Pre- and Post-Partum Nutrition and Metabolism

Total parenteral nutrition in surgical infants
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Introduction
The newborn infant is in a ‘critical epoch’ of development. Nutritional deprivation may adversely affect not only the infant as a whole but also individual organs, notably the brain, leading to stunted physical and intellectual development [1]. In the surgical infant malnutrition is associated with increased morbidity and mortality; therefore, it is important that nutritional integrity is maintained regardless of the severity of the illness or organ failure. Surgical infants are likely to be deprived of enteral nutrition for some period during their treatment. The nutritional management of these vulnerable patients has improved over the past 20 years following the introduction of parenteral nutrition (PN).

Our group has recently investigated several problems related to metabolism and nutrition of surgical infants. The energy requirements and substrate utilization of surgical newborn infants receiving PN has been studied using the combined techniques of indirect calorimetry and stable isotope tracer techniques. The aim of this article is to review briefly our recent contribution in the field of nutrition and metabolism of surgical newborn infants receiving PN. The article will discuss: (i) the partition of energy metabolism and the energy requirement; (ii) the major pathways of metabolic utilization of intravenous protein, carbohydrate and fat.

Patients
The criteria for entry into the metabolic studies described below were that the infants should not weigh more than 5.0 kg, that they should not require ventilatory support, that they should not have a significant cardiac lesion, that they should not be septic, and that they should not have a congenital metabolic defect. All the infants studied required PN because it was anticipated that the gastrointestinal tract could not be used for at least 1 week after an operation for gastrointestinal tract anomalies. The study started at least 3 days post-operatively, when the general condition of the infants had stabilized. Premature and low birthweight infants were kept in an incubator in a thermonuclear environment.

Methods
Energy expenditure and substrate utilization
Respiratory gas exchange was measured by open-circuit computerized indirect calorimeter. Energy expenditure was calculated from oxygen consumption (\(\text{VO}_2\)) and carbon dioxide production (\(\text{VCO}_2\)) according to the principles of indirect calorimetry [2]. Non-protein respiratory quotient was calculated from \(\text{VCO}_2\), \(\text{VO}_2\), and urinary nitrogen excretion. Differential utilization of carbohydrate and fat was calculated from the non-protein respiratory quotient [2–6]. The rate of carbohydrate utilization is defined as the sum of oxidation and conversion to fat (lipogenesis) [4,6]. The rate of fat utilization is defined as the difference between the rate of fat oxidation and synthesis from carbohydrate [4–7]. Urine was collected for 3 days through an adhesive plastic collector draining into a sterile bottle [8] and urinary nitrogen was determined by the micro-Kjeldhal method [9].

Protein turnover
Whole-body protein turnover was calculated using a simplified model of protein dynamics [10], which assumes that the plasma free amino acid pool is in continuous and instantaneous equilibrium with the intracellular pool, which together compose a single homogeneous pool exchanging with body protein. Protein synthesis and breakdown were estimated by infusing intravenously the stable isotope \([13C]\)leucine. The \(13C\) enrichment of expired air and the plasma enrichment of \(13C\)-\(\alpha\)-keto-isocaproic acid were determined by gas chromatograph mass spectrometry [11–13]. \(\text{VCO}_2\) was measured by indirect calorimetry.

Energy requirement
The components of total energy expenditure are resting energy expenditure (REE), energy for thermoregulation, energy for physical activity, and energy cost of weight gain [14,15]. Indivi-
energy needs depend principally upon REE, but are affected also by physical activity, environmental temperature, food intake and growth. In resting infants receiving parenteral nutrition in a thermoneutral environment, REE is the main component of total energy expenditure. REE varies from day to day and between individuals [15,16]. Data from studies in preterm and full-term neonates suggest that the inter-individual variability of REE may be as much as 70% [16]. An estimation of REE is therefore essential for designing artificial infant feeds [17], particularly since it may vary amongst otherwise comparable individuals, and from day to day. Measurement of an infant’s REE requires complicated equipment (i.e. indirect calorimeter) which is not always practical to use in the clinical setting. An equation for predicting REE is thus particularly useful for estimating energy requirements.

In a study of continuous measurement of energy expenditure by indirect calorimetry for 12 h we demonstrated that: (i) energy expenditure variability among surgical neonates depends on inter-individual differences during rest and activity; (ii) physical activity contributes only up to 9% of the total energy expenditure [15]. In a subsequent study we made 122 measurements of REE in 46 stable, non-ventilated surgical infants [18]. The observed values ranged between 25 and 49 cal/kg per min (36–71 kcal/kg per day) indicating that REE may vary by as much as 2-fold amongst individuals in similar clinical conditions. Using a multiple stepwise regression analysis we described an equation to predict the basal energy requirements of stable surgical infants using easily measurable parameters. Three body size measurements correlated significantly with REE (cal/min): weight in kg (r, 0.87; P < 0.00001), body surface area in m² (r, 0.86; P < 0.00001), and lean body mass in kg (r, 0.81; P < 0.00001). Five other independent variables correlated significantly with REE (cal/kg per min): heart rate in beats/min (r, 0.50; P < 0.00001), postnatal age in days (r, 0.49; P < 0.00001), caloric intake in cal/kg per min (r, 0.44; P < 0.00001), gestational age in weeks (r, 0.43; P < 0.00001), and rectal temperature in °C (r, 0.19; P = 0.04). Weight, heart rate, age, gestational age, and temperature were regarded as independent predictor variables of REE for the multiple stepwise regression analysis. Three variables entered the following highly significant equation:

REE (cal/min)

\[= -74.436 + [34.661 \times \text{weight (kg)}] \\
+ [0.496 \times \text{heart rate (beats/min)}] \\
+ [0.178 \times \text{age (days)}]
\]

\((r, 0.92; F = 230.07; \text{significance } F < 0.00001)\)

The error in predicting REE from the equation was \(-0.95 \pm 3.65\%\) [18]. The multiple regression equation described can be used to predict basal energy requirements in stable surgical infants. Total energy requirements can therefore be estimated as REE plus the energy requirements of growth. This latter component is approximately 5 kcal/g of tissue deposited [19], which would amount to an additional 50 kcal/kg per day in a full term infant growing at 10 g/kg per day.

**Substrate utilization**

The caloric needs for total PN are provided by carbohydrate and lipid. Protein is not used as a source of energy, since the catabolism of protein to produce energy is an uneconomic metabolic process compared to the oxidation of carbohydrate and fat which produces more energy at a lower metabolic cost. The ideal total PN regimen therefore should provide enough amino acids for protein turnover and tissue growth, and sufficient calories to minimize protein oxidation for energy.

**Carbohydrate**

Glucose is the natural energy source for body cells and is the primary energy substrate in PN. The amount of glucose that can be infused safely depends on the clinical condition and maturity of the infant. The ability of neonates to metabolize glucose may be impaired by prematurity and low birth weight. Carbohydrate conversion to fat (lipogenesis) occurs when glucose intake exceeds metabolic needs. The risks associated with this process are 2-fold: accumulation of the newly synthesized fat in the liver [20]; and aggravation of respiratory acidosis resulting from increased CO₂ production, particularly in patients with compromised pulmonary function [21]. On the basis of 21 metabolic studies carried out on 11 surgical infants receiving PN we have demonstrated that there is a negative linear relationship between glucose intake (g/kg per day) and fat utilization (oxidation and conversion to fat) expressed in g/kg per day \((y = 4.547 - 0.254x; r, -0.937; P < 0.0001)\) [22]. From this equation we calculated that 'net fat synthesis from glucose'
Pre- and Post-Partum Nutrition and Metabolism

exceeds 'net fat oxidation' when the glucose intake is greater than 18 g/kg per day. We also found a significant relationship between glucose intake and \( \text{VCO}_2 \) (mls/kg per min) (\( y = 3.849 + 0.183x; r, 0.825; P<0.0001 \)). The slope of this relationship was steeper when glucose intake exceeded 18 g/kg per day (\( y = 2.62 + 0.244x; r, 0.746; P \leq 0.05 \)), than when glucose intake was less than 18 g/kg per day (\( y = 5.30 + 0.069x; r, 0.264; P = 0.461 \)). Thus the conversion of glucose to fat results in a significantly increased production of CO\(_2\). Glucose intake exceeding 18 g/kg per day is also associated with a significant increase in respiratory rate and plasma triglyceride levels. In summary this study demonstrated that:

1. glucose intake is the principle determinant of carbohydrate and fat utilization;
2. the maximal oxidative capacity for glucose in infants is 18 g/kg per day, which is equivalent to the energy expenditure of the infant;
3. if glucose is given in excess of maximal oxidative capacity: (i) net fat oxidation ceases; (ii) net fat synthesis begins; (iii) the thermogenic effect of glucose increases and the efficiency with which glucose is metabolized decreases; (iv) CO\(_2\) production increases, and respiratory rate increases; (v) plasma triglyceride levels increase.

It is advisable, therefore, in stable surgical newborn infants requiring PN not to exceed 18 g/kg per day of intravenous glucose intake [4,22].

**Fat**

Since 1961 safe commercial intravenous fat emulsions have become widely used. These preparations have a high caloric value (9 kcal/g fat), prevent essential fatty acid deficiency [23,24] and are isotonic, allowing adequate calories to be given via a peripheral vein [25]. A number of studies in both adults and infants have indicated that a combined infusion of glucose and lipids might confer a metabolic advantage over a glucose infusion alone, because it lowers the metabolic rate and increases the efficiency of energy utilization [26–28].

Fat tolerance has been extensively studied by monitoring fat clearance from plasma. However, clearance from plasma does not imply that the fat is being utilized to meet energy requirements, since it may be being stored instead [4,29]. Our group has studied intravenous fat utilization by performing an 'Intralipid utilization test' [4]. This consisted of infusing for 4 h Intralipid 10% in isocaloric and isovolemic amounts to the previously given mixture of glucose and amino acids. Gas exchange was measured by indirect calorimetry to calculate the patient's \( \text{VO}_2 \), \( \text{VCO}_2 \), and net fat utilization (see Methods). The study showed that: (i) surgical infants adapt rapidly (within 2 h) to the intravenous infusion of fat; (ii) more than 80% of the exogenous fat can be oxidized; (iii) CO\(_2\) production is reduced during fat infusion as a consequence of the cessation of carbohydrate conversion to fat [4].

However, this study did not measure the rate of fat utilization during a mixed intravenous diet including carbohydrate, amino acids and fat. We have therefore performed 32 indirect calorimetry studies on stable surgical newborn infants receiving fixed amounts of carbohydrate and amino acids and variable amounts of intravenous long-chain triglycerides fat emulsion. Patients were divided into two comparable groups according to the intake of carbohydrate. Infants in group A (18 studies) received 10 g/kg per day of glucose, 2.5 g/kg per day of protein as crystalline amino acids and 0 to 6 g/kg per day of fat. Infants in group B (14 studies) received 15 g/kg per day of glucose, 2.5 g/kg per day of protein and from 0 to 6 g/kg per day of fat. The results of these studies indicate that at a carbohydrate intake of 15 g/kg per day (56.3 kcal/kg per day) the proportion of energy metabolism derived from fat oxidation does not exceed 20% even with a fat intake as high as 6 g/kg per day. At a carbohydrate intake of 10 g/kg per day this proportion can be as high as 50% [30]. According to these data net fat oxidation seems to be significantly influenced by carbohydrate intake. Net fat oxidation was directly correlated to the calorie gap between REE and carbohydrate intake (\( y = 1.715 - 0.073x; r, 0.9; P<0.0001 \)) (Figure 1). When the intake of glucose calories exceeds the basal energy requirements of the infant, net fat oxidation is minimal regardless of fat intake [30]. In order to use intravenous fat as an energy source, it is therefore necessary to maintain carbohydrate intake below basal energy requirements.

Commonly used fat emulsions for PN in paediatrics are based on long-chain triglycerides.
Carbohydrate (CHO) intake and resting energy expenditure (REE) are predictive of net fat oxidation. The rate of intravenous fat oxidation during total PN can be theoretically enhanced by the addition to the intravenous diet of l-carnitine and/or medium-chain triglycerides (MCT). Important differences have been observed between MCT and LCT with respect to physical and metabolic properties. MCT are cleared from the blood stream at a faster rate and are oxidized more completely for energy production than LCT. Therefore, they seem to serve as a preferential energy source for the body. We recently performed a study designed to investigate the effects of MCT on intravenous fat utilization during total PN in stable surgical newborn infants [31]. We studied two groups of surgical infants receiving total PN: one group received LCT-based (100% LCT) fat emulsion and the other group received an isocaloric amount of MCT-based (50% MCT+50% LCT) fat emulsion. In infants receiving carbohydrate calories in excess of measured REE (56 kcal/kg per day) net fat oxidation was not enhanced by the administration of MCT-based fat emulsion. Conversely in infants receiving carbohydrate calories below REE (41 kcal/kg per day) the administration of MCT fat emulsion increased net fat oxidation from 0.6±0.2 to 1.7±0.2 g/kg per day. The administration of MCT-based fat emulsion did not increase the metabolic rate of the infants.

Protein-sparing effect of carbohydrate and fat

In contrast to healthy adults who exist in a state of neutral nitrogen balance, infants need to be in positive nitrogen balance in order to achieve satisfactory growth and development. Infants are efficient at retaining nitrogen, and can retain up to 80% of the metabolizable protein intake on both oral and intravenous diets [32–34]. Protein metabolism is dependent upon both protein and energy intake. The influence of dietary protein is well established. An increased protein intake has been shown to enhance protein synthesis [35,36], reduce endogenous protein breakdown [37], and thus enhance net protein retention [33,37].

On the other hand, the influence of non-protein energy intake on protein metabolism is more controversial. Protein retention can be enhanced by giving carbohydrate or fat [38–43], which are thus said to be protein sparing. Although some studies have suggested that the protein-sparing effect of carbohydrate is greater than that of fat [38–40], others have suggested that the protein-sparing effect of fat may be either equivalent to, or greater than, that of carbohydrate [41–43]. One initial study from our group has shown that the addition of fat calories to the intravenous diet reduces protein oxidation, protein contribution to the energy expenditure, and increases protein retention [43]. In order to investigate further this positive effect on protein metabolism we studied the various components of whole protein metabolism by the combined technique of indirect calorimetry and stable isotope (13C-leucine) tracer technique (see Methods). Two groups of neonates receiving isonitrogenous and isocaloric total PN were studied [44,45]. In group A (high fat) infants (n = 9) received 10.0 g/kg per day of dextrose and 4.0 g/kg per day of fat; in group B (high carbohydrate) infants (n = 9) received 19.0 g/kg per day of dextrose and 0.5 g/kg per day of fat. There was no significant difference between the two groups with regard to any of the components of whole-body protein metabolism: protein synthesis, protein breakdown, protein oxidation/excretion, and total protein flux (Figure 2). This study confirms previous observations that infants have high rates of protein turnover, synthesis and breakdown, which may be up to eight times greater than those reported in adults. In newborn infants receiving PN, synthesis and breakdown of endogenous body protein far exceed intake and oxidation of exogenous protein. Infants are avid retainers of nitrogen and carbohydrate and fat have an equivalent effect on protein metabolism. This study has positive implications for the use of intravenous fat in the intravenous diet.
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Ketone bodies are formed at the last phase of lipid energy metabolism; they are major vectors of energy transport during fasting and high dietary fat intake. Ketogenesis is highly regulated and changes markedly in different physiological states, including the fetal-neonatal transition [1]. Medically, ketone bodies are implicated in obesity, epilepsy, diabetes and in severe, sometimes fatal inborn errors.

Inborn errors of metabolism result from mutation of one of the genes mediating intermediary metabolism. From the standpoint of metabolic control analysis, in inborn errors the control of the entire pathway is determined by the site of the deficient enzyme. Inborn errors are thus valuable reference points from which to assess the biological importance of a metabolic pathway. In this article we use the two inborn errors of ketogenesis to illustrate their contribution to current knowledge of lipid energy metabolism.

**Ketone body metabolism**

The metabolism of ketone bodies (Figure 1) can be viewed as a single metabolic pathway spanning two organs, the liver (ketogenesis) and an extrahepatic tissue (ketolysis). The pathway contains five enzymes. Two enzymes are specific to ketogenesis, mitochondrial HMG-CoA synthase (mHS) and HMG-CoA lyase (HL). One enzyme,