 11 children survived, they stayed in the PICU for a median of 126 hours (range 30-207). The median interval between appearance of petechiae and admission to the PICU was 6.5 hours (range 3.5-15). There was a significant difference between non-survivors and survivors for the interval between appearance of petechiae and admission to the PICU (3.5 vs 9.0 hours, $p<0.05$). Concomitant therapy during the study period included antibiotics, administration of plasma and inotropics for all patients. Ten patients required mechanical ventilatory support and sedation with benzodiazepines. The 11 survivors received inotropic therapy for a median of 52 hours (range 9-170), 6 of them were still on inotropic therapy after 48 hours. The parameters to monitor severity of disease were significantly different between non-survivors and survivors; PRISM-score (29 vs 15, $p<0.01$), arterial lactate levels (7.4 vs 2.9 mmol/l, $p<0.01$) and CRP levels (34 vs 81 mg/l, $p<0.01$) (table 2, fig. 1). In survivors, compared with levels on admission lactate levels decreased significantly after 24 hours and normalized after 48 hours and CRP levels were significantly increased after 24 and 48 hours.

Cortisol/ACTH

On admission non-survivors had significantly lower serum cortisol levels than survivors (0.55 vs 0.91 µmol/l, $p<0.01$), whereas the ACTH levels were extremely high in those who did not survive (1469 vs 71 ng/l, $p<0.01$)(table 2, figure 2). The median cortisol level of the survivors was within the normal reference value for stressed children (>1.5 baseline value) whereas that of the non-survivors was within the normal range for healthy children. The median ACTH level for non-survivors was much higher compared with normal reference values, for survivors it remained within the normal range. The ratio cortisol/ACTH was significantly different between non-survivors and survivors ($p<0.01$) and correlated well with parameters to monitor the severity of disease; PRISM ($r= -0.76$, $p<0.01$), lactate ($r= -0.63$, $p<0.01$) and CRP ($r= 0.58$, $p<0.05$) (table 3). Twelve hours after admission median levels of cortisol (0.69 µmol/l) and ACTH (24 ng/l) decreased in those who survived, but did not reach a significant difference in comparison with levels on admission; on the second day after admission levels of cortisol and ACTH were significantly lower in comparison with levels on admission (table 2). In none of the patients a circadian rhythm could be detected in the 3 samples taken on the second day of admission.

Thyroid hormones

On admission, data of non-survivors and survivors showed significant differences in levels of rT_3 (0.95 vs 1.71 nmol/l, $p<0.05$), the ratio T_3/rT_3 (0.69 vs 0.20, $p<0.01$) and TSH (1.12 vs 0.32 nmol/l, $p<0.05$), whereas the levels of T_3, T_4 and fT_4 were not significant different between the two groups (table 2, fig. 3). In comparison with normal reference values the levels of T_4 and T_3 were decreased in both non-survivors and survivors and those of rT_3 were increased. The median fT_4 and TSH levels were within the normal reference range. On admission there were significant correlations between rT_3 levels and lactate levels ($r= -0.74$, $p<0.01$), the ratio T_3/rT_3 and lactate levels ($r= 0.70$, $p<0.01$) and TSH levels and PRISM score ($r= 0.57$, $p<0.05$) (table 3). After 48 hours survivors showed significantly increased levels of TSH and the ratio T_3/rT_3 and significantly decreased levels of rT_3 and fT_4 in comparison with levels on admission whereas levels of T_3 and T_4 did not change significantly. For survivors all 48 hour median levels of T_3, T_4 and rT_3 remained below normal reference values whereas median fT_4 and TSH levels remained within the normal reference values (fig. 2). After 48 hours there was a significant difference between the level of rT_3 (1.33 vs 0.62 nmol/l, $p<0.05$) and the ratio T_3/rT_3 (0.21 vs 1.14, $p<0.05$) for patients with or without inotropic support.

Insulin/glucose

Levels of insulin and glucose and the ratio insulin/glucose were lower in non-survivors compared to survivors but statistical significance was not reached (table 2, fig. 4). None of the children was hypoglycemic, one child was hyperglycemic (14.3 mmol/l) on admission. For survivors no significantly different time course changes were found for insulin and glucose levels and the ratio insulin/glucose (fig. 4). There were no significant correlations between insulin, glucose and the ratio insulin/glucose and the parameters to monitor the severity of disease (table 3).

NEFA

On admission non-survivors had significantly lower NEFA levels than survivors (0.44 vs 0.93 mmol/l, $p<0.05$) (table 2, fig. 1). Median NEFA levels for both non-survivors and survivors remained within reference values on admission. NEFA levels decreased significantly after 48 hours in comparison with the levels of admission and after 24 hours. Levels of NEFA correlated negatively with lactate ($r= -0.62$, $p<0.01$) (table 3).

Nitrogen excretion

Nitrogen excretion was assessed in 9 survivors. Nitrogen excretion was not significantly different between the first 24 hours and the second 24 hours after admission (296 mg/kg/day (range 143-369) vs 206 mg/kg/day (range 152-324)).

Caloric intake

For survivors the median difference between actual energy intake and calculated resting energy expenditure was –38% (range –83% to +24%) during the first 24 hours after admission and –33% (range -67% to +26%) during the second 24 hours after admission.

Time course in non-survivors

Four of the 5 non-survivors died within 12 hours because of circulatory failure. One child died after 40 hours. For this child the interval between appearance of petechiae and admission to the PICU was the longest (8 hours) whereas the cortisol level on admission in this child was the highest (0.73 µmol/l). This child showed to have a slight but probably inadequate improvement of the level of cortisol (0.69 µmol/l after 12 hours and 0.80 µmol/l the second day) and decreased levels of ACTH which remained above normal reference values (304 ng/l after 12 hours and 163 ng/l the second day). Furthermore there was an ability after 24 hours to increase the levels of rT3 (from 0.95 – 1.65 nmol/l), CRP (from 34 to 111 mg/l) and NEFA (from 0.44 to 0.77 mmol/l). The level of lactate however increased from 9 mmol/l to 11.2 mmol/l. In this child shock persisted, suffered from recurrent convulsions and died after a bradycardia.

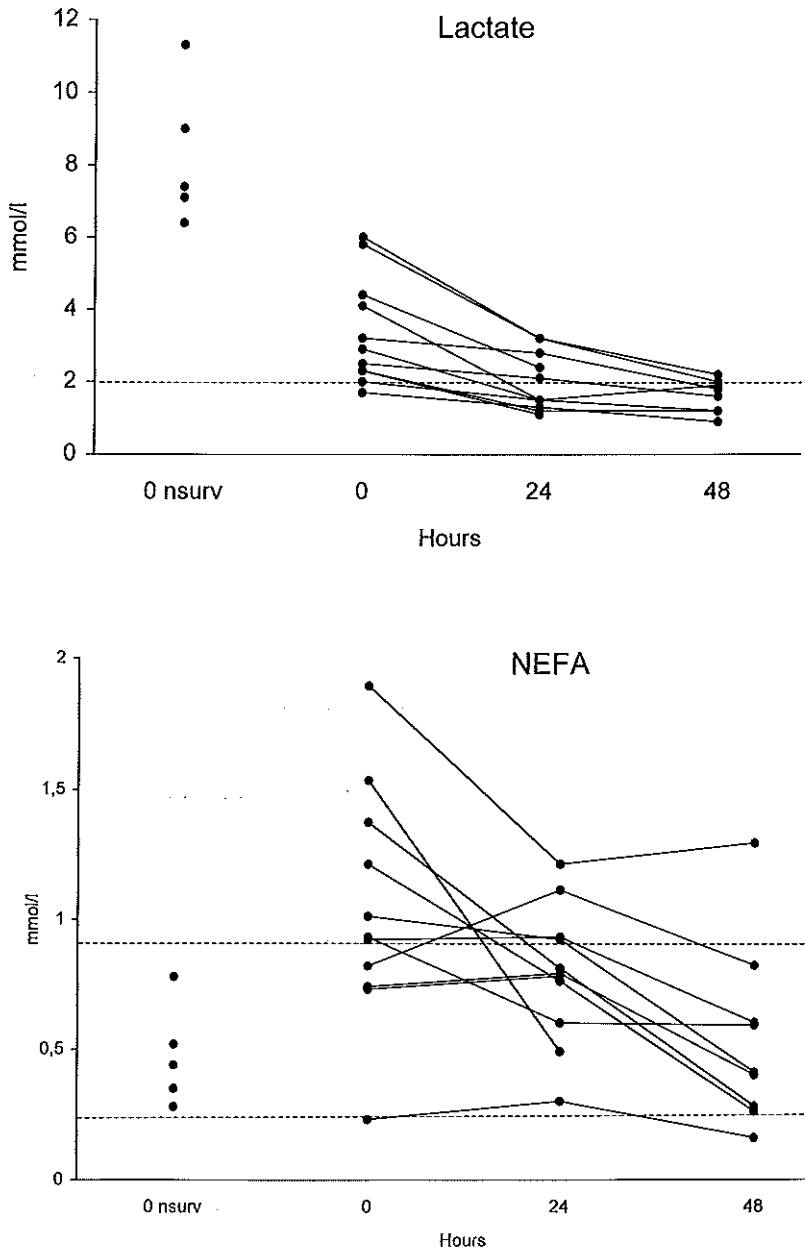


Figure 1 Levels of lactate and NEFA on admission for non-survivors (0 nsurv) and survivors (0) and the time course of these these levels for survivors after 24 and 48 hours. Reference values below or between dotted lines.

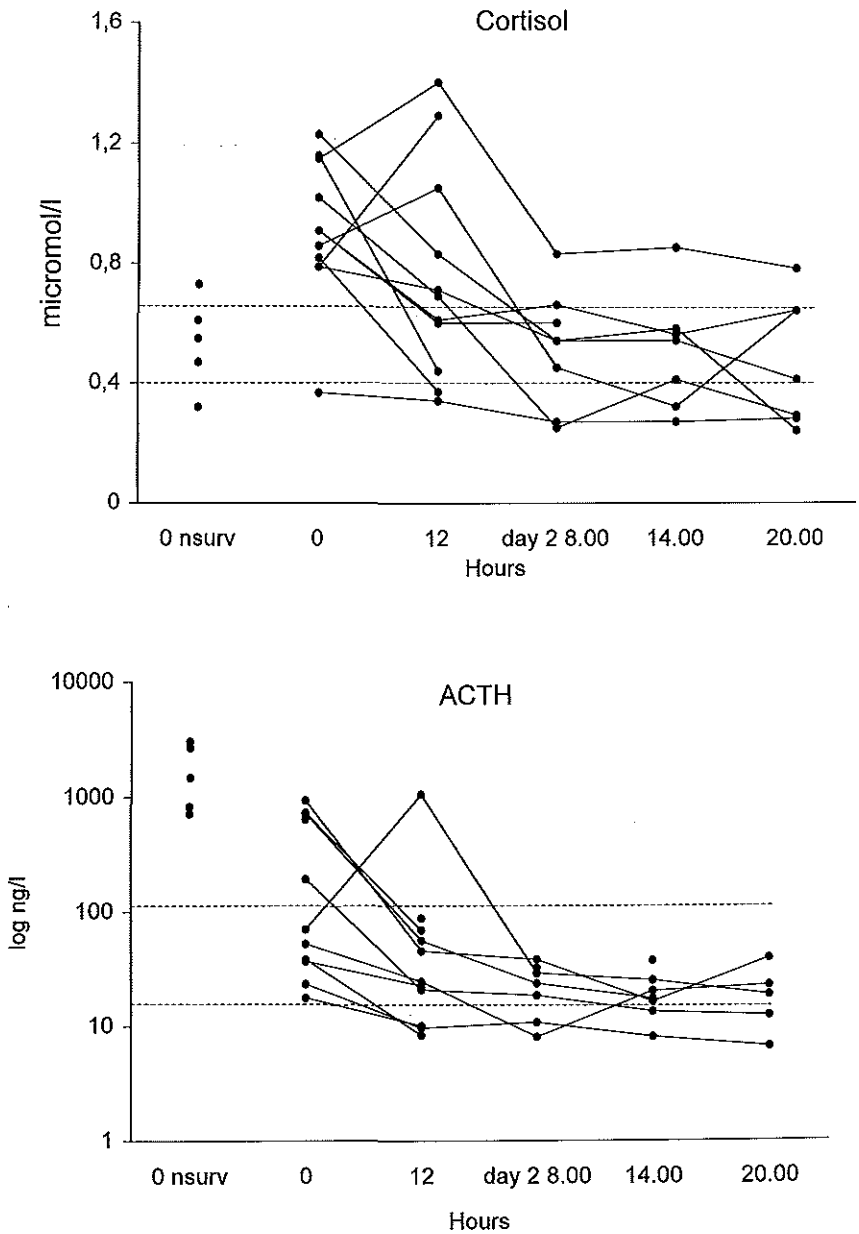


Figure 2 Levels of cortisol and ACTH on admission non-survivors (0 nsurv) and for survivors (0) and the time course of cortisol and ACTH levels for survivors after 12 hours and on day 2 at 8.00 h, 14.00 h and 20.00 h. Reference values between dotted lines.

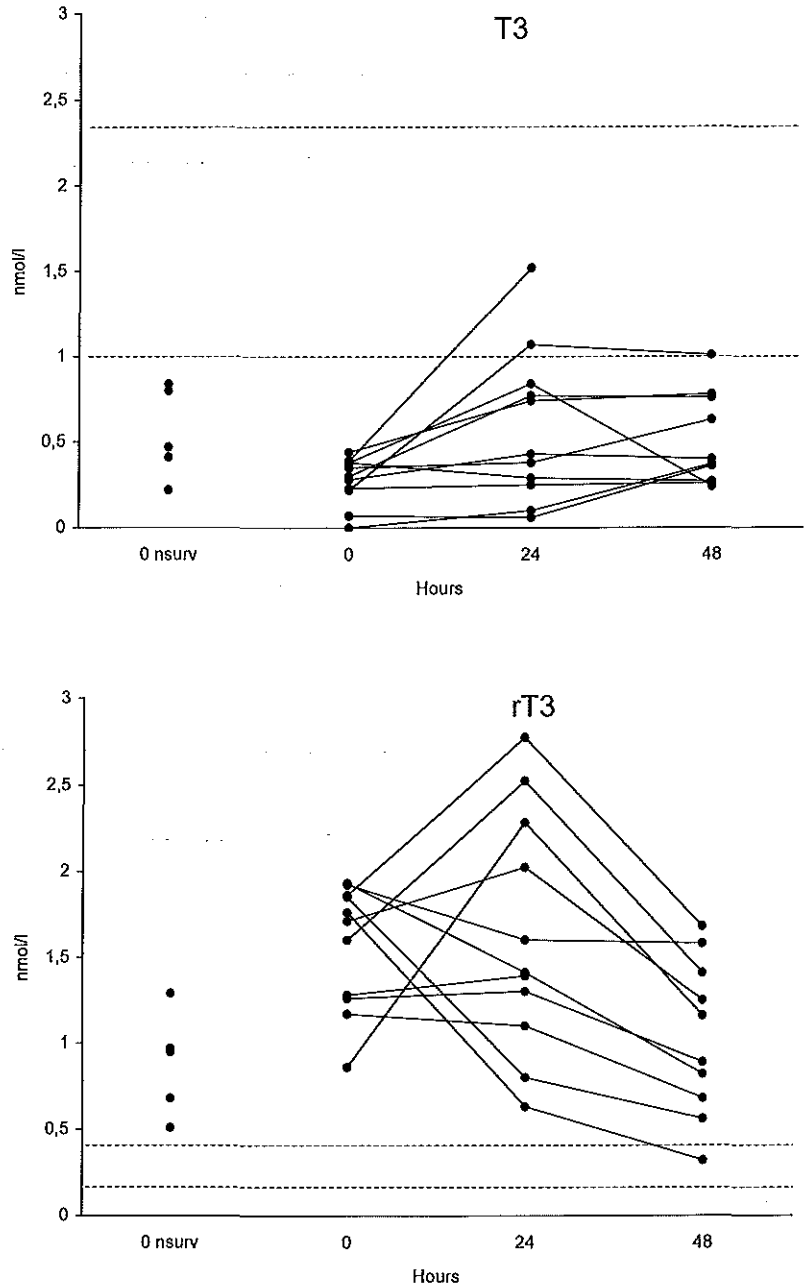
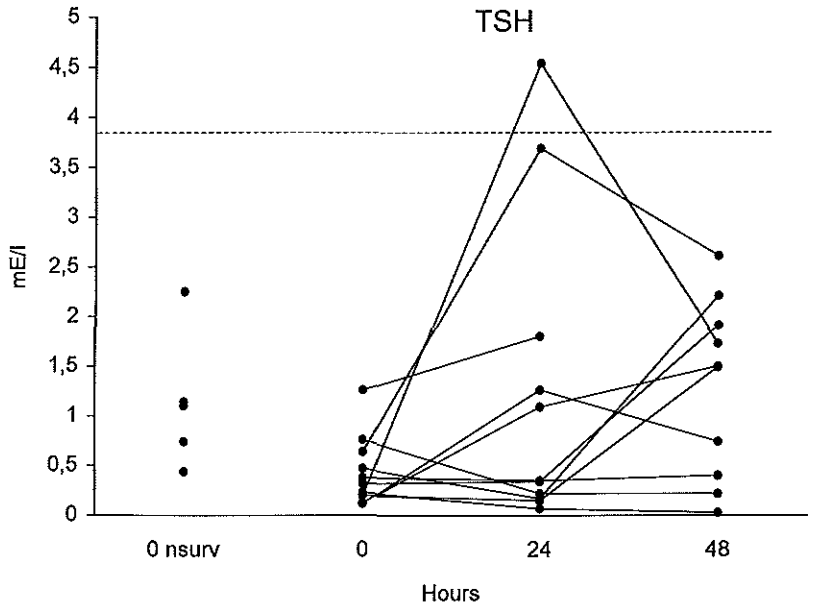


Figure 3 Levels of T_3, rT_3, TSH and ratio T_3/rT_3 on admission for non-survivors (0 nsurv) and for survivors (0) and the time course of these levels for survivors after 24 and 48 hours. Reference values below or between dotted lines.


TSH
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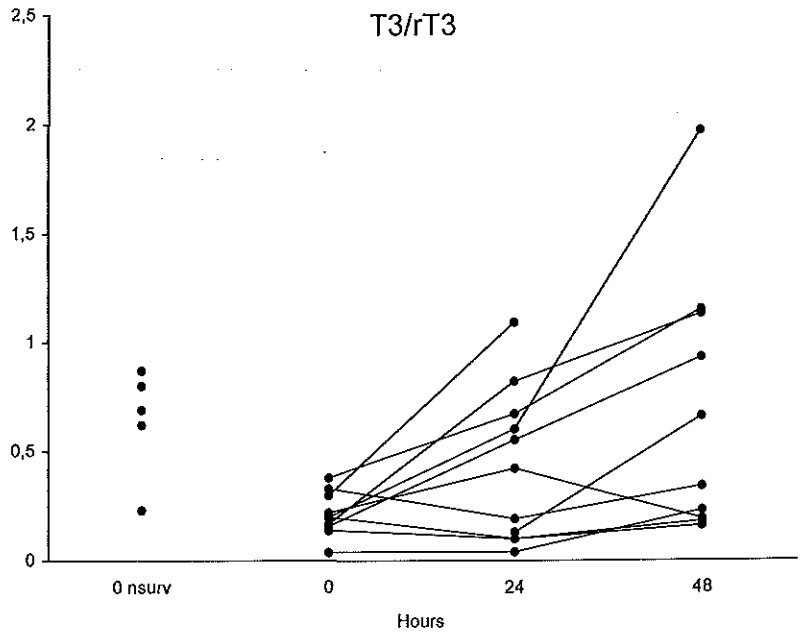
Hours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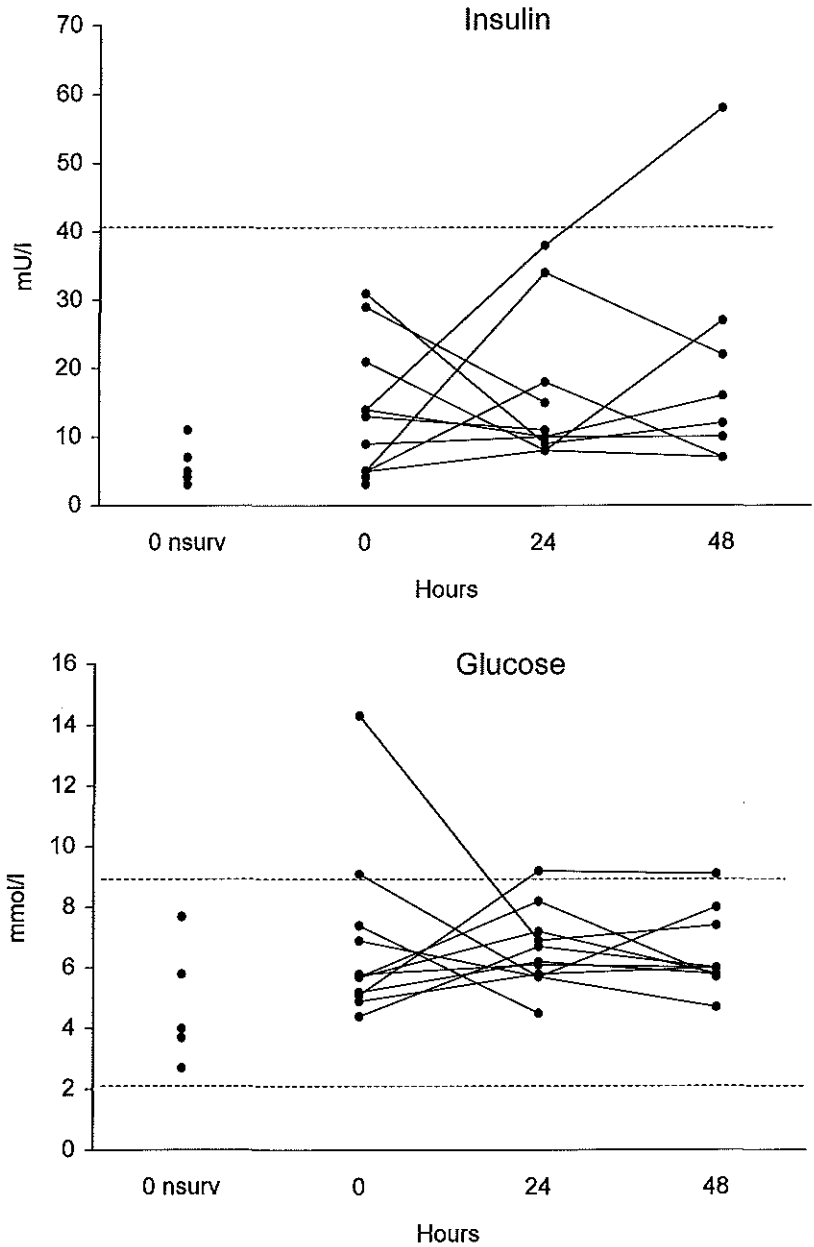

Figure 4 Levels of insulin and glucose on admission for non-survivors (0 nsurv) and survivors (0) and the time course of these these levels for survivors after 24 and 48 hours. Reference values below or between dotted lines.

Table 2 Endocrine and metabolic differences between survivors and non-survivors on admission and time course of survivors

		Non-Survivors		Survivors						Normal reference
		T=0		T=0		T=24[nb]		T=48		
PRISM		28	(19-32)	15	(7-27)[s**]					
Cortisol	µmol/l	0,55	(0.32-0.73)	0.91	(0.37-1.23)[s**]	0.54	(0.25-0.83)[a*]			0.2-0.6
ACTH	ng/l	1469	(712-3010)	71	(18-946)[s**]	21	(1-38)[a*]			20-100
Cortisol/ACTH		0.50^{-3}	(0.10^{-3}-0.90^{-3})	16.1^{-3}	(0.6^{-3}-45.6^{-3})[s**]	28.8^{-3}	(8.3^{-3}-42.1^{-3})[a*]			
TSH	mE/l	1.12	(0.44-2.25)	0.32	(0.12-1.26)[s*]	0.35	(0.07-4.54)	1.49	(0.03-2.61)[c*]	< 4.5
T_4	nmol/l	42	(29-61)	44	(29-64)	46	(21-110)	40	(30-85)	64-132
T_3	nmol/l	0.47	(0.22-0.84)	0.33	(0.07-0.44)[s*]	0.43	(0.06-1.52)	0.39	(0.24-1.01)	1.1-2.6
rT_3	nmol/l	0.95	(0.51-1.29)	1.71	(0.86-1.93)[s**]	1.41	(0.63-2.77)	1.03	(0.32-1.68)[b**c*]	0.15-0.43
T_3/rT_3		0.69	(0.23-0.87)	0.20	(0.04-0.38)[s**]	0.42	(0.04-1.09)	0.50	(0.16-1.97)[b*c*]	
fT_4	pmol/l	14.1	(9.5-17.1)	15.0	(12.6-24.1)	12.7	(7.7-35.8)	11.5	(8.6-21.5)[c*]	11-25
Insulin	mU/l	5	(5-11)	13	(5-31)	10.5	(8-38)	14.0	(7-58)	
Glucose	mmol/l	4.0	(2.7-7.7)	5.7	(4.4-14.3)	6.2	(4.5-9.2)	6.0	(4.7-9.1)	2.6-11
Insulin/glucose		1.8	(0.7-1.9)	2.0	(0.7-5.3)	1.8	(1.1-4.1)	2.4	(1.2-6.4)	< 50
CRP	mg/l	34	(21-41)	81	(22-144)[s**]	225	(116-321)[a**]	162	(47-286)[c*]	< 5
Lactate	mmol/l	7.4	(6.4-11.3)	2.9	(1.7-6.0)[s**]	1.5	(1.1- 3.2)[a*]	1.7	(0.9-2.2)[c*]	< 2.0
NEFA	mmol/l	0.44	(0.28-0.78)	0.93	(0.23-1.89)[s*]	0.79	(0.30-1.21)	0.41	(0.16-1.29)[b*c*]	0.3-1.1

all values are expressed as median and range, * $p<0.05$ ** $p<0.01$

[s] significant difference between non-survivors and survivors

[nb] for cortisol and ACTH T=24 is 8.00 AM day 2

[a] significant difference between T=24 and T=0

[b] significant difference between T=48 and T=24

[c] significant difference between T=48 and T=0

	Lactate	CRP	PRISM
Cortisol	ns	-0.69**	0.71**
ACTH	0.59*	ns	ns
Cort/ACTH	-0.63**	0.58*	-0.76**
TSH	0.62*	ns	0.57*
T_4	ns	ns	ns
T_3	ns	ns	ns
rT_3	-0.74*	ns	ns
T_3/rT_3	0.70**	ns	ns
fT_4	ns	ns	ns
Insulin	ns	ns	ns
Glucose	ns	ns	ns
Insulin/glucose	ns	ns	ns
NEFA	-0.62*	ns	ns

*p<0.05 **p<0.01 ns = no significant correlation

Table 3 Non linear significant correlation-coefficients (Spearman) between endocrine parameters, NEFA and parameters to monitor severity of disease (lactate, CRP and PRISM score) on admission

DISCUSSION

Our study shows that children who do not survive meningococcal sepsis have an impaired adrenal response, altered thyroid hormones and decreased levels of NEFA, associated with a higher severity of disease score on admission. The observed endocrine and metabolic changes are of possible clinical importance to reconsider therapeutic strategies.

One of the most striking alterations in our study concerned a significant difference in cortisol/ACTH response between non-survivors and survivors on admission. Non-survivors showed an inadequate cortisol response in combination to very high ACTH levels whereas survivors showed a normal stress response with significantly higher cortisol levels in combination with moderately increased ACTH levels. The ratio cortisol/ACTH was strongly correlated with survival and parameters to monitor the severity of disease. Low cortisol levels in non-survivors and high cortisol levels in survivors have been found previously in children with meningococcal sepsis but in these studies ACTH levels were not determined (21, 22). Surprisingly, in critically

adult patient with sepsis of various origins the highest levels of cortisol were correlated with increased mortality (23, 24). This difference in cortisol levels in children with meningococcal sepsis might be explained by the occurrence of severe adrenal hemorrhage, shown previously post mortem and nowadays with echography (25), resulting in loss of adrenal function. The severe adrenal hemorrhage is a characteristic feature in children not surviving from meningococcal sepsis and has been described previously as the Waterhouse-Friderichsen syndrome (21, 22). The beneficial effects of steroid treatment, as recently reported in adults, raises the question if it will also benefit children with meningococcal sepsis (26). It is suggested that treatment with supplemental steroids will only benefit selected children with an abnormal adrenal function (25). Recently, adrenal function was evaluated in children with septic shock of various origins by an ACTH stimulation test on admission. Adrenal insufficiency was associated with increased inotropic requirements and duration of shock, however not with mortality (27). Based on these results the authors stated that a placebo controlled trial with steroids would require at least 500 children to detect a reduction in mortality from 30 to 15%. Our study results indicate that because of the very rapid and aggressive course of meningococcal sepsis (4 of our 5 non-survivors died within 12 hours) steroid therapy might only benefit a limited number of children because the infection process might have gone beyond any currently available therapeutic approach. Nevertheless future studies are warranted to identify and treat these children.

On day 2 survivors showed significantly lower cortisol levels compared with the cortisol levels on admission and after 12 hours. The cortisol levels where within normal reference values, however without a circadian rhythm. These findings suggest a persisting hyperactivity of the adrenal gland despite normalization of cortisol and ACTH levels.

Thyroid function tests on admission showed that both non-survivors and survivors had decreased levels of T_3 and T_4, increased levels of rT_3, normal levels of fT_4 and no compensatory increased levels for TSH. These alterations in the thyroid axis, which are called the "euthyroid sick syndrome" have been described previously in critically ill infants and children (8-12). Non-survivors, however, showed significantly higher T_3 levels and lower rT_3 levels compared to survivors. Low levels of T_3 and increased levels of rT_3 are explained by an adaptive mechanism aimed at preventing protein catabolism and lowering energy requirements in severely ill patients. It might thus be postulated that non-survivors are not able to adapt in the same way as survivors (28-31). Most striking changes in thyroid function tests after 48 hours in children who survived were significant decreased levels of rT_3 and an increased ratio T_3/rT_3

but the levels remained below normal reference values. Our results are consistent with two previous studies in children. A study of critically ill children with infections showed in the beginning of the disease increased levels of rT_3 and also a decrease in rT_3 in the terminal stage (10). An other study in children who survived following cardiac surgery showed initially increased rT_3 levels which returned towards normal levels 48 to 72 hours after surgery. T_3 levels remained low during this period (12). The pathogenesis of the altered thyroid function in the "euthyroid sick syndrome" is not clear. This syndrome may be mediated by interleukine-1 and 6 and tumor necrosis factor and can be induced or aggravated by dopamine, glucocorticoids, while somatostatin may play a suppressive role (9, 32-35). In our study we found a significantly lower rT_3 level and a higher ratio T_3/rT_3 in patients in which inotropic support was ended after 48 hours compared to those that were still on treatment after 48 hours. It remains the question whether these alterations in rT_3 levels are caused by the suppressive influence of inotropics or results from the degree of illness.

In our study levels of insulin and glucose were lower for non-survivors compared to survivors but significance was not reached. No alterations in levels of insulin and glucose were found during the first 48 hours. None of the children had hypoglycemia. This is however a known complication in children with meningococcal sepsis (15, 36). Only one patient was hyperglycemic and in none of the patients insulin levels were markedly elevated. This is in contrast with studies of critically ill adults showing hyperglycemia and glucose intolerance with elevated insulin levels as hallmarks of stressed metabolism (37). Whether children with septic shock have a different insulin/glucose response compared to adults is not known. An indication for an altered insulin/glucose response was given in a study of septic infants (38). Despite the necessity of increased glucose requirements to maintain normoglycemia in these infants hyperinsulinemia was not observed (38).

There is evidence in adults to suggest that NEFA may be the preferred fuel for oxidation following severe trauma and it is important, therefore, that NEFA is readily available to the tissues (39). In our study we found on admission significantly lower NEFA levels in non-survivors compared to survivors. Previous studies in critically ill children and adults after trauma reported also that the lowest NEFA concentrations were seen in the most severely injured patients (40, 41). Results from animal studies demonstrated that during hypovolaemia there is an impairment of adipose tissue perfusion limiting the availability of albumin to transport NEFA out of adipose tissue. In addition local hypoxia, together with a rise in the systemic lactate concentration, act to stimulate re-esterification of NEFA (42, 43). Our study supports the existence of this phenomena as a significant negative correlation between lactate and NEFA levels was found

($p<0.05$, $r= -0,62$). For survivors NEFA levels showed a significant decrease after 48 hours and a significant decrease for lactate levels after 24 hours indicating improvement of the impaired circulation and diminished lipolysis.

The magnitude of urea nitrogen excretion in the urine (reflecting protein breakdown) of survivors during the first and second day after admission was higher compared with previous data of a group of critically ill children with various clinical diagnosis (19). Previous studies in critically ill adult patients showed that protein breakdown remained increased after the return to baseline values of the stress hormones and cytokines (44). Provision of exogenous nutrition could not prevent the absolute rate of protein breakdown but an improvement in protein synthetic rate could be achieved (45, 46). In a study of critically ill mechanically ventilated children it was shown that it was possible to improve nitrogen retention with exogenous nutrition designed to meet the energy expenditure (47). In our study the caloric supply during the first and second 24 hours was respectively 38% and 33% below the calculated values for resting energy expenditure. It has to be investigated if a normocaloric or hypercaloric feeding regimen can diminish this high urinary nitrogen excretion during the first and second 24 hours that we have seen in our study.

On admission we found that lactate levels correlated with alterations in the pituitary/adrenal axis (ACTH and ratio cortisol/ACTH), thyroid hormones (TSH, rT_3 and ratio T_3/rT_3) and with levels of NEFA. At the moment the question remains unanswered whether these endocrine alterations play a crucial role in survival or represent secondary effects of the impaired peripheral circulation reflected in increased lactate levels. The insufficient adrenal function might contribute to a sustained circulatory instability leading to fatal outcome and future treatment with steroids might be crucial for survival of some of these patients.

In conclusion this study showed significant differences between non-survivors and survivors at admission in the levels of cortisol, ACTH, thyroid hormones and NEFA. Furthermore these levels correlated well with the parameters to monitor the severity of disease. Within 48 hours survivors showed significant changes in the levels of cortisol, ACTH and thyroid hormones but the levels remained abnormal compared to normal reference values whereas NEFA levels normalized. In the last 20 years there have been important developments in the supportive treatment of children with meningococcal septic shock. The future will lay in the break-up of deleterious events regarding the hormonal and metabolic axis and at the moment our results call for studies to assess the beneficial effect of steroid treatment in children with meningococcal sepsis.

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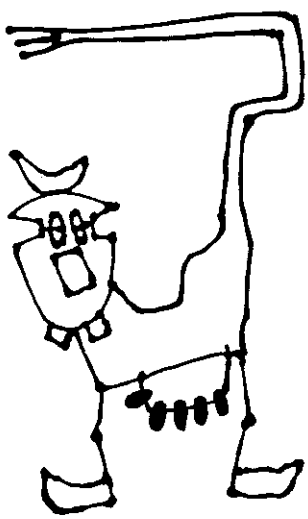
Part 5

General discussion
Summary
(Samenvatting)



Chapter 8

General discussion

1 Introduction: the problem of nutritional assessment in critically ill children

At the moment there is no golden standard for nutritional assessment and support in critically ill children. This is due to the fact that several specific problems are unsolved in using nutritional rules for critically ill children as well as the difficult conditions in the pediatric intensive care to evaluate nutrition requirements;

- there is a paucity of validation data of several techniques for assessing nutritional status in critically ill children (e.g. indirect calorimetry, bioelectrical impedance, dual x-ray absorptiometry);
- there are logistical and practical problems to collect an adequate amount of blood or urine to analyze different metabolic and hormonal parameters;
- the diversity in clinical presentations and the various age groups make it difficult to perform studies in large homogeneous patient groups and to compare different feeding protocols;
- one has to taken into account the growth of a child as well as the effects of malnutrition on the development of a child;
- because of the brief median stay of children on a pediatric intensive care most attention will focus on the primary medical problem, in stead of nutritional status;
- there is a paucity of studies in critically ill children to prove the benefit from early nutritional support as a motivation for further clinical research;
- because of an accelerated time course of critically illness in most of the children the metabolic, hormonal and nutritional alterations will vary per patient per day;
- it is questionable if the metabolic response to injury and sepsis described in critically ill adult patients by Cutherberson and characterized by an ebb and flow phase is the same for infants and children. The decreased metabolic rate of the ebb phase and the increased metabolic rate of the flow phase were not observed in studies of critically ill infants and children. It has been shown that energy expenditure not only varies markedly between different diseases but also within the same disease (1-3).

Therefore nutritional support of critically ill children should be different from recommendations regarding nutritional support in critically ill adult patients. It is important to establish rules for nutritional assessment and to find sensitive nutritional parameters that can be used on a daily base to predict nutritional status. But improvement of the nutritional status as a single goal is not really important. The aim of nutritional assessment and subsequent nutritional intervention should be an improvement of the nutritional status of the child in order to ascertain normal growth and development. Therefore it is advocated to start nutritional support as early as possible to prevent nutritional depletion of macronutrients and micronutrients. Cunningham stated that especially for infants, the empirical wisdom that "the absence of evidence is not evidence of absence" should be invoked to support early nutrition intervention (4).

We have given a general overview and discussion of the currently established and non-established metabolic and endocrine parameters to be used for nutritional assessment of the critically ill child (chapter 1). We defined specific aims to study some of the metabolic, endocrine and nutritional aspects of the critically ill child (chapter 2).

1.1 ASSESSMENT OF INDIRECT CALORIMETRY

1.1 Technical considerations

At present the only accurate clinical means of determining daily energy expenditure (EE) in the critical care setting is to measure it with indirect calorimetry. However the method of the open system indirect calorimetry has been shown to have several disadvantages during its use in the critically ill mechanically ventilated child. Only patients in a stable haemodynamic condition, without changing metabolic acid-base status (e.g. dialysis), with an inspired oxygen fraction (FiO_2) below 0.6 and with no air leaks around the endotracheal tube can be adequately measured. We showed using a ventilated lung model that when low levels of oxygen consumption (VO_2) in combination with low tidal volumes were applied the accuracy of the indirect calorimeter diminished with increasing levels of FiO_2 (chapter 3). As a consequence the method is difficult to perform for low weight infants consuming low levels of oxygen and who are ventilated with low tidal volumes. Furthermore indirect calorimetry can usually not be applied in the most severely ill child the first days after admission. An important reason for the inaccuracy of these measurements is that the handling of gas with low concentrations of oxygen and carbon dioxide are beyond the specific working performances of most indirect calorimeters. Some methods are described to increase the accuracy of the method:

- sampling of gas not from the outlet port of the ventilator but sampling the gas directly from the expiratory tube can improve the measurement results (5);
- to overcome the problem of tube leakage Deakers et al advocated the use of cuffed endotracheal tubes in small infants and older children. The use of a cuffed endotracheal tube was found to be safe and not associated with an increased risk of postextubation stridor or significant long-term sequelae (6);
- there is no possibility to solve the problem of a FiO_2 above 0.6 using the open method of indirect calorimetry using the Haldane equation to calculate VO_2. Applying an internal bellow for mixing oxygen and air within the ventilator might diminish the fluctuation of FiO2. In our study however we did not find a difference in the instability of FiO_2 between a ventilator with an internal bellow and a ventilator without an internal bellow (chapter 4);
- to solve the problem of the lost air from tube leakage different methods have been used to determine expiratory gas leaks in children:
  - a loose-fitting face mask placed over an infant's endotracheal tube collecting leaked expiratory gases that are monitored by a capnometer (7);
  - a head box placed over the child's head, so that all expired gas leak around the endotracheal tube is captured for analysis (8);
  - pulmonary function test devices based on pneumotachometer flow measurements (9);
  - detection of CO_2 escaping from the lips or nares (10);
  - and auscultation of airflow at the level of the vocal cords.

The use of these different methods is of significant importance for assessing expiratory tube leakage but is difficult to perform in daily practice. In particular auscultation alone is not an adequate method to determine airleak (8). We compared the difference between inspiratory and expiratory tidal volume measurements of the ventilator to calculate tube leakage. With this method we found a correlation between tube leakage and the value of measured EE. One percent higher tube leakage resulted in a decrease of 1,3% of measured EE (chapter 4).

1.2 Prediction of energy expenditure

If it is not possible to perform indirect calorimetric measurements because of the technical limitations, it is suggested to calculate a basal metabolic rate (BMR) using a prediction formula. Measurements of the BMR have been performed since early this century in healthy children. Classically, these BMR measurements required the patient to sleep in the energy metabolism laboratory after a 12 to 14 hours fast in an environment with controlled humidity and temperature. From these data different investigators derived several prediction formulas. Many authors compare values of

BMR obtained from prediction formula with values obtained with indirect calorimetry in the clinical setting. However, in the clinical setting it is not possible to measure BMR in the classical way because the non- ventilated child is measured not in a basal but in a resting condition (e.g. watching television) and the mechanically ventilated child is measured in the intensive care environment usually with sedation. In these circumstances not the classically BMR is measured but a resting energy expenditure (REE). These values of REE are usually compared with one of the following prediction formula used to calculate the BMR:

- the Harris-Benedict equation based on height and weight is the most commonly used formula in adult patients (11).

Several prediction equations or tables were published for children:

- Talbot developed a table to calculate BMR in children using weight or height (12);
- the expert committee of the Food and Agriculture Organization, World Health Organization, and United Nations University (FAO/WHO/UNU) developed two equations to calculate REE for children, one equation only using weight and one using weight and height (13);
- Schofield developed also two equations, one for weight, one for height and weight (14).

Furthermore in 3 reports the body surface area was used to calculate the BMR:

- Robertson and Reid described standards for BMR of normal adults in Britain (15);
- Fleish developed a "metabocalculater" (16);
- Boothby et al published the Mayo normogram (17).

Kaplan et al and Firouzbakhsh et al investigated the reliability of different prediction equations (the WHO equation, the Harris-Benedict equation, the Schofield equation for weight and for weight and height) respectively in a group of children with clinical nutritional problems and in a group of healthy children. They compared these data with measured values for REE. Schofield's equation for height and weight was found to be the most accurate predictor for REE (18, 19). Kaplan et al however stated that in view of the wide variability in REE measurements, they believed that REE should be measured in patients in whom knowledge of caloric expenditure is required for clinical care. Thomson et al applied the same prediction equations in a group of healthy infants and in a group of infants with cystic fibrosis and found that one could even not rely on one of the predictive equations (20). Pencharz et al experienced for clinical purposes the weight-only equations according to Schofield to suffice in most instances (21). Taken together, one should account for the wide individual variability in REE when using prediction formula of BMR for clinical care.

In studies of mechanically ventilated children different prediction equations to calculate BMR were used to compare with the measured values of REE. In these studies a wide range in the ratio of measured EE to predicted BMR was found. Coss-Bu et al evaluated the use of the Harris-Bendict and Talbot predictive equations with indirect calorimetric values in a group of 55 mechanically ventilated children. They concluded that neither the Harris-Benedict nor the Talbot method will predict REE with acceptable precision for clinical use (1). We compared in a group of 50 mechanically ventilated children the measured EE with Schofield's prediction equation for weight. Unless a significant correlation between measured and predicted EE we also found a wide range of individual measurements (chapter 5). We agree with the conclusion of Coss-Bu et al that indirect calorimetry appears to be the only useful way of determining REE or TDEE in mechanically ventilated children.

One should however take into account that the measured EE of all the children in our study were below the normal energy intake for healthy children but were in a range below or above the predicted values for BMR (see fig. 1). In the recovery phase of critical illness the energy need can increase to levels above the energy need for normal healthy children (unpublished data). Therefore we think that prediction equations could be used to get a rough impression of the EE. Energy intake could be based on these values to avoid markedly underfeeding or overfeeding at the onset of critical illness.

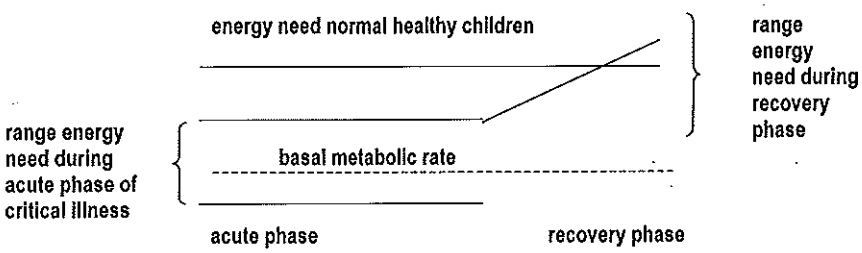


Figure 1 Energy need during acute phase and recovery phase of critically ill children.

Because of the difficulty to obtain accurate measurements of height in the pediatric intensive care setting the use of an equation with only weight is most practical and therefore preferred. Because the Dutch pediatric association recommends the use of Schofield's equation for weight for all children independent of their disease, it is also our standard to calculate BMR with Schofield's equation.

1.3 OTHER METHODS TO CALCULATE ENERGY EXPENDITURE (EE)

Another technique that has been introduced to measure EE is the so-called double-labeled water technique ($^2H_2{}^{18}O$). This technique determines the rate of CO_2 production from the difference in the turnover of deuterium ^2H and ^{18}O (22). This technique has been used so far as a research procedure to calculate total daily energy expenditure of normal infants and older children (23, 24), and has been used in several clinical studies e.g. infants with bronchopulmonary dysplasia (25), infants with congenital heart disease (26, 27) and children with cystic fibrosis (28). It is however doubtful if this method will find a common place in the intensive care unit, since it only measures CO_2 production and therefore does not allow the accurate measurement of EE at a given moment. It only assesses changes over prolonged periods of time. An advantage of this method is that it allows measurement of EE outside the hospital.

EE can also be determined by a method based on the Fick principle, relating the arterio-venous oxygen and carbon dioxide gas-content difference and cardiac output (called circulatory indirect calorimetry). Studies have shown a significant correlation between circulatory and standard respiratory indirect calorimetry (29). This method necessitates the use of a pulmonary artery catheter, which is hardly used in the pediatric intensive care, and therefore not a practical option to use for daily measurements of EE.

There are also some none-calorimetric methods which rely on the relationship between EE and various physiological parameters of an individual, such as heart rate, minute ventilation or electromyography. Similar approaches have tried to correlate EE with indexes of physical activity (i.e. pedometer) (30-33). It is doubtful if one of these methods will find a place in an intensive care setting because these methods rely on physiologic responses of normal healthy people and not on pathophysiologic responses in critical illness.

1.4 SUBSTRATE UTILIZATION

The method of indirect calorimetry allows the calculation of overall substrate utilization in the body. Different terminology is used to describe the handling of substrates; substrate disappearance rate, substrate oxidation and substrate utilization are used to describe the same process. Chiolero stated that indirect calorimetry does not measure the true oxidation rates of carbohydrates, lipids and proteins but only

their overall disappearance rates (22). Frayn stated that the apparent rates of oxidation of substrates should be interpreted as net rates of "utilization" (34). The apparent rate of carbohydrate oxidation is the sum of the rates of utilization for oxidation and for lipogenesis minus the rate at which carbohydrates are formed from amino acids. The apparent rate of fat oxidation is the difference between the rates of oxidation and synthesis from carbohydrate. In other words substrates are oxidized in different ways and indirect calorimetry measures the sum of oxidation rates, which is called the total utilization of a substrate.

We studied substrate utilization in a group of critically ill mechanically ventilated children with different clinical diagnosis (chapter 6). The study was cross-sectional and all children received a different amount of enteral or parenteral feeding. In this study some interesting observations were found regarding glucose and fat metabolism;

- in 3 patients we expected a respiratory quotient > 1.0 because of the high carbohydrate intake of > 9 mg/kg/min we administered but the respiratory quotient (RQ) values remained < 1.0. We concluded that in the stressed critically ill child similar as in the stressed critically ill adult patient two processes with glucose might occur. At first there is a continuous conversion of glucose to fat that causes the RQ to remain below < 1.0. Secondly, glucose supplied above the utilization rate might be converted to glycogen;
- fat utilization was not significantly different between children with a positive and children with a negative nitrogen balance. Because the fat intake of the children with a positive fat balance was significantly higher than the measured utilization rate we postulated that fat storage would occur in these patients. On the other side the fat intake in the children with a negative nitrogen balance was lower than the measured utilization rate and we suggested that in these patients endogenous fat would be utilized.

There were however several limitations of our study to come to definite conclusions. First, the study was performed in a heterogeneous group of critically ill children on different feeding regimens. Secondly, utilization data obtained with indirect calorimetry utilization were not compared with true oxidation rates of the substrates. Therefore we should be careful to draw general conclusions about substrate utilization rates of critically ill children. Prospective randomized controlled feeding intervention trials should be performed in children with the same disease to elucidate substrate utilization in patient groups. Furthermore isotopic labeling techniques will give a better understanding of the changes in substrate flows.

1.5 USE OF THE RESPIRATORY QUOTIENT (RQ)

It is not always clear in the literature if the respiratory quotient is calculated by only dividing VCO_2 and VO_2 or if nitrogen excretion data are considered to calculate a non-protein RQ (npRQ). When the RQ is close to 0,80, the npRQ and RQ are essentially identical but as the RQ deviates from 0.80, there will be a difference between the RQ and the npRQ. It is important to use the npRQ when substrate utilization is derived from pre-calculated tables because it is has been shown that failure to use nitrogen excretion in the calculation of a npRQ can result in errors in substrate utilization in the range of 50% to 100% (35). When the RQ is used as a value to ascertain under- and overfeeding, this difference of RQ and npRQ is of less clinical significance because these values will be used as rough estimates. Furthermore indirect calorimeters will give the RQ values instantly and reliable npRQ data will be obtained afterwards when 24 hours nitrogen excretion data are known. We used in our study npRQ values in chapter 5 and RQ values in chapter 6. One should take into account that values obtained by only using the RQ will show slightly decreased values compared to npRQ values.

The value of the measured RQ can be used in different ways to predict overfeeding and underfeeding:

- a RQ value of 0.85 is considered to be normal, a RQ value > 1.0 represents lipogenesis and overfeeding. In our studies we found a RQ > 1.0 in children with varying glucose intake;
- a combination of the measured RQ with the RQ of the macronutrients (RQmacr) administered can be helpful in differentiating under- or overfeeding. The RQmacr can be obtained from a table published by Lusk (modified) after determining the carbohydrate to fat ratio for the total nonprotein calories of the infused regimen (36). The measured RQ can be compared with the RQmacr and if the measured RQ is assumed to approximate the RQmacr, RQ = RQmacr ± 0.05, a prediction of overfeeding and underfeeding can be made (37).

We used this method to calculate the percentage of under- and overfeeding in a group of mechanically ventilated children (chapter 6). We found in 47% of the children that the RQ approximated the RQmacr, in 22% the RQ was above the RQmacr while in 31% of the children the RQ was below the RQmacr. Because we found a significant relation between the difference of RQ-RQmacr and the ratio caloric intake/ measured EE we stated that in case of a caloric intake which is lower than the measured EE a RQ lower than the RQmacr will suggest lipolysis. In case of a higher caloric

intake than the measured EE a RQ higher than the RQmacr will suggest lipogenesis and overfeeding. We think that the use of RQ in this way is a first attempt to better differentiate under- and overfeeding.

1.6 INDIRECT CALORIMETRY: PRACTICAL GUIDELINES

Indirect calorimetry should be a part of a nutritional assessment program. The question is how and when to use this method in the pediatric intensive care: Is it necessary to measure every day EE or can one rely on one EE measurement at the onset of disease to use for caloric supply on subsequent days.

The only recommendations given in the literature are:

a to measure energy expenditure individually because of the great variability of EE.

b to use a RQ > 1.0 to detect overfeeding.

From our observations some additional guidelines can be derived using indirect calorimetry in mechanically ventilated children:

c total daily energy expenditure can be estimated from a 2 hour measurement period if tube leakage remains below 10% (chapter 4).

d there is an increase of 6% in energy expenditure per grade Celsius increased body temperature (chapter 4).

e there is a significant difference between patients with a positive or negative N-balance and the ratio caloric intake/total measured energy expenditure (chapter 6). This means that caloric intake should be at least the measured energy expenditure.

f determination of 24 hours urea nitrogen excretion is necessary to calculate protein intake and nitrogen balance (chapter 6)

g a RQ above > 1.0 will detect carbohydrate overfeeding (chapter 6)

h a combination of the RQ and the RQ of the macronutrients administered can be helpful in differentiating under- or overfeeding (chapter 6).

Furthermore we recommend:

i to add in young infants 4 kcal/desired gram growth per day above the measured EE after the acute phase of disease

j to perform repeated measurements of EE and RQ daily until the maximum amount of feeding is achieved in order to determine over- or underfeeding. If a maximum is achieved measurement of EE and RQ can be performed once or twice a week depending on age (e.g. growing infant) or severity of disease (e.g. child recovering from meningococcal sepsis with severe wounds).

Future studies should be performed to evaluate the beneficial effect of indirect calorimetry on several clinical outcome variables in critically ill children. These variables should not only include mortality and length of hospital stay but also e.g. infectious complications, duration of ventilation and healing time of wounds. Furthermore follow-up studies regarding growth and neurocognitive development should elucidate the effect of early nutritional intervention. Therefore indirect calorimetric studies should not only be performed in mechanically ventilated children but measurements should also be performed in the spontaneous breathing child recovering from a critical illness to optimize nutritional therapy.

2 Endocrine and metabolic assessment

2.1 THE NEUROENDOCRINE RESPONSE IN THE CRITICALLY ILL CHILD

As described before it is questionable if the metabolic response to injury and sepsis in critically adult patients characterized by an ebb and flow phase is similar for infants and children. We investigated the time course and variability of the endocrine and metabolic responses in children with meningococcal sepsis during the first 48 hours of admission (chapter 7). We found significant differences between non-survivors and survivors in hormones of the pituitary-adrenal axis, thyroid hormones and non-esterified free fatty acids (NEFA). Levels of insulin and glucose were lower in non-survivors but did not reach statistical significance compared to survivors. As a major cause of these differences we postulated the influence of the impaired peripheral circulation reflected in increased levels of lactate. Survivors showed within 48 hours normalization of levels of cortisol and ACTH but a circadian rhythm was absent. The most striking changes in thyroid hormones were seen in levels of rT_3 and the ratio T_3/rT_3. Levels of insulin and glucose showed a variable pattern in the first 48 hours.

We questioned if any endocrine parameter can be used to judge the return to anabolism. It seems rational to look for the normalization of an anabolic hormone such as the thyroid hormones and not to evaluate the normalization of the "counterregulatory hormones" such as cortisol. Prolonged measurements of rT_3 in relation with other parameters such as nitrogen balance might be necessary to prove if rT_3 can be used as a marker for anabolism. Furthermore the rT_3 value has to be used in combination with the beneficial effect of early nutritional support. No prospective studies in critically ill children have been performed so far to evaluate the use of endocrine parameters for nutritional assessment. Only in one study the

effect of severe head injury on whole body energy expenditure and hormonal mediators during the first 72 hours after admission was investigated (2). The authors found a relationship between T_3 and energy expenditure that was surprising because the positive influence of T_3 on energy expenditure is known to be a long-term and not a short-term one. The authors stated that there might also a rapid onset, short-lived effect of T_3 on energy expenditure.

We believe that the evaluation of the endocrine response during critical illness might be a valuable tool in the concept of nutritional assessment. To elucidate this concept future studies should be designed to evaluate the endocrine response in relation with severity of disease parameters and in relation with parameters currently used in nutritional assessment. Furthermore endocrine parameters should be studied in relation with nutritional intervention trials to show the sensitivity of endocrine parameters to predict recovery to anabolism. For clinical purposes it will be necessary to have the possibility to perform laboratory tests which provide results immediately. If endocrine parameters are immediately available future research can focus on performing neuro-endocrine function tests. The hypothesis of inappropriate neuro-endocrine function can be validated and it should be studied whether endocrine interventions in acute or prolonged critical illness might have beneficial metabolic effects and might accelerate the recovery of those patients who need it most. For example supplementation of steroids in children with septic shock is probably warranted because in our study we found on admission significant lower cortisol levels in children who did not survive from meningococcal septic shock. We believe that a randomized placebo controlled study with steroids should be performed to show the beneficial effects of steroid therapy in children with meningococcal septic shock. In this study it will be necessary to perform adrenal function tests on any time of the day in a clinical setting to find these children who will benefit from steroid therapy. Future studies should elucidate the pathophysiology of the neuro-endocrine response and the possibilities for adjunctive therapy.

2.2 METABOLIC ASSESSMENT

A disease process may result in an increased loss of nutrients or an increase in metabolism of these substances, all causing an increase of need for these nutrients. Nutritional depletion or deficiency may occur if the intake of these nutrients are not supplied in the same amount as there is need for. One of the goals of nutritional assessment is to determine these depletions and deficiencies. Nutritional depletion can be subdivided into depletion of macronutrients and depletion of micronutrients. Depletion of macronutrients can be divided into caloric malnutrition (i.e. depletion

of carbohydrates and fat) and protein malnutrition. Depletion of micronutrients can be divided in depletion of elements (i.e. phosphate, magnesium, calcium), trace elements (i.e. zinc, selenium, copper, iron, fluor) and vitamins.

The use of biochemical indices for assessing the nutritional status or depletion of protein macronutrients of the critically ill child has long been focused on the visceral proteins such as albumin, pre-albumin, retinol-binding protein and transferrin. Previous studies showed that pre-albumin and retinol-binding protein were the most suitable proteins for assessing changes for somatic growth and recovery of metabolism. In these studies pre-albumin was used as a parameter for somatic growth in relation to the feeding supplied. We studied pre-albumin levels in a group critically ill children and found a significant difference in pre-albumin levels on admission and 4 days after admission (0.10 g/l vs 0.17 g/l) (38). In these children feeding was started 24 hours after admission and the changes we observed could be interpreted as restoration of visceral protein synthesis. No studies were performed to decide whether given the level of a visceral protein one needs to start or increase parenteral or enteral feeding. In some studies a combination of parameters were used to guide nutritional support:

- Chwals combined serial measurements of visceral proteins (pre-albumin, CRP) with serial measurements of total urinary nitrogen excretion, energy expenditure and respiratory quotient to demonstrate the resolution of acute stress. With resolution of acute stress nutritional supplements are increased. Chwals did not describe exact guidelines to use this metabolic monitoring system and it is questionable if it is sensitive enough to predict the earliest resolution of acute stress;
- Pressac et al advocated the use of the prognostic inflammatory and nutritional index (PINI), a combination of two markers of infection (CRP and alpha1-acid glycoprotein) and two markers of malnutrition (albumin and pre-albumin), as a useful scoring system. They stated that alterations in the PINI formula may occur from hour to hour and can contribute to the adaptation of therapeutic strategies. We think that this PINI scoring system is more useful to predict inflammatory changes and is a less sensitive scoring system for restoration of acute stress because of the long half life of the used parameters for malnutrition. Proteins with a short half-life such as IGF-1 (2-6 hours) showed to have a predictive value for the nutritional status in adults. Use of IGF-1 as a nutritional marker might probably a better marker to detect resolution of catabolism in children but no studies were performed so far;
- Steinhorn et al advocated the use of a pediatric risk of mortality score (PRISM score) or a therapeutic interventi on scoring system (TISS) as useful markers of altered needs in critically ill children (39). In their study the PRISM score correlated

with oxygen consumption and PRISM score and TISS correlated with total urinary nitrogen excretion. They concluded that the strong correlation of illness scoring systems and biochemical markers of stress provides a method for making plans for nutritional support that are independent of the diagnosis and relate only to the degree of illness. The limitations of their study were that only 12 children were investigated and the collected data reflected only the first day of information;

- We performed a study in 37 mechanically ventilated infants and children and did not find a correlation between PRISM and TISS scores and oxygen consumption (40). Only an enumeration of PRISM and TISS scores showed a significant positive correlation with oxygen consumption. Furthermore we only found a negative correlation between TISS and nitrogen balance and not between PRISM scores and nitrogen balance. From our results we could not support the idea of Steinhorn et al that PRISM and TISS scores can be relevant in prescribing nutritional support.

Little is known about the depletion of micronutrients such as trace elements and vitamins in critically ill children. There has been documentation for increased vitamins and mineral requirements during stress. Reasons for the increased requirements are: a) administered drugs may increase micronutrient requirements and b) a decreased absorption due to varying degrees of bowel atrophy. DeBiasse et al published guidelines for vitamin administration for the critically ill hospitalized adult patient. They advocated to increase all vitamin supplementation ten times above the recommended daily allowances, except for vitamin D. In some diseases (i.e. renal failure) vitamin supplementation should be limited because the disease alters the safety level of vitamins. The vitamins should be given enterally because most intravenous preparations do not provide adequate concentrations. The micronutrients selenium and zinc were increased 50% and 300% respectively (41). Wesley advised to supply trace elements (zinc, copper, manganese, chromium and selenium), and both water- and fat-soluble vitamins in amounts sufficient to meet estimated daily requirements with periodic checks for isolated deficiencies (42). We can conclude that attention should be focused to the determination and supply of micronutrients such as phosphate, magnesium, calcium, zinc and thiamin (vitamin B1).

Taken together it can be concluded that at the moment there is no single metabolic parameter or combination of metabolic and severity of disease parameters which can be used as a golden standard to guide nutritional support of the critically ill child. We advocate to develop an "acute scoring system" for the first few days of critical illness. In our opinion such a system might consist of a combination of simple metabolic, endocrine and physiologic parameters. These parameters reflect clinical recovery (body temperature, mean arterial blood pressure and CRP), recovery of

catabolism and influence of nutritional support (respiratory quotient, urinary nitrogen excretion, rT_3, IGF-1). After the acute phase (>3 days) this combination of parameters could be simplified without using the physiologic parameters and replacement of pre-albumin for IGF-1. Because of the short half-life of IGF-1 this parameter seems to be of more importance in the acute phase than in the recovery phase of critical illness but this assumptions have to be investigated.

2.3 BODY COMPOSITION

Changes in nutritional status have been traditionally assessed by alterations in body composition. Several techniques were developed for the assessment of human body composition that can be divided in traditional and new methods. Of the traditional methods anthropometry (and especially weight) is still an important tool in the pediatric intensive care. The measurement of weight is important because:

- on admission as the starting value and for calculating medication;
- on admission to detect previously developed protein-energy malnutrition;
- after the initial phase of disease the critically ill child tends to gain large amounts of weight due to third spacing of fluid during the time of acute metabolic stress. This occurs simultaneously with catabolism of endogenous protein, fat and carbohydrate stores. Serial measurements of weight can be used to evaluate the increase or decrease of third spacing of fluid;
- in the recovery phase of disease weight can be used to determine changes in nutritional status.

In the pediatric intensive care, except weight, anthropometric techniques are hardly performed because of the practical limitations of these measurements and the difficulty to interpret these results mostly due to the third spacing of fluids. Because an important number of children admitted to the pediatric intensive care unit have congenital anomalies or have a history of prematurity it is advocated to use disease-specific growth references (43).

New methods were developed to assess body composition that can probably be used in daily practice on a pediatric intensive care unit. Most promising techniques are bioelectrical impedance (BIA) and the dual X-ray absorptiometry (DXA). These techniques can be performed at the bedside and will give immediate information about body composition. Until now these techniques were only validated for healthy children above 3 years of age. However, in two postoperative cardiac surgery studies the use of the BIA was investigated in children < 3 years of age. In these studies BIA measurements showed changes in total body water (44, 45). Further research should

elucidate the value of these techniques for daily practical use on a pediatric intensive care. If only research is the purpose of assessment of body composition traditional methods such as double labeled water and new methods such as neutron activation analysis can be applied (46).

In summary we conclude that there are established biochemical parameters and body composition techniques which can be used in determining the nutritional assessment of the pediatric intensive care patient. The value of recently detected biochemical parameters and body composition techniques in combination with severity of disease scoring systems should be determined in critically ill children. We advocate to distinguish levels of nutritional assessment and to apply these depending on the phase and severity of illness. In table 1 we propose 4 levels of nutritional assessment with established and not yet established parameters. Level 1 should be performed in all patients on admission. Level 2 should be applied in patients with present protein-energy malnutrition on admission or predicted prolonged intensive care and hospital stay derived from a high PRISM score (>3 days). Level 3 should be performed in prolonged critical illness (>3 days). Level 4 consists of parameters which values should be established for daily practice as well as techniques only to be used for research.

Table 1 Levels of nutritional assessment for the pediatric intensive care patient ⇒

Level 1	**Should be done in all patients on admission**		
	– weight, height, head circumference	(E)	
	– Pediatric risk of mortality score (PRISM), on admission	(E)	
	– Pediatric index of mortality (PIM), on admission		(NE)
	– Therapeutic intervention scoring system (TISS), daily	(E)	
Level 2	**Should be done in patients with either:**		
	present protein-energy malnutrition on admission or expected		
	prolonged intensive care and hospital stay (>3 days)		
	Measurements include:		
	– prealbumin, twice a week	(E)	
	– glucose, urea, creatinine, daily	(E)	
	– calcium, magnesium, phosphate, daily	(E)	
	– triglycerides, daily (during intravenous fat supply)	(E)	
	– zinc, daily		(NE)
	– indirect calorimetry, daily	(E)	
	– nitrogen excretion and nitrogen balance, daily	(E)	
	– urine glucose, protein, ketones, daily	(E)	
	In children with septic shock additional		
	– cortisol, daily		(NE)
	– if cortisol level is low ACTH test		(NE)
Level 3	**Prolonged critical illness (>3 days)**		
	– cortisol, weekly		(NE)
	– if cortisol level is low; ACTH test		(NE)
	– vitamin status, weekly		(NE)
	– carnitine, weekly		(NE)
Level 4	**For future use (to be established):**		
	Laboratory parameters:		
	– urine 3-methyl histidine		
	– urine cortisol		
	– IL-6	**For research only:**	
	– IGF-1	– fat balance	
	– rT_3	– double labeled water	
	– T_3/rT_3	– labeled glucose	
	– leptin	– labeled amino acids	
	Body composition techniques:	– labeled fatty acids	
	– BIA, DXA, TOBEC	– muscle biopsies	
	– knenometry		

NB: levels 1, 2 and 3 are highly recommended for the established parameters (E), the non established parameters (NE) should be investigated urgently because of the clinical importance of these parameters

3 Nutritional support

The most important element in nutritional support in the intensive care setting is to have a standard feeding protocol in which 3 questions should be considered:

- when to feed: indications for nutritional support;
- what to feed: composition of nutritional formula and enteral vs parenteral feeding;
- how to feed: how to administer enteral or parenteral nutrition.

Application of such a protocol will be the most important step forwards to treat the (malnourished) intensive care patient. The working group on nutrition and metabolism of the European Society of Intensive Care Medicine published a practical approach in 1998 for enteral nutrition for adult intensive care patients (47). These recommendations consisted not only of the supply of macronutrients, micronutrients and immunomodulating agents but also recommendations for feeding and organ dysfunction, feeding preparations and conditioning and routes of feeding. At the moment such a practical approach is not yet published for critically ill children but the concept of this working group should be translated for the critically ill child.

When to feed: Indications for nutritional support

For assessing the total nutritional status of a patient several parameters have to be evaluated. Souba stated that identification of the malnourished adult patient at risk is important because besides established indications for the use of nutritional support there is a list of unproven indications requiring further study (48). There are accepted guidelines for the time to start additional nutritional support to the acute catabolic adult patient such as (49):

- the duration of the catabolic state and non satisfactory nutrient intake is expected for longer than 1 week;
- the patient has been without nutrition for 5 days and;
- the patient is already malnourished.

These guidelines for adult patients are difficult to translate for critically ill infants and children. However, in the absence of such guidelines, it seems appropriate to at least apply these minimum requirements to children but it can be expected that the time frames are shorter. Because in contrast to adults, critically ill infants and children are in a state of growth, development and organ maturation in our opinion nutritional support should be started as early as possible.

What to feed: composition of nutritional formulas

Unfortunately current recommendations for nutritional support in critically ill pediatric patients are not based on randomized trials with feeding intervention studies. Knowledge concerning substrate intake and substrate utilization can be derived from adult studies and studies concerning mostly surgically treated newborn infants. Knowledge concerning energy expenditure can be derived from a few studies of mechanically ventilated children. However, some important conclusions can be drawn from the studies in infants and children and from the results of our studies:

- there is a wide variability in total daily energy expenditure in critically ill children (chapter 3);
- the total daily energy requirements can be higher or lower than values of resting energy expenditure. This means that in general the total daily energy requirements of the critically ill child will be lower than the total daily energy requirements for healthy children;
- there is a considerable risk for overfeeding in the critically ill child for carbohydrate, fat and protein;
- there might be an individual maximum of oxidative capacity for carbohydrate, fat and protein;
- carbohydrate overfeeding can be determined by measuring the respiratory quotient, a RQ >1.0 indicates overfeeding (chapter 5 and 6);
- fat overfeeding can be determined measuring plasma triglycerides levels or comparing fat intake with fat utilization;
- protein needs can be determined by measuring urinary nitrogen excretion (chapter 5 and 6);
- protein retention can be increased by a balanced glucose/fat solution;
- there might be an optimal non-protein calorie-to-nitrogen ratio to enhance protein retention;
- our studies on energy metabolism and substrate utilization were performed crossectional. This means that we had only one measurement per patient on one of the days during the stay on the intensive care. The duration and effects of the acute metabolic response to illness or severe stress could have been evaluated

more accurately by repeated measurements in individual patients of energy expenditure, calculation of substrate utilization and daily determination of nitrogen balance. In this way nutritional support could probably have been optimized per individual patient. It remains however to be seen to what extent it is possible to decrease protein loss with aggressive nutritional support in the acute metabolic stress period;

- in most studies that were performed in children and adults the influence on substrate utilization of different parenteral nutritional regimens was investigated. The effect of enteral feeding protocols on the substrate utilization in critically ill children has not been studied sofar. We measured substrate utilization in infants and children who were either on parenteral or enteral nutrition and assumed a high absorption of the administered enteral feeding. One should take into account this assumption and consider gastro-intestinal abnormalities interpreting results of substrate intake and utilization.

Taken together, based on the presently available data we would like to suggest the following recommendations for feeding the critically ill child:

Energy requirements

The reference method to evaluate the energy need is indirect calorimetry. A pragmatic estimate of energy requirements can be obtained using Schofield's equation for resting energy expenditure. In young infants 4 kcal/gram growth should be added if growth is desired. One should account for 10-15% loss of energy when enteral feeding is supplied.

Protein requirements

The method to evaluate the protein need is to calculate urinary nitrogen excretion. Protein need can range in the severely ill child from 1 to 4 g/kg/day. We recommend to start with enteral or parenteral 1 g protein/kg/day and to increase the amount depending on the need and level of blood urea.

Proteins administered with fresh frozen plasma should not be taken into account. Standard enteral formulas can be administered because there is no evidence to use protein diet formulas.

Glucose requirements

We recommend to administer enteral or parenteral 4-8 mg/kg/min glucose depending of the severity of disease and the tolerance of the patient. The method to evaluate carbohydrate overfeeding is measuring a respiratory quotient or to determine hyperglycemia or glucosuria.

Fat requirements

The parenteral fat intake is in general lower compared to the enteral fat intake because there is a maximum capacity to hydrolyze the administered parenteral fat emulsions. Furthermore the absorption of enteral fat is 80-90%. When parenteral feeding is started we recommend to start with a low amount of fat, 0,5 g/kg/day, in the acute phase of illness because of the risk of fat overloading. In general, a least 2-3% of calories should be linoleic acid, in order to prevent fatty acid deficiency. The method to evaluate fat overload is to measure plasma triglycerides and fat intake should be increased depending on this level. The fat intake can be gradually increased to an amount of 3-4 g/kg/day. When enteral feeding is supplied an amount of 1-1,5 fat should be given initially. This amount can be increased gradually to an amount of 7-8 g/kg day in small infants and 3-4 g/kg in older children.

Glucose-fat ratio and nonprotein calorie/nitrogen ratio

The ideal relative concentrations of carbohydrates and fat have not been fully determined in critically ill children and will be different for parenteral feeding and enteral feeding. Furthermore it has been suggested that nitrogen intake can be maximized by providing nonprotein calorie/nitrogen ratios of approximately 100:1 for severely stressed patients and about 150:1 for non-critically stressed patients.

When parenteral feeding is administered it can be calculated from the recommendations for carbohydrate and fat that the non-protein energy contribution of carbohydrates will be 80-90% and for fat 10-20% in the beginning of disease. With increasing parenteral fat emulsions the contribution of fat might increase to 50%. The nonprotein calorie/nitrogen ratio for the recommended amount is 70:1 to 100:1 kcal/gN.

When standard enteral feeding is supplied the energy contribution of carbohydrates and fat is fixed. The energy contribution of fat is with 50% the highest for infant formula and decreases to 35% for enteral feeding of older children. The nonprotein calorie/nitrogen ratios for these formulas is 175:1 to 250:1 kcal/gN. There is however one standard formula (Nutrison Energy, Nutricia, Zoetermeer, the Netherlands) with a high energy and protein content which have nonprotein calorie/nitrogen ratio, 130:1 kcal/gN.

Taken together the different compositions of parenteral feeding enables the clinician to change the energy contribution of carbohydrates and fat and the nonprotein calorie/nitrogen ratio far more easily than with enteral feeding. However, the concept that

enteral feeding should be preferred whenever possible is gaining acceptance because of the preservation of gut function and avoidance of infectious complications (47). In our opinion the administration of standard enteral formula will be of more importance compared to different compositions of parenteral nutrition but this statement has to be supported by appropriate clinical trials.

Adjunctive therapies

The need for new therapeutic approaches to improve the metabolic and clinical efficacy of nutritional therapy has been emphasized increasingly. Adjunctive therapies in enteral and parenteral nutrition are being actively investigated.

Recently Van den Berghe et al suggested possible endocrine intervention options in critical illness. Studying the effects of either combined peripheral hormonal substitution or hypophysiotropic releasing peptide administration can validate their hypothesis of inappropriate neuro-endocrine function. The latter may demonstrate that selected pituitary-dependent axes can readily be reactivated in the chronic phase of critical illness, with preserved peripheral responsiveness. Intervening at the hypothalamic-pituitary level appears a safer strategy than the administration of peripherally active hormones, as the presence of feedback inhibition protects from dose-related side effects. It remains to be determined whether endocrine interventions in prolonged critical illness will result in beneficial metabolic effects and will, ultimately, accelerate the recovery of those patients who need it most (50).

At the moment administration of growth hormone (GH) in adult and pediatric burn patients showed beneficial effects. However administration of GH in the acute catabolic state is at the moment disputed because of the high mortality found in adult intensive care patients. Administration of exogenous GH during critical illness might give an imbalance between GH and IGF-1which can lead to an inadequate IGF-1 response that may unmask the negative effects of GH.

There is lack of data for a beneficial anabolic effect of insulin in critically ill children. In our opinion supply of insulin should be restricted to treatment of known metabolic disturbances such as hyperkalemia and severe hyperglycemia.

Studies with T_4 and T_3 administration have failed to demonstrate clinical benefit in critically ill adult patients and studies in critically ill children are not performed (51).

New adjunctive therapies with bioactive peptides such as glutamine are a matter of intense discussion. Some studies with glutamine of critically ill adults and premature infants showed beneficial results but it is the question if these results warrant a study in critically ill children.

Novel lipid products such as omega-3 polyunsaturated fatty acids are studied at the moment in combination formula and because of the important properties of these lipids further study will be of interest

Of importance will be to detect the shortage of conditionally essential amino acids, vitamins and trace elements not only in the acute phase but also during recovery. It is of interest if early supplementation of these nutrients will enhance recovery.

Feeding and organ dysfunction

Liver and kidney dysfunction are common complications during treatment of the critically ill child and nutritional support has to be adjusted. Formulas with branched-chain amino acids might relieve encephalopathy in liver failure. Treatment with glucose and essential amino acids may improve outcome and renal function in adult patients with acute renal failure (48). Effects of nutritional support on outcome and survival have to be investigated in critically ill adults and children.

How to feed: administration of enteral and parenteral nutrition

Although there are advantages and disadvantages to the gastric and transpyloric routes of feeding, we recommend transpyloric rather than gastric feeding in the critically ill child. Critical illness can seriously impair gastric emptying despite the presence of a functioning small bowel. We routinely are successful in placing pH-guided transpyloric feeding tubes; ice water and/or erythromycin can be helpful. We start on a low level of continuous feeding in children with high physiologic instability. Otherwise enteral feeding will started within 24 hours with 50% of the desired volume and increased to 100% within 48 hours after admission. If it is not possible to feed transpyloric, continuous gastric feeding will be started and gastric motility agents will be added. Despite it benefits it is not possible to give all patients enteral nutrition. Gastric retention, diarrhea, and abdominal distention can limit the use of enteral feeding. However, the enteral route of feeding should be used, even with small amounts, unless it is absolutely contraindicated (for example bowel obstruction,

intractable diarrhea). To meet nutritional requirements the enteral and parenteral routes should be used simultaneously. The parenteral feeding will be administered either by peripheral infusion or by a central line. Due to the complications such as sepsis with the use of parenteral feeding, we will always try the enteral approach first.

Final remarks

There are several technical considerations and limitations applying indirect calorimetric measurements on a pediatric intensive care. Especially measurements in mechanically ventilated infants necessitating increased inspired oxygen concentrations are difficult to perform and tube leakage should remain below 10%. Being aware of these technical considerations and limitations indirect calorimetry is a useful tool in the concept of nutritional assessment

Indirect calorimetric measurements have broadened our insight in energy metabolism and substrate utilization of the critically ill child. The energy expenditure of the mechanically ventilated critically ill child has been shown to be lower than the energy expenditure for normal healthy children. Utilization of administered glucose and fat seems to have a maximum in the critically ill child, beyond this maximum glucose is converted into fat and fat might be stored in liver and adipose tissue.

To get a better insight in catabolism, besides the metabolic response, the endocrine response of the critically ill child is of interest. The correlation of the endocrine influences on substrate utilization will increase our knowledge about the pathophysiologic alterations in the critically ill child. Further studies should not only try to answer the question which endocrine parameter might be used to predict resolution of catabolism but also give an answer to the question if there is a place for adjunctive endocrine intervention in critically ill children.

It is a challenge to determine the various metabolic, endocrine and nutritional aspects of the critically ill child. Because of the diversity of clinical pictures and the different time course of the various clinical pictures different approaches might be necessary.

Nutritional support, provided in an effort to minimize wasting of macronutrients and micronutrients, to support immune function, and to facilitate tissue repair and wound healing, remains a major part of the management of the critically ill and injured child. Ideally, efficacy should be evaluated not in terms of a laboratory test or a

theoretical advantage but in terms of measurable clinical outcomes such as morbidity, mortality, length of hospital stay, the growth and development. However, at the moment there is only little evidence to prove how critical nutrition is for the critically ill patient and there is a need for prospective, randomized controlled clinical trials (52).

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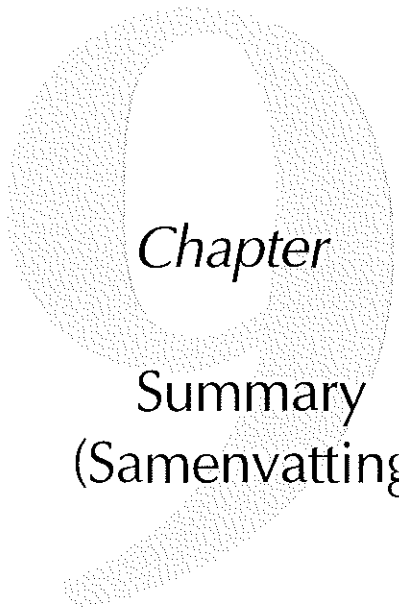

Chapter 9

Summary (Samenvatting)

Summary

Nutritional support is an essential aspect of the clinical management of pediatric intensive care patients because the diversity in clinical presentation and the various age groups dictates a patient tailored approach.

Chapter 1 summarizes the objectives of the present thesis that aimed at:

1 validation of an indirect calorimeter for clinical use in mechanically ventilated children;
2 duration of measurements necessary to estimate accurate 24 hour energy expenditure;
3 energy expenditure and substrate utilization of mechanically ventilated children;
4 evaluation of endocrine and metabolic parameters in the time course of critically ill children to identify parameters that can be used to predict return to anabolism to improve nutritional support.

Chapter 2 provides a general overview of metabolic, endocrine and nutritional aspects of critically ill children. The concept of nutritional requirements has changed from the traditional standpoint (i.e., growth or weight maintenance) to a broader functional outcome. Nutrients not only posses nutritional and metabolic functions but they also actively affect the physiologic and pathophysiologic events. Specific metabolic, endocrine and nutritional assessment parameters have to be determined as an important prerequisite to tailor these nutritional requirements.

In **chapter 3** we tested the accuracy of an indirect calorimeter in a ventilated lung model for measurements of low rates of gas exchange and varying FiO_2. The calorimeter appeared accurate for low levels of oxygen consumption and carbon dioxide production during mechanical ventilation with FiO_2 levels approximating 0.40. With a higher FiO_2 the increase in deviation of VO_2 for single measurements was found to be of clinical relevance. An important cause of the inaccurate measurements with increasing FiO_2 was found to be the increased fluctuation of the delivered FiO_2 on higher levels of FiO_2. This study showed us the technical limitations using an indirect calorimeter in small mechanically ventilated infants.

In **chapter 4** we studied in 19 mechanically ventilated children how accurately total daily energy expenditure of mechanically ventilated can be estimated from periods of less than 24 hours. We found that in a clinical situation in patients with a tube leakage <10% total daily energy expenditure can be estimated from a 2 hour measurement period. In the same patient group we showed that the influence of body temperature resulted in an increase of 6% of energy expenditure per grade Celsius. In another group of 5 mechanically ventilated children with a tube leakage of more than 10% we showed that an increased tube leakage influenced the energy expenditure measurements significantly.

In **chapter 5** we performed indirect calorimetry measurements in a group of 50 mechanically ventilated children to determine the energy requirements. We compared these results with the predicted metabolic rate, the caloric intake and the nitrogen balance. Although there was a close correlation between the measured and predicted energy expenditure the wide range of individual measurements made it obvious that the use of a prediction of energy expenditure is inappropriate for clinical purposes. The ratio of caloric intake/measured energy expenditure was found to be significantly higher in the patients with a positive nitrogen balance compared with those with a negative nitrogen balance. From these findings we stated that feeding according the measured energy expenditure could be a guideline for nutritional support. Furthermore we showed in this study that the respiratory quotient could be used to detect carbohydrate overfeeding which was the case in 6 patients. We postulated that there seems to be a maximum carbohydrate oxidation rate in the individual stressed patient because carbohydrate overfeeding was seen using different levels of carbohydrate intake.

In **chapter 6** we performed further analysis on substrate utilization data in a group of 36 mechanically ventilated patients. We found that fat and glucose utilization were not significantly different in patients with a positive or negative nitrogen balance, despite markedly different substrate intake. We suggested that in patients with a negative nitrogen balance endogenous fat was utilized and in patients with a positive nitrogen balance fat storage would occur. Furthermore we found that protein utilization was significantly lower in children with a positive nitrogen balance. This could be explained by the higher protein intake and/or by the nitrogen sparing effect of a higher fat intake. In this study the measured respiratory quotient was compared with the respiratory quotient of the macronutrients administered and was found to be helpful in differentiating under- and overfeeding.

In chapter 7 we investigated the endocrine and metabolic stress response in a group of 16 children with meningococcal sepsis. Comparison between non-survivors and survivors showed significant differences between hormones of the pituitary-adrenal axis, thyroid hormones and non-esterified free fatty acids. Non-survivors showed an inadequate response cortisol response in combination to very high ACTH levels whereas survivors showed a normal stress response with significantly higher cortisol levels in combination with moderately increased ACTH levels. The cause of the endocrine and metabolic differences might be the impaired peripheral circulation reflected in increased lactate levels. Children who survived showed a significant decrease in non-esterified free fatty acids and in hormones of the pituitary-adrenal axis acids 48 hours after admission. A circadian cortisol rhythm however was still absent. Despite changes in the level of thyroid hormones survivors and non-survivors these levels were in both groups below the normal reference levels. In survivors after 48 hours most striking changes in thyroid function tests were seen in significant decreased levels of rT3 and an increase ratio of T3/rT3. From this study we concluded that the observed endocrine and metabolic changes are of possible clinical importance to design further therapy. At this moment a study to assess the beneficial effects of steroid supplementation during meningococcal sepsis is warranted.

In **chapter 8** we discussed our results in context with the literature. We discussed the limitations of indirect calorimetry in mechanically ventilated children and the challenge to determine the various metabolic, endocrine and nutritional aspects of the critically ill child. We provided a scheme for levels of nutritional assessment and recommended a scheme for nutritional support for the critically ill child.

Samenvatting

Voeding is een essentieel onderdeel van de behandeling van ernstig zieke kinderen op een pediatrische intensive care. De diversiteit van klinische ziektebeelden in verschillende leeftijdsfasen maakt dat het voedingsbeleid aan het individu en aan de fase van ziekzijn moet worden aangepast.

Hoofdstuk 1 geeft een samenvatting van de vraagstellingen in dit proefschrift:

1 Wat is de klinische bruikbaarheid van een indirecte calorimeter, een apparaat wat in staat is indirect het energieverbruik te meten, bij kinderen die kunstmatig worden beademd?
2 Hoe lang moet minimaal een energiemeting duren zodat deze meting representatief is voor het energieverbruik van 24 uur?
3 Wat is het energieverbruik en hoe worden de voedingsstoffen verbrand bij kinderen die kunstmatig worden beademd?
4 Leidt evaluatie van metabole en hormonale veranderingen bij ernstig zieke kinderen tot een betere voorspelling van herstel en opbouw van de stofwisseling zodat deze kinderen beter gevoed kunnen worden?

Hoofdstuk 2 laat een algemeen overzicht zien van de stofwisseling, de hormonale- en de voedingsaspecten van het ernstig zieke kind. De opvatting over de voedingsbehoefte van het ernstig zieke kind is veranderd van een traditioneel standpunt, waarbij gekeken werd naar groei en ontwikkeling, naar een standpunt met een bredere kijk op het functioneren van het kind. Voedingsstoffen zijn niet alleen belangrijk voor de directe energiestofwisseling en opbouw van het lichaam, maar zijn ook actief betrokken bij het goed functioneren van het lichaam tijdens allerlei omstandigheden. Het is van belang te zoeken naar specifieke stofwisselingproducten (metabole veranderingen), veranderingen van hormonen en meetmethoden die de voedingstoestand in kaart kunnen brengen, om op maat aan de voedingsbehoefte van het ernstig zieke kind te kunnen voldoen.

In **hoofdstuk 3** werd de nauwkeurigheid van een indirecte calorimeter (energiemeter) voor gebruik tijdens kunstmatige beademing getest. Hierbij werd gebruik gemaakt van een kunstlong waarin een kleine butaanvlam brandde waarbij weinig zuurstof werd verbruikt (consumptie) en weinig kooldioxide werd geproduceerd. Deze vlam werd beademd met een klein volume met een oplopende hoeveelheid zuurstof. De calorimeter bleek tot een zuurstofpercentage van 40% nauwkeurig waarden voor zuurstofconsumptie en kooldioxideproductie te kunnen meten. Bij een hoger percentage zuurstof week de gemeten zuurstofconsumptie in individuele gevallen te veel af van wat klinisch nog acceptabel was. Een belangrijke oorzaak voor deze onnauwkeurigheid bleek te zitten in het feit dat de zuurstof die uit de beademingsmachine komt bij hogere percentages te sterk fluctueert. Deze studie toonde ons de technische beperkingen van een indirecte calorimeter indien deze gebruikt wordt bij zuigelingen die kunstmatig worden beademd.

In **hoofdstuk 4** werd bij een studie van 19 kunstmatig beademde kinderen aangetoond dat een meetperiode van 2 uur een representatieve afspiegeling was voor het energieverbruik van 24 uur, mits de lekkage van de tube waarmee het kind werd beademd niet meer dan 10% bedroeg. Tevens werd aangetoond dat een verhoging van de lichaamstemperatuur met een graad Celsius een verhoging van het energieverbruik van 6% gaf. Bij een groep van 5 kinderen met een wisselende tubelekkage van meer dan 10% werd aangetoond welke invloed deze tubelekkage had op het gemeten energieverbruik.

In **hoofdstuk 5** werd de indirecte calorimeter gebruikt om het energieverbruik bij een groep van 50 kunstmatig beademde kinderen te meten. Deze resultaten werden vergeleken met waarden voor energieverbruik voorspeld aan de hand van standaardformules. Tevens werd het gemeten energieverbruik vergeleken met de actuele energie-inname en de actuele eiwitinname met de eiwituitscheiding (stikstofbalans). Deze studie liet zien dat ondanks het feit dat er voor de gehele groep kinderen een duidelijk verband werd gevonden tussen gemeten en voorspeld energieverbruik, de standaardformule voor de klinische toepassing niet bruikbaar was vanwege een enorme spreiding van de individuele metingen. Verder werd aangetoond dat de verhouding energie-inname versus gemeten energieverbruik duidelijk hoger was bij kinderen met een positieve stikstofbalans ten opzichte van kinderen met een negatieve stikstofbalans. Wij stelden dan ook dat een voeding die een energie hoeveelheid bevat welke overeenkomt met het gemeten energieverbruik als richtlijn gebruikt dient te worden om het ernstig zieke, kunstmatig beademde kind te voeden.

De verhouding van de gemeten koolzuurproductie en de zuurstofconsumptie wordt uitgedrukt in het respiratorisch quotiënt (RQ). Deze waarde kan gebruikt worden om de bijdrage van koolhydraten en vetten in de stofwisseling te berekenen. Als de waarde boven de 1 komt betekent dit dat koolhydraten worden omgezet in vet en er sprake is van overvoeding met koolhydraten. Dit was het geval bij 6 van de 50 gemeten kinderen. Omdat bij verschillende hoeveelheden van glucose-inname de RQ-waarde boven de 1 was, veronderstelden wij dat het ernstig zieke kind een individueel bepaald maximum heeft om glucose te kunnen gebruiken voor de energie-stofwisseling.

In **hoofdstuk 6** werd er in een groep van 36 kunstmatig beademde kinderen verder onderzoek verricht naar de manier waarop de voedingsstoffen (koolhydraten, vetten, eiwitten) in het lichaam worden verbrand. Wanneer gekeken werd naar de stikstofbalans, positief of negatief, werd er geen verschil gezien in de mate van verbranding van koolhydraten en vetten, ondanks het feit dat er een verschillende inname van deze stoffen bestond. Wij suggereerden dat bij de kinderen met een negatieve stikstofbalans lichaamsvet wordt verbrand als energiebron en dat bij kinderen met een positieve stikstofbalans het vet wat het lichaam niet direct nodig heeft als energiebron, wordt gestapeld in het lichaam. Daarnaast werd aangetoond dat bij de kinderen met een positieve stikstofbalans het eiwitverbruik duidelijk lager was. Dit kon enerzijds verklaard worden door de hogere eiwitinname of anderzijds door het feit dat voeding met een hoger vetgehalte voor een deel kan voorkomen dat eiwit wordt afgebroken. In deze studie werd het RQ, gemeten met de calorimeter, vergeleken met het "RQ" berekend uit de energiebijdrage van koolhydraten en vetten in de voeding. Vergelijk van deze twee RQ's bleek van waarde om een onderscheid te kunnen maken tussen overvoeding en ondervoeding.

In **hoofdstuk 7** werden de metabole en hormonale veranderingen bestudeerd bij een groep van 16 kinderen met een ernstige vorm van meningococcenziekte (nekkramp met bloedvergiftiging). Met betrekking tot de spiegels van hypofyse-, bijnier-, en schildklierhormonen, en in de productie van vrije vetzuren in het bloed, werden duidelijke verschillen gezien tussen de kinderen die overleden en de kinderen die overleefden. Bij de kinderen die overleden waren de lage waarden van het cortisol (bijnierhormoon) en de hoge waarden van het adrenocorticotroop hormoon (hypofyse) opvallend, hetgeen wijst op een inadequate respons van de bijnier bij deze groep. De oorzaak voor de gevonden verschillen binnen deze 2 groepen zou gezocht kunnen worden in de zeer slechte doorbloeding van de weefsels bij de kinderen die overleden, hetgeen afgeleid kon worden aan een duidelijk verhoogde waarde van het melkzuur (lactaat) in het bloed. De kinderen die overleefden werden gedurende 48 uur gevolgd.

Het gehalte van de hormonen van de hypofyse en de bijnier namen daarbij sterk af. Het normale dagritme van de afgifte van het bijnierhormoon cortisol was afwezig. De waarden van een aantal schildklierhormonen bleven verlaagd, alleen de waarde van het schildklierhormoon rT_3 liet een duidelijke verandering zien.

Naar aanleiding van de bevindingen in deze studie concludeerden wij dat de veranderingen in hormoonspiegels en stofwisselingsproducten van mogelijk klinisch belang zouden kunnen zijn in het onderzoek naar aanvullende therapie voor deze kinderen. Op dit moment bestaat dan ook de vraag verder onderzoek te kunnen verrichten naar het voordelig effect van steroïden bij kinderen met een meningococcenziekte.

In **hoofdstuk 8** werden de resultaten van onze studies in context met de literatuur besproken. We bediscussieerden de beperkingen van het gebruik van de indirecte calorimeter voor gebruik bij kunstmatig beademde kinderen en de uitdaging om de verschillende metabole, hormonale en voedingsaspecten van het ernstig zieke kind te bepalen. Wij maakten een schema waarbij verschillende niveaus werden aangegeven om de voedingstoestand van het ernstig zieke kind te kunnen bepalen. Tot slot kwamen wij tot een aanbeveling van een adequaat voedingsschema voor het ernstig zieke kind.

10

Chapter

Dankwoord
Curriculum vitae
List of publications

Dankwoord

Een woord van dank gaat allereerst uit naar alle kinderen en hun ouders voor hun bereidheid deel te nemen aan dit onderzoek. Daarnaast naar het personeel van de afdeling intensive care pediatrie voor hun belangrijke bijdrage aan alle uitgevoerde onderzoeksactiviteiten.

Ik ben in de afgelopen jaren ondersteund door veel studenten van wie ieder een bijdrage leverde aan een deel van het onderzoek: zonder hun hulp was ik nooit zo ver gekomen. Niet alleen dank ik mijn "blondies": Jennifer Verhoeven, Floortje van Eijck, Marinke Westerterp en Femke de Groof, maar ook Eleonora Jongen, Nicolette Arends, Marieke Meinardi, Annemarie Bruynzeel, Boukje van Rijn, Erik van de Klaarwater en Sander Koëter. Arts-onderzoeker Esther de Kleijn wil ik bedanken voor haar bereidheid mee te werken en haar eigen onderzoeksactiviteiten uit te breiden. Daarnaast verzorgde zij een belangrijk deel van de begeleiding van de studenten.

Onontbeerlijk was de ondersteuning van Frans Jacobs en Wim Hop. Frans was onmisbaar als technisch steunpunt en "regelneef" voor allerlei software- en hardware-benodigdheden. Daarnaast heeft zijn enthousiasmerende en relativerende kijk op veel andere zaken dit plan doen slagen. Ook Wim hield de kijk op het leven duidelijk, maar dan vanuit een "statistisch" oogpunt.

Als medegrondleggers van mijn onderzoek wil ik graag Jan Hazelzet en Anita Hokken bedanken. Uit het woud van hun ideeën heb ik uiteindelijk mijn plan getrokken. Ook mijn collegae Edwin van der Voort, Matthijs de Hoog en Corine Buysse dank ik voor de ondersteuning tijdens mijn onderzoek.

Ik dank mijn promotoren Hans Büller en Dick Tibboel waarmee ik van het begin af aan een zeer plezierige samenwerking heb gehad. De snelheid waarmee dit proefschrift tot stand is gekomen is mede aan hen te danken.

Marijke van Balen, Annelize van Dijk, Arend en Rita Sesink-Clee en Monique van Rooyen dank ik voor de minutieuze correcties en de fraaie vormgeving van mijn proefschrift.

De paranimfen Sandra van den Berg en Frank Joosten dank ik dat zij mij al deze jaren terzijde hebben willen staan.

Lieve Lia, Pieter, Max en Daniek: het boek is klaar. We kijken terug op een prettige tijd. Ook ik heb genoten van alle momenten dat ik thuis was, op school kwam, voetbalde en op tijd was voor het eten. Nog maar een boekje?

Curriculum vitae

De auteur werd geboren op 19 mei 1960 te Nijmegen. In 1978 behaalde hij het VWO-diploma aan het Canisius College/Mater Dei te Nijmegen. In datzelfde jaar begon hij met de studie Scheikunde aan de Katholieke Universiteit te Nijmegen. Na het halen van het propedeuse-examen in 1979 ging hij verder met de studie geneeskunde. In maart 1987 behaalde hij het artsexamen. Van 1987 tot 1988 was hij werkzaam als intensivist op de volwassen intensive care van het Catharina Ziekenhuis te Eindhoven (hoofd: dr. W. van der Ham). Op 1 juni 1988 begon hij zijn opleiding tot kinderarts op de afdeling kindergeneeskunde van het Catharina Ziekenhuis te Eindhoven (opleider: dr. J.J.J. Waelkens). Op 1 april 1990 werd de opleiding voortgezet in het Sophia Kinderziekenhuis (hoofd en opleider: prof. dr. H.K.A. Visser) Op 1 juni 1993 werd hij ingeschreven in het specialistenregister. In maart 1993 vervolgde hij de opleiding tot kinderarts-intensivist op de afdeling Extra Zorg van het Sophia Kinderziekenhuis (hoofd: drs. E. van der Voort). Twee jaar later werd deze opleiding afgerond en werd hij geregistreerd als subspecialist. Vanaf 1 juni 1993 is hij als staflid verbonden aan de subafdeling intensive care pediatrie van het Sophia Kinderziekenhuis (hoofd: prof. dr. H.A. Büller). Het onderzoek dat heeft geleid tot dit proefschrift werd uitgevoerd op de afdeling intensive care pediatrie en bij de centraal instrumentele dienst van het Sophia Kinderziekenhuis.

Tot zijn aandachtsgebieden behoren tevens alle aan slaap gerelateerde ademhalings-problemen bij kinderen, de thuiszorg van kinderen met een tracheacanule en de thuiszorg van kinderen die bewaakt worden met een hartslag-ademhalings monitor. Sinds 1997 is hij medisch adviseur van TEFA-Portanje op het gebied van thuis-monitoring en voeding. Daarnaast is hij secretaris van de sectie intensive care voor kinderen van de Nederlandse Vereniging voor Kindergeneeskunde.

De laatste 5 jaar probeert hij het conditionele niveau van medewerkers van het Academisch Ziekenhuis Rotterdam te verbeteren door het organiseren van roei-trainingen en wedstrijden voor de AZR bedrijfsacht. Hij is getrouwd met Lia Schoots, klinisch geriater en heeft 3 kinderen, Pieter, 7 jaar, Max, 6 jaar en Daniek, 3 jaar.

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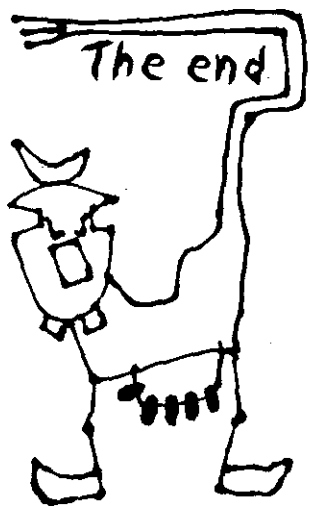
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