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

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Summary
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, cumulative negative protein-energy balance with loss of LBM is associated with an increased incidence of infections, fewer ventilator-free days, a prolonged time of recovery to normal physiological functions resulting in increased length of stay (LOS) in the pediatric intensive care unit (PICU). 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. Over the past decade, overall mortality rates of specific childhood diseases have improved at the expense of a growing population of chronically ill children, which has resulted in an increased population of patients with underlying chronic illness and subsequent malnutrition upon admission to a PICU.

The principal aim of this thesis was to investigate the effect of high (5 g/kg/d) versus age-related, normal protein intake on whole-body protein synthesis (WBPS), -breakdown (WBPB), and net balance in children with acute or chronic disease using stable isotopic infusion technique. As a model for these different disease states, we studied young children following cardiac surgery and school age children with cystic fibrosis (CF), respectively. 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. Finally, in anticipation of the finding that it is important to deliver an adequate amount of protein to critically ill children, we studied 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.

In Chapter 2 we observed no difference in endogenous proteolysis in young children following cardiac surgery, in response to a normal-carbohydrate/low-protein (NormCarb/LoProt) enteral diet with a carbohydrate intake of 7.5 mg/kg/min and protein intake of 0.7 g/kg/d, compared to high carbohydrate intake (HiCarb/LoProt diet: glucose 10 mg/kg/min and protein 0.7 g/kg/d). We therefore speculated that proteolysis was already maximally suppressed by insulin concentrations in response to the NormCarb intake, and that a higher carbohydrate intake with consequent higher insulin concentrations did not have an additional effect on proteolysis. Furthermore, due to insufficient availability of exogenous amino acids (AAs), WPBS was low in both groups, resulting in equally negative net whole-body protein balance. There were also no differences in plasma glucose or AA concentrations between groups. We observed no episodes of hypoglycemia in either group. Additionally, there was a statistically significant lower serum cortisol concentration together with a trend towards lower levels of catecholamines in the
HiCarb/LoProt group compared to the NormCarb/LoProt group. We concluded that, although glucose infusion-induced hyperinsulinemia is a safe strategy with a possible mitigatory effect on the stress response, it does not improve whole-body protein balance. Therefore, it cannot be advocated as a meaningful strategy in reversing negative protein balance in critically ill children.

Subsequently, in infants after low-to-moderate-complexity cardiac surgery, we aimed to improve whole-body protein balance with a short-term high-protein (HP, 5 g/kg/d) diet, compared to a normal-protein (NP, 2 g/kg/d) enteral diet (Chapter 3). Contrary to our expectations, we observed a positive net whole-body protein balance in both groups, without statistically significant difference between groups. Additionally, there were no significant differences in WBPS and WBPB between the HP and NP group. In fact, in the HP group, there was higher valine oxidation together with higher blood urea nitrogen concentrations, suggesting an overload of exogenous AAs and increase in ureagenesis. In both groups, in response to a normal carbohydrate intake of ~6.0 mg/kg/d, we measured plasma insulin concentrations that were in the same range as in the NormCarb/LoProt group of our previous study discussed in Chapter 2. In this study, endogenous proteolysis was already maximally suppressed by plasma insulin concentrations in response to normal carbohydrate intake, without additional effect of higher insulin concentrations. We concluded that in infants after low-to-moderate-complexity cardiac surgery, a short-term HP diet cannot increase WBPS, and does not improve net whole-body protein balance, compared to a NP diet.

Since an increasing number of children admitted to a PICU have a chronic underlying disease with concomitant malnutrition, we also studied the effects of 3 diets with incremental (1.5, 3 and 5 g/kg/d protein, respectively) dietary intake of protein on WBPS, WBPB and net protein balance in children with CF with stunted growth requiring tube feeding (Chapter 4). The study had a crossover design, whereby each patient received three cycles of a 4-day diet, each separated by a 6-week wash-out period. Interestingly, in this group of chronically ill children we demonstrated that whole-protein balance could be drastically improved as a result of 30% enhancement of WBPS during the HP diet. WBPB did not change significantly between diet-groups. Additionally, we observed a trend towards increased plasma insulin concentration and decreased plasma glucagon concentration between the low, intermediate and high-protein diets respectively. This trend was not statistically significant. With carbohydrate intake set at ~5.0 mg/kg/min during all diets, we hypothesized that the observed differences in insulin and glucagon concentrations were the result of different amounts of AAs between groups.

In the last two chapters of this thesis, in anticipation of the finding that it is important to deliver adequate protein intake in a timely fashion to critically ill children, we studied the prescription and delivery of calories and protein in a subset of children with LOS > 3 days on
our tertiary PICU. In **Chapter 5**, we describe that before the institution of an NST only 40% and 70% of our patients received nutrition on days 1 and 2 respectively, resulting in overall protein malnutrition in almost 85% of the patient days. Additionally, we demonstrated that the predefined goal of caloric intake was reached as late as day 5 of admission, whilst actual delivery of proteins stagnated at around 75% of the target from day 5 until the end of the observation period (day 10). The major cause of malnutrition on our PICU was inadequate prescription of nutrition, rather than insufficient delivery (e.g. IC-related procedural interruptions, for which the patient has to be fasted).

Finally, we studied the effect of the implementation of a nurse-driven feeding algorithm together with the institution of an NST on actual energy and macronutrient intake in our patients (**Chapter 6**). Following the introduction of the algorithm and NST, the percentage of enteral nutrition delivered on day 1 doubled from 40% to 78%, and on day 2 increased from 60% to 92%. By the third day, more than 85% of nutritional targets were reached compared to day 4 prior to the introduction of the protocol. We concluded that an NST plays an important role in increasing prescription and subsequent delivery of calories and macronutrients to patients on a PICU.

In **Chapter 7** (general discussion) we reviewed and discussed the implications of our results. We concluded that in young children following cardiac surgery, early enteral nutrition with normal protein (NP) intake of 2 g/kg/d, but not high carbohydrate intake-induced hyperinsulinemia, can reverse negative net whole-body protein balance in the immediate postoperative phase. Therefore, in the immediate phase following pediatric cardiac surgery, emphasis should be focused upon the prompt delivery of normal amounts of protein. High protein (HP) intake of 5 g/kg/d does not serve to improve WBPS or net protein balance, and therefore cannot be recommended over standard protein intake.

In contrast, in school-age children with chronic illness (CF with stunted growth), WBPS and net protein balance can be improved by provision of a higher (5 g/kg/d) than currently recommended intake of protein. Further studies are necessary to demonstrate a possible effect on increased LBM and improved linear growth and body composition.

Finally, the implementation of a nurse-driven feeding algorithm, together with the institution of an NST, increases early prescription and consecutive delivery of calories and macronutrients to patients in the first days following admission to a PICU. The most important future goals for an NST should be to focus on the identification of patients who are at high risk for clinical malnutrition, and to develop a tailor-made nutritional approach. Additionally, the specific metabolic demands of the increasing population of technology-dependent children needs to be clarified.