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## Indirect calorimetry: a potential but as yet unrealized technique for guiding nutritional management

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Among those who study nutrition in preterm and small for gestational age (SGA) newborn infants, there is the hope that someday there will be a simple, reliable, and accurate bedside measure of nutrient utilization to help guide nutritional management, much like blood gas and pulse oximetry measurements help guide the use of respirators and oxygen. This certainly is a hope well expressed in the very interesting article by Soares et al.<sup>1</sup> ("Indirect calorimetry: a tool to adjust energy expenditure in very low birth weight infants") in this edition of the *Jornal de Pediatria*. In the meantime, we are limited to using tables and charts of nutrient utilization that have been based on sophisticated (and definitely not "bedside") direct

and indirect calorimetry research in newborn infants. Most of the existing guidelines for feeding preterm neonates are based on the nutrition required by normally grown term infants who are fed milk or formula. However, these guidelines are not particularly useful when attempting to address the highly variable metabolism and growth of preterm and SGA infants. This failure to define optimal nutrition in different neonatal populations likely contributes significantly to our inability to achieve normal growth rates in these infants. Indeed, most centers still report that close to 100% of preterm infants are growth restricted and SGA by term gestation.

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Data from animal models also have provided estimates of the nutrition required in the human fetus in utero in order to achieve optimal growth rates. Such estimates are realistic when one considers that normal in utero fetal growth has been considered the goal for growth of the preterm infant. From such studies in fetal animal models, we now know that the growth of the fetus requires relatively large amounts of protein for growth of lean body mass and similar amounts of carbohydrates and lipids for growth of fat mass. Requirements for energy production also are quite high, as energy is necessary not only for maintaining electrochemical gradients across cell membranes throughout the body, but also for the remarkably high rates of synthesis of proteins and complex carbohydrates, lipids, and fat that are characteristic of fetal growth during gestation. The nutrient requirements for all of these metabolic processes are higher in the late second and early to mid-third trimester when the fractional growth rate of the fetus is much higher. The only exception is that the calorie requirements for energy deposition in adipose tissue increase markedly over the third trimester of gestation.

Not surprisingly, therefore, the protein and energy requirements for preterm infants are increasingly higher as the infant is born more preterm. Amino acid requirements are about 4 g/kg/day at 24-28 weeks gestation, but only about 2 g/kg/day at term. Similarly, glucose utilization rates are about twice as great at 24 weeks gestation (6-8 mg/kg/min) as they are at term (3-4 mg/kg/min). These nutrient requirements match the higher fractional growth rates in early vs. later gestation. Together these factors have been used by clinicians to estimate and provide increased amounts of nutrients to preterm infants by fortifying human milk and using relatively concentrated "preterm formulas." Studies such as those by Kashyap et al. have documented contributions of both energy intake and protein intake to weight gain, but other studies have emphasized that above the 40-50 kcal/kg/day energy requirements for maintenance metabolism, increased weight gain of lean body mass (muscle and bone) is regulated primarily by protein intake, while any further increases in energy intake primarily contribute to increased growth of adipose tissue and body fat content.<sup>2,3</sup>

Thus, two approaches to study preterm infants to determine their nutrient requirements have been developed.<sup>4</sup> The first is measurement of energy expenditure (EE) to determine energy requirements (as carbohydrate and lipid), and the second is measurement of body composition to determine relative growth of lean body mass and fat mass. For many years the "mainstay" method for the assessment of lean and fat mass has been caliper measurement of skin and subcutaneous tissue thickness (e.g., triceps skin fold thickness). More recently dual X-ray absorptiometry (DXA) has been used for such measurements. Other techniques, such as ultrasound and magnetic resonance imaging, also are showing considerable promise.

EE measurements have shown remarkable consistency when done accurately, with values of 40-50 kcal/kg/day in late preterm and term infants measured relatively commonly, consistent with the value of ~50 kcal/kg/day estimated for the third trimester human fetus in utero.<sup>5</sup> EE values are higher per kg of body weight in very preterm infants when fed sufficiently and in SGA infants, as shown in the article by Soares et al.<sup>1</sup> in this edition of the *Jornal de Pediatria*. This is due primarily to their need for greater energy production to meet their increased rates of radiant and evaporative (mostly) as well as conductive (less so) heat losses due to their higher surface area to body mass ratio. It has been reasonable, therefore, to conclude that clinicians could use EE measurements to guide nutritional management. This is certainly possible, but with certain notable cautions.<sup>6</sup>

First, EE varies considerably depending on the ambient temperature. Unless infants are studied under thermal neutral conditions, it is difficult if not impossible to know whether the EE measured represents just maintenance metabolism or that plus a variable amount of energy produced by non-shivering thermogenesis to maintain body temperature. Unfortunately, there are no simple and reliable ways to determine whether a particular infant is in a thermal neutral environment in which oxygen consumption and energy production to maintain body temperature are minimal. Charts must be used, representing previous research, but this is not a satisfactory approach for those inclined to measure EE directly and "at the bedside" to guide nutritional management.

Second, EE increases directly with energy intake, at least over the range from low to sufficient rates of energy intake.<sup>7,8</sup> Thus, if one does not feed preterm infants at all or very much, their metabolic rates fall as rates of protein (primarily) and lipid/complex carbohydrate (less so) synthesis diminish. Some investigators have misinterpreted such lower EE measurements in preterm infants who were underfed as evidence that they did not need more food when the reality was exactly the opposite. One should be sure, therefore, that EE measurements are made when the infant is receiving normal amounts of food, and if not, that the insufficient food intake is noted so that adjustments in energy intake are appropriate for the size and age of the infant and not just the result of how much food the infant is receiving.

Third, and from a similar perspective, overfed infants might have increased rates of EE due to excessive synthesis of fat from carbohydrates, particularly glucose. Fat production from excess glucose is an energy-expensive process. It also produces excess CO<sub>2</sub> and a lower respiratory quotient value and with indirect calorimetry could lead to the erroneous conclusion that fat is being oxidized preferentially to carbohydrate. Misinterpretation of such conditions could lead to even further administration of excess carbohydrate, only making the metabolic abnormalities even worse. In this regard, it is interesting and important to note that while many are now

paying better attention to the higher rates of protein required for very preterm infants, which then are scaled downwards as the infant is closer and closer to term when protein requirements for the slower growth rate of term infants are lower, this practice has not been applied as much to energy nutrition. It still is the case that the very high energy requirements of the very preterm infant are continued, even as the infant is either born closer to term or gets closer to term while in the neonatal intensive care unit. As a result, such infants get hyperglycemic very easily and also end up at term much fatter than they would have been had they remained in utero.

Fourth, providing energy above the requirements for normal rates of EE does not produce more growth of lean body mass, which is dependent on protein intake and has a limit above which growth does not increase but body fat content does increase. Not surprisingly, therefore, the most common growth pattern in preterm infants who have been fed less protein and more energy than they need is growth restriction of body length and lean body mass but excess growth of adipose tissue.

Fifth, as discussed previously in other research articles and editorials, measurement of EE using indirect calorimetry is not easily performed in preterm infants.<sup>9</sup> Accurate measurements of oxygen consumption and CO<sub>2</sub> production require consistent and careful set up of equipment, very stable flows of oxygen and/or air to the infant (note that wall oxygen units in most hospitals do not provide the constant values of oxygen concentration that are required for such measurements), methods to prevent air leaks around the face or endotracheal tube, highly accurate measurements of oxygen concentration in the air that the infant breaths in and the CO<sub>2</sub> in the air that the infant exhales, as well as the air flow rate itself.<sup>10</sup> There also are large differences in results among different types of research indirect calorimeters as well as large variations in results from commercially available calorimeters. Each of these needs to be calibrated independently, and before making measurements in any infant or group of infants, such as by measuring oxygen consumption and CO<sub>2</sub> production from a burning flame of alcohol.<sup>11</sup>

Finally, appropriate interpretation of EE measurements requires a broad perspective on adaptations the infant has made to previous nutritional intakes as well as what can happen when different energy intakes are provided for extended periods. For example, measuring higher EE rates in SGA infants who had intrauterine growth restriction from placental insufficiency does not mean that they simply should be "fattened up" with greater energy intakes. Recent evidence from animal and human studies indicates that intrauterine growth restricted (IUGR) infants have increased propensity for cellular glucose and fatty acid uptake and production of body fat stores. As a result, over feeding of these nutrients can lead to excessively rapid growth of body fat during early life, which clearly can lead to increased development of obesity, insulin

resistance, and type 2 diabetes mellitus (the "metabolic syndrome") later in life.<sup>12</sup>

While one should not further malnourish such infants, developing nutritional strategies and management to maintain their growth leaner rather than fatter has the potential to provide a better pattern of growth. In this regard, measurement of EE by indirect calorimetry in SGA/IUGR infants might be very helpful in determining their EE response to greater or lesser energy intakes and in relation to how well such energy intakes promote growth of lean body mass. Clearly, therefore, further studies of EE, such as the one noted in the article by Soares et al.<sup>1</sup> in this edition of the *Jornal de Pediatria*, are going to be very helpful to determine not just the energy needs of a given infant but the response of that infant to different energy intakes. Such studies also should be conducted longitudinally, as infants have quite different nutritional requirements and rates of nutrient metabolism right after birth, several days later, and weeks later.<sup>8</sup> When coupled with measurements of change in lean and fat body mass components, such measurements should provide a more robust and accurate appraisal of the type, composition, and amount of nutrients for newborn infants of all ages, shapes, and sizes, hopefully, thereby producing a longer and healthier life.

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