Aspects of protein metabolism in children in acute and chronic illness
Geukers, Vincent

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General discussion
INTRODUCTION

In both acute and chronic disease states, negative protein balance with loss of lean body mass (LBM) has detrimental effects on short-term and/or long-term clinical outcome. In critically ill children, ongoing proteolysis and loss of protein mass is associated with a higher risk of infections, persisting critical illness, and increased length of stay (LOS) in the pediatric intensive care unit (PICU) (1, 2). Additionally, a malnourished state due to chronic illness increases the risk of respiratory infections, hospitalization or long-term institutional care, and is associated with an increase in economic burden (3, 4). Over the past decade, overall mortality rates of specific childhood diseases have improved at the expense of a growing population of chronically ill children (5). This has resulted in an increased sub-population of PICU patients with underlying chronic illness and subsequent malnutrition upon admission (6, 7).

In a systematic review of protein balance studies in mixed-population critically ill children it has been shown that in this population a positive protein balance can relatively easily be achieved by moderate intake of calories: 57 kCal/kg/d and protein: 1.5 g/kg/d (8). At present, it is not known if a higher protein intake can further stimulate protein synthesis and improve net whole-body protein balance.

The principal aim of this thesis was to investigate the effect of high protein (HP, 5 g/kg/d) versus, age-related normal protein (NP) intake, on whole-body protein synthesis (WBPS), -breakdown (WBPB), and net balance in children with acute or chronic disease using stable isotopic infusion technique. Additionally, since initial administration of basic glucose infusions with only slow introduction of macronutrients is standard care in many ICUs, we studied the effect of glucose intake-induced hyperinsulinemia on whole-body protein metabolism in children following cardiac surgery. As a model for these different disease states, we studied respectively, young children following cardiac surgery, and school age children with stunted linear growth due to cystic fibrosis (CF).

Young children following cardiac surgery form a relatively homogenous group with respect to age and weight distribution, age-related normal values for LBM accretion, and a uniform stress model in terms of surgical procedure and the use of a cardiopulmonary bypass (CPB) circuit. Therefore, this group serves as a suitable model for studying the effect of protein intake in acutely ill children. In children with CF, increased muscle mass and LBM are important for normal growth and good pulmonary function (9–11). However, due to both chronic and superimposed acute inflammation, increased proteolysis and episodes of negative protein balance occur, resulting in stunted linear growth in the majority of patients. Therefore,
pediatric CF is both a relevant and suitable model for studying the effects of different levels of dietary protein intake on protein balance in chronic disease.

In the final part of this thesis, in anticipation of the finding that it is important to deliver an adequate amount of protein to critically ill children, we studied the prescription and delivery of calories and protein in our tertiary PICU, and the effect of a feeding algorithm together with the institution of a nutritional support team (NST) on actual energy and macronutrient intake in our patients.

**MAIN RESULTS OF OUR STUDIES**

In our studies in very young children (< 36 mos) following low-to-moderate-complexity cardiac surgery, we demonstrated that glucose infusion-induced hyperinsulinemia does not reverse negative net whole-body protein balance in the immediate postoperative phase. Additionally, we showed that in this population net whole-body protein balance is positive after early enteral intake of the internationally recommended age-related ‘normal’ amount of protein (NP, 2 g/kg/d) (12). Provision of a short-term HP (5 g/kg/d) diet does not result in further stimulation of WBPS and increased net protein balance. Therefore, in our view, neither glucose infusion-induced hyperinsulinemia, nor higher than ‘standard’ protein intake, can be recommended over early intake of age-related normal amounts of protein in the immediate postoperative phase after pediatric cardiac surgery.

In contrast to children with acute illness, we demonstrated in a group of chronically ill school-age children with CF-related growth stunt that whole-protein balance could be drastically improved as a result of 30% enhancement of WBPS during a 4-day HP diet, compared to the lower (1.5 g/kg/d) and upper (3 g/kg/d) limits of internationally recommended, age-related protein intake (12). Whether these effects would be sustained with a prolonged diet, and thus lead to catch-up linear growth and improvement of body composition, requires further investigation.

In a study in our own tertiary PICU, we found that only 40% and 70% of our patients received appropriate nutrition on days 1 and 2 respectively, resulting in overall protein malnutrition in almost 85% of the patient days. The major cause of malnutrition on our PICU was inadequate prescription of nutrition, rather than insufficient delivery. Following the introduction of a feeding algorithm and a nutrition support team (NST), the percentage of delivered enteral nutrition doubled from 40% to 78% on day 1, and increased from 60% to 92% on day 2 with > 85% of nutritional targets being reached on day 3. We concluded that an NST
plays an important role in improving prescription and consecutive delivery of calories and macronutrients to patients on a PICU.

CRITICAL APPRAISAL

In contrast to our studies in young children following cardiac surgery, we observed increased WBPS and net protein balance due to a high-protein intake in chronically ill school-age children with CF related growth stunt. Between these two experimental settings, the main differences were: patients with acute versus chronic illness, and very young age (< 3 yrs) versus school-age (7–12 yrs) patients. In the following critical appraisal of our results we will put forward the possible explanations for the different effects of a high protein diet that we have observed in these study groups.

‘Normal’ and ‘high’ protein intake compared to physiologic needs

According to the 2007 WHO/FAO/UNU evidence-based recommendations for protein intake, the mean safe level (i.e. the estimate for physiologic need for protein intake plus 2 SDs) for children < 2 yrs gradually decreases from 1.8 g/kg/d at age 1 mo to 1.0 g/kg/d by age 2 yrs (13). This decrease in recommended protein intake is congruent to the decrease in protein accretion rate from birth to the age of 2 yrs. However, in the Netherlands, amongst many other countries, this upper safety limit has been adopted as recommended daily allowance (RDA) for protein (14). Moreover, a study shows that median actual intake in babies and toddlers is even higher at 1.8–3.5 g/kg/d (15). With recommendations and actual intake higher than estimated for physiological needs, in our studies, a ‘normal’ protein intake of 2 g/kg/d might already have been relatively high for the studied age group, without expected additional effect of an even higher protein intake of 5 g/kg/d.

In school-age children, the situation is reversed. A study in healthy school-age children using a stable-isotope technique determined protein requirements to be 1.3 to 1.55 g/kg/d (16). However, currently recommended protein intake for 9–13 yr old Dutch children is 0.8–1.2 g/kg/d, with a population safe upper limit of 4 g/kg/d (14). Therefore, the RDA for protein in this age group might be too low for healthy children. In school-age children with CF, despite the fact that 25 to 30% of patients have LBM depletion with loss of muscle mass (17), literature on optimal protein intake is scarce. Historically in CF, scientific and therapeutic emphasis has been on ‘high-fat-high-energy’ diet, with use of pancreatic enzyme replacement therapy. As far as we are aware, there is only one pediatric study using a stable isotope technique. This
was carried out in a limited number of children with CF and demonstrated a 70% increase of WBPS and balance after feeding with a leucine-rich essential amino acid (AA) mixture, when compared to an iso-nitrogenous AA mixture (18). The results of three long-term outcome studies using enriched, oral diets with different amounts (between 0.8 and 1.2 g/kg/d) of protein intake are contradicting (19–21). International guidelines provide no recommendations for optimal protein intake in children with CF (22–25). In our study in children with CF, we have demonstrated that in this population optimal protein intake might be at the high end of the spectrum between recommended and safe protein intake in the general age-matched population.

In conclusion, in young children following cardiac surgery, a possible explanation for the absence of observed effect on WBPS and balance of HP intake compared to NP diet, is partly due to the fact that NP intake might already be in surplus of age-related physiological needs. In contrast, in school-age children with CF, optimal protein intake has been less investigated, and might lie at the high end of the spectrum between recommended and safe protein intake in the general age-matched population.

**Acute versus chronic illness**

In our studies, we have observed that in acutely ill children in the immediate postoperative phase following cardiac surgery, the net negative whole-body protein balance in the absence of AA can be reversed to a positive balance with NP intake of 2 g/kg/d. This is an important finding, since 50% of the cumulative protein deficits in PICU patients are caused within the first 48 hrs of admission (26). We did not find an additional effect on WBPS and balance of HP intake of 5 g/kg/d compared to NP intake. In fact, we observed increased oxidation and higher blood urea nitrogen concentration as indicators of excess AA intake in the HP group, compared to the NP group.

In a small study in neonates (n = 18) following general surgery, Duffy et al showed an improvement of the protein balance 72 hrs after surgery due to decreased endogenous protein breakdown in the group with AA intake of 3.9 ± 0.5 g/kg/d, compared to normal protein intake of 2.3 ± 0.4 g/kg/d (27). However, in this study, the high protein intake group also received a higher amount of total calories compared to the normal protein group (91 and 75 kCal/kg/d, respectively). Therefore, the measured effect cannot be assumed as being solely attributable to a higher protein intake. In a systematic review in low birth weight infants, Premji et al identified 6 studies that demonstrated improved nitrogen accretion rates with high protein intakes of 4–6 g/kg/d, compared to age-related reference protein intake of 3 g/
kg/d (28). However, the same studies also found adverse metabolic effects such as azotemia and metabolic acidosis, and information on clinically relevant outcome measures were lacking (28). Five out of six studies predating 1995, in a time in which the AA balance of feeding solutions did not meet present-day standards, resulted in azotemia.

Typically, critical illness causes a hypermetabolic stress response characterized by mobilization of nutrients and energy via lipolysis, proteolysis, glycogenolysis and gluconeogenesis (1, 29, 30). In addition, in cardiac surgery, use of a cardiopulmonary bypass circuit (CPB) induces complement activation, endotoxin release, leukocyte activation, and the release of many pro-inflammatory mediators, adding to the stress response (31). However, in newborns and infants following cardiac surgery, the hypermetabolic response is only short-lived or can be altogether absent, with return to baseline levels < 48 hrs (29, 32–34). These observations are in concert with other studies in infants that also reported only a limited stress response on day 1 after general surgery, and in mechanically ventilated infants with viral respiratory tract infection, with a prompt resolution within 48 hrs (35–40). An explanation for this phenomenon is the immaturity of the neonatal immune system which can react to injury with a decreased hyper-inflammatory response (41, 42). Newborns and infants react to cardiac surgery and exposition to a CPB circuit with a pro- and anti-inflammatory response, without tendency to the extremes of either side (43). Additionally, it has been hypothesized that in post-surgical neonates a superimposed (hypermetabolic) stress response is lacking due to an obligatory redirection of energy, normally used for growth, to fuel the stress response (38). Our observation that a positive protein balance in young children following cardiac surgery can be achieved by a NP intake of 2 g/kg/d is in concordance with this hypothesis.

We concluded that in acutely ill young children in the immediate postoperative phase following cardiac surgery, the inflammatory and metabolic effects of disease are limited and short-lived. In this setting, protein synthesis is maximally stimulated by early (< 48 hrs) enteral intake of a normal amount of protein (2 g/kg/d), with maximal suppression of proteolysis by a normal carbohydrate intake (6–7.5 mg/kg/min), which results in a net positive whole-body protein balance.

Chronic diseases, such as chronic obstructive pulmonary disease (COPD), asthma and CF are characterized by ongoing low-grade systemic inflammation and intercurrent infections (44, 45). The liver, as the main production site of acute phase reactants, extracts an increased proportion of dietary AAs to support this inflammatory response (first-pass effect) (46). In addition, the extraction of certain dietary essential AAs results in an unbalanced AA profile in the systemic circulation, which is suboptimal for skeletal muscle anabolism (47). As a result, in children with chronic inflammation due to CF, decreased peripheral protein synthesis...
(muscle) and negative net protein balance cause insufficient gain of LBM and result in stunted linear growth (48, 49). In contrast to acutely ill children, we were able to stimulate protein synthesis and improve whole-body protein balance at a HP intake of 5 g/kg/d, compared to a NP intake of 1.5 and 3 g/kg/d, in stunted children with CF. We speculate that this was the result of surplus amounts of AAs with the HP diet, such that increased splanchnic extraction had proportionally less influence on post-portal AA profile.

Specifically in CF, it is interesting to appreciate the role of the anabolic hormone insulin, whose production is reduced as a result of pancreatic insufficiency (50). Insulin has proteolysis-inhibiting properties (51). Of all the AAs, leucine is known to have the strongest insulin-secretion stimulating properties (52). Interestingly, with increasing intake of protein (and leucine, concomitantly) we observed a trend towards higher plasma insulin concentrations at equal carbohydrate intake. Simultaneously, there was a trend towards a decrease in protein breakdown, although this was not statistically significant.

We conclude that in stunted school-age children with CF, higher amounts of dietary protein than currently recommended improves protein balance. This is caused by increased protein synthesis, via improvement of systemic AA availability. Additionally, AA-induced higher plasma insulin concentrations might contribute to this effect. In children with CF, long-term outcome studies are needed to examine the effect on linear growth and body composition of a HP diet.

**Pediatric versus adult critical illness**

A systematic review of protein balance studies in mixed-population critically ill children shows that in this population a positive protein balance can relatively easily be achieved by moderate intake of calories and protein 1.5 g/kg/d (8). This is in agreement with our own observations. However, to date, there are no studies that have demonstrated a correlation between improved protein balance and better long-term clinical outcome measures. As previously discussed, higher amounts of protein intake have no clear additional effect on protein balance, and may in fact be harmful.

In contrast, a recent systematic review of 13 studies in mixed population ICUs demonstrated that the optimal -in terms of protein balance- and safe -in terms of side effects- protein intake in critically ill adult patients might be as high as 2.0–2.5 g/kg/d (53). This is almost three times higher than the recommended amount of 0.8 g/kg/d protein intake in metabolically stable adult patients and healthy individuals (54). It is also higher than the recommended intake of 1.5 g/kg/d in a frequently cited study in the literature regarding protein provision in critically ill adults (55).
Additional to the aforementioned fact that in young children NP intake might already be in surplus of age-related physiologic needs, we hypothesize that other factors may play a role in the striking difference in the effect on protein balance of HP diet in children and adults.

Firstly, within comparable diagnostic groups, the inflammatory and nutritional response to illness is age-related. In reaction to elective cardiac surgery, as opposed to adults, infants and young children show only a short-lived and mild stress response (32, 33, 56–58). This relatively mild, short-lived inflammatory and metabolic stress response to injury and infection with prompt resolution within 48 hrs, can also be seen in children after general surgery, and in mechanically ventilated infants with viral respiratory tract infections (35, 37, 38, 40, 59).

Additionally, the incidence of multi-organ failure (MOF) following severe trauma is estimated to be only 3% in children < 16 yrs with a mortality rate of 17%, compared to 25% and 35% in adults, respectively (41, 60). Also, acute respiratory distress syndrome (ARDS) in response to infection or trauma is also much more uncommon in children than in adults (13 versus 79 cases per 100,000 person-years) (61, 62). As a result of different inflammatory reactions to illness, a substantial number of patients in an adult ICU, in contrast to PICU patients, suffer from so called “prolonged critical illness” (63, 64). This condition is characterized by ongoing inflammation and a catabolic state lasting a number of weeks and resulting in high mortality (65). In the Netherlands, overall crude mortality on the adult ICU is 9% (source: NICE, Nationale Intensive Care Evaluatie, The Dutch Intensive Care Registry), compared to only 3% on a PICU (63).

It is hypothesized that in neonates and young children the innate anti-inflammatory status, which prohibits the fetus from an immune response to maternal antigens, is preserved to such an extent that they react with increased anti-inflammatory IL-10 and decreased proinflammatory interleukin production to stress (42). The concept of a gradually arising low grade, chronic pro-inflammatory status with aging, which is absent or not fully developed in the early phase of life, is referred to as “inflammaging” (66).

In a more catabolic population, nutritional interventions can be expected to have greater impact than in short-lived critical illness in children (65). Alternatively, in neonates after surgery, it is hypothesized that a measurable, superimposed (hypermetabolic) stress response is lacking due to an obligatory redirection of energy and AAs, normally already used for growth, to fuel the stress response (38).

Secondly, due to small PICU population sizes, low number of ventilation days, short LOS on a PICU, and an already low mean mortality rate (3%), nutritional interventional studies in PICU patients often lack statistical power to demonstrate changes in clinically relevant outcome
measures. As an example, in a trial with the primary aim of reducing LOS on a PICU by 1 day via early start of enteral nutrition, an estimated sample size of 3,948–5,590 patients was needed for sufficient power of the study (67). In order to overcome this methodological problem, in pediatric critical care literature, often different patient groups are combined within a study (e.g., post surgery, sepsis, trauma, respiratory failure, congenital heart disease, burns, etc.). As an example, in the aforementioned systematic review of protein balance studies in critically ill children, the results of very heterogeneous diagnostic groups were presented in a cumulative fashion (8). This methodology does not appreciate the differences in inflammatory and metabolic stress response between diagnostic groups. The importance of strict stratification of patient categories has been strikingly illustrated during the past decade by the discussion on the potential benefit of tight glycemic control in adult critically ill patients that turned out to be beneficial for the surgical but not medical population. Moreover, in the future, the subgroup of technology-dependent patients with chronic illness and concomitant malnutrition upon admission will further expand, both in number and in diversity (63, 68). At present, it is not clear what the specific metabolic effects are of underlying chronic illness, congenital abnormalities, or increased work of breathing. Therefore, in future research the nutritional demands of these children should be studied.

The above mentioned arguments make a strong plea for increased and extensive collaboration within a national network of nutritional specialists. This would enable sufficiently powered studies that aim at improving relevant long-term (linear growth, body composition, muscular strength, quality of life), as opposed to short-term (ventilator days, LOS, mortality) or surrogate (delivered percentages of goals) outcome measures (69).

**IMPLICATIONS FOR NUTRITIONAL SUPPORT IN THE PICU**

Since 2007, as part of the performance indicators for healthcare institutions, the Dutch Health Care Inspectorate (HCI) has performed an annual national survey of risk factors for clinical malnutrition. In their latest report, the HCI published that 77% of adult patients and 63% of pediatric patients were screened for malnutrition during the first 4 days following hospital admission (70). Of the adults and children who were screened, 46% and 77% respectively were reported as underfed with adequate protein intake (70). In the PICU population, malnutrition can be reduced by early recognition of at risk patients by means of prompt, regular and comparative nutritional assessments (71).

We have demonstrated that on our PICU, after the introduction of a nurse-driven feeding algorithm and the introduction of a nutrition support team (NST), the percentage of delivered
ental nutrition doubled from 40% to 78% on day 1, and increased from 60% to 92% on day 2 with > 85% of nutritional targets being reached by day 3. We concluded that a bottom-up feeding protocol, together with an NST play an important role in increasing prescription and consecutive delivery of calories and macronutrients to patients in the first few days following admission to a PICU. This improvement of nutritional care practice is relevant, since 50% of the cumulative protein deficits in PICU patients exist within the first 48 hrs of admission (26). Moreover, despite their higher disease severity score, we were able to feed a higher percentage of patients after introduction of the nutrition protocol, compared to the control period. This has also been demonstrated in adult critically ill patients (72). This means that improving macronutrient intake is also feasible and safe in patients with more severe illness and consequent higher risk for clinical malnutrition. Our observations are in line with other publications in critically ill children (73–75). Also, in adult intensive care settings, a nutrition support algorithm can improve energy and protein delivery to patients (72, 76). The important facilitating role of the intensive care nurse for the successful implementation of a nutrition guideline has been acknowledged (77).

To date, however, there is no evidence supporting the notion that protocol- and NST-driven nutrition improve the clinically relevant outcomes of the PICU population (78). The only strong correlation that exists between a nutritional intervention and clinically relevant outcome in both critically ill adults and children, is the early (< 24 hrs after admission) start of enteral nutrition (EN). In adult surgical and medical ICU patients, early EN significantly reduces mortality and infection rate (79–81). Additionally, a recent multi-center trial including > 5,000 critically ill children from 12 North-American PICUs with LOS of ≥ 96 hrs, showed a strong and statistically significant association between early EN and lower mortality in a subgroup of the PICU population (odds ratio, 0.51; 95% confidence interval: 0.34 to 0.76, p = 0.001) (67).

In our view, these results convincingly show that the efforts of an NST, enforced by a feeding algorithm, should be directed towards prompt initiation of EN within 24 hrs after admission. As previously discussed, age-related intakes of carbohydrate and protein are sufficient to meet dietary needs in critically ill children, provided that they are delivered in the early phase of admission. Additionally, NSTs should focus on the identification of high-risk patients upon admission (e.g., patients with predicted prolonged critical illness on admission, and recognition of patients who are already malnourished upon admission).
CONCLUSIONS

We conclude that in catabolic young children following cardiac surgery, protein synthesis and whole-body protein balance cannot be reversed by high carbohydrate intake-induced hyperinsulinemia. In this population, anabolism can be induced by age-related standard intakes of carbohydrate and protein (NP), but can not be further stimulated by isocaloric HP intake. Possible explanations are a short-lived and mild course of the postoperative inflammatory and hypermetabolic stress response, and an already relatively high provision of proteins by the age-related standard diet, compared to actual physiologic needs. To date, in young children following cardiac surgery, a higher than standard protein intake can not be recommended. In the field of nutritional therapy in the PICU, future research should focus on the development of a more balanced AA composition of feeding formulas, and the supplementation of essential and situational dispensable AA. Studies should be adequately statistically powered in order to demonstrate effect in clinically and metabolically distinct patients groups, with relevant long-term, as opposed to short-term clinical or surrogate, outcome measures.

In contrast, in chronically ill school-age children with CF and stunted linear growth, HP intake can improve net whole-body protein balance by enhancing protein synthesis together with a statistically non-significant blunting effect on endogenous proteolysis, compared to age-related NP intake. In this patient population, increased catabolism due to a protracted pro-inflammatory state, together with too low protein intake in the recommended standard diet, might explain this positive effect on protein balance of HP diet. In children with CF, long-term outcome studies are needed to examine the effect on linear growth and body composition of a HP diet.

In the setting of a PICU, the introduction of an aggressive nurse-driven feeding protocol, together with the institution of an NST, is an effective and safe tool to improve prescription and delivery of energy and macronutrients. In the future, efforts of the NST should be directed towards the identification (upon PICU admission) of subpopulations of patients that are at higher risk for clinical malnutrition. Further, the goal should be an early (< 24 hrs) delivery of enteral intake containing normal amounts of carbohydrate and protein to all patients. Additionally, the specific metabolic demands of the increasing population of technology-dependent children needs to be clarified.

Finally, future research should be increasingly directed towards clinically relevant long-term (linear growth, body composition, muscular strength, quality of life), as opposed to short-term clinical (ventilator days, LOS) or surrogate (blood concentrations of biomarkers, delivered percentages of goals) outcome measures.
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