Performance of Predictive Equations Specifically Developed to Estimate Resting Energy Expenditure in Ventilated Critically Ill Children

Corinne Jotterand Chaparro, PhD[1,2], Patrick Taffé, PhD[3], Clémence Moullet, BSc[1], Jocelyne Laure Depeyre, BSc[1], David Longchamp, MD[2], Marie-Hélène Perez, MD[2], and Jacques Cotting, MD[2]

Objective To determine, based on indirect calorimetry measurements, the biases of predictive equations specifically developed recently for estimating resting energy expenditure (REE) in ventilated critically ill children, or developed for healthy populations but used in critically ill children.

Study design A secondary analysis study was performed using our data on REE measured in a previous prospective study on protein and energy needs in pediatric intensive care unit. We included 75 ventilated critically ill children (median age, 21 months) in whom 407 indirect calorimetry measurements were performed. Fifteen predictive equations were used to estimate REE: the equations of White, Meyer, Mehta, Schofield, Henry, the World Health Organization, Fleisch, and Harris-Benedict and the tables of Talbot. Their differential and proportional biases (with 95% CIs) were computed and the bias plotted in graphs. The Bland-Altman method was also used.

Results Most equations underestimated and overestimated REE between 200 and 1000 kcal/day. The equations of Mehta, Schofield, and Henry and the tables of Talbot had a bias ≤10%, but the 95% CI was large and contained values by far beyond ±10% for low REE values. Other specific equations for critically ill children had even wider biases.

Conclusions In ventilated critically ill children, none of the predictive equations tested met the performance criteria for the entire range of REE between 200 and 1000 kcal/day. Even the equations with the smallest bias may entail a risk of underfeeding or overfeeding, especially in the youngest children. Indirect calorimetry measurement must be preferred. *(J Pediatr 2017;184:220-6).*

See editorial, p 10

In critically ill children, maintaining a caloric intake close to the energy need will improve recovery.[1] Scientific societies recommend measuring resting energy expenditure (REE) by indirect calorimetry as the gold standard method, especially in children with malnutrition or suspected altered metabolism.[1,2] Nevertheless, recent studies have shown that REE is measured in a minority of pediatric intensive care units (PICUs).[3-6] PICUs face an additional difficulty in that the sole device currently validated for use in critically ill patients—the Deltatrac II calorimeter (Datex-Ohmeda, Helsinki, Finland)[7,8]—is no longer being manufactured.

In the absence of indirect calorimetry measurements, current guidelines propose estimating REE with predictive equations while highlighting that the available equations lack precision, but they do not offer advice on which equations to use.[1,2] Worldwide and European surveys[5,6] have shown that in most PICUs, REE is estimated using the common predictive equations of Schofield[9] and the World Health Organization,[10] which were developed for use in healthy children. Specific equations for critically ill children have been designed.[11-13] Several studies have concluded that the equations of White lack precision, however.[12,14-17] Although Meyer et al[12] developed 3 new predictive equations using diagnostic categories, the validity of these equations has not yet been evaluated. In 2015, Mehta et al[13] designed an equation using measured carbon dioxide production (VCO_2) and a fixed respiratory quotient (RQ) of 0.89. A recent study conducted in children after cardiopulmonary bypass identified RQ as the most important determinant of the bias with the VCO_2-based equation.[18] Kerklaan et al[19] demonstrated that REE estimated with the equation of Mehta,[13] using VCO_2 measured by a SERVO-i ventilator (Maquet, Rastatt, Germany) with a Capnostat III sensor (Maquet), was not sufficiently accurate for children weighing <15 kg. We hypothesized that some available predictive equations should not be used in ventilated critically ill children. Therefore, the objective of this study was to determine, based on indirect calorimetry measurements, the biases of predictive equations

LoA	Limits of agreement	REE	Resting energy expenditure
MEE	Measured energy expenditure	RQ	Respiratory quotient
PICU	Pediatric intensive care unit	VCO_2	Carbon dioxide production

From the [1]Department of Nutrition and Dietetics, School of Health Professions, University of Applied Sciences Western Switzerland, Geneva 1227, Switzerland; [2]Pediatric Intensive Care Unit, Medico-Surgical Department of Pediatrics, University Hospital of Lausanne, Lausanne 1011, Switzerland; and [3]Institute of Social and Preventive Medicine, Lausanne 1010, Switzerland

Partially funded by the DORE Funds of the Swiss National Science Foundation (13DPD3-114074 2) and the Marisa Sophie Foundation. The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.12.063

developed specifically for ventilated critically ill children or developed for a healthy population but frequently used in the PICU.

Methods

This secondary analysis study used our data on REE measured by indirect calorimetry in ventilated critically ill children in a prospective study on protein and energy needs performed in the PICU of the University Hospital of Lausanne, Switzerland.[20] All children (from birth to age 16 years) admitted to the PICU between January 2008 and April 2010 were eligible for inclusion in the study if they had an expected duration of mechanical ventilation ≥72 hours. Exclusion criteria were as follows: fraction of inspired oxygen >60%, an air leak around the endotracheal tube >10%, chylothorax, chronic or acute renal disease, severe loss of inflammatory fluid through a pleural or peritoneal drain, exudative enteropathy, therapeutic hypothermia, birth weight <2.5 kg, and gestational age <36 weeks. The protocol and study were approved by the Ethics Committee of the University Hospital of Lausanne. Written informed consent was obtained from the parents of all included patients.

Indirect Calorimetry Measurements

Measurements of REE by indirect calorimetry (Deltatrac II) and of total urinary nitrogen by chemoluminescence (Antek 7000 analyzer; Antek, Houston, Texas)[21] were obtained daily from admission until extubation. The calorimeter was calibrated monthly using the ethanol-burn technique, adapted for pediatric values. Before measurements, the calorimeter was preheated for 1 hour and calibrated using a reference gas mixture. Infants were ventilated with a Babylog ventilator (Dräger, Lübeck, Germany). Children weighing >4 kg were ventilated with a Galiléo ventilator (Hamilton Medical, Bonaduz, Switzerland). REE was measured for at least 60 minutes, if possible at the same time each day during a quiet period without planned procedures. When an event occurred (change in fraction of inspired oxygen, physiotherapy, agitation or suctioning of the endotracheal tube), the measurement was interrupted, and then not resumed until at least 30 minutes later. REE was calculated using the modified Weir equation,[22] which includes the measured total urinary nitrogen. The first 10 minutes of measurement were discarded to exclude artifacts. A steady state was defined as a coefficient of variation of VCO_2 ≤10% for at least 25 consecutive minutes.[23] Steady state was not achieved for 5 measurements, which were not used for analysis.

Predictive Equations to Estimate REE in Ventilated Critically Ill Children

We predicted REE using equations specifically developed for ventilated critically ill children: the equations of White et al 1 and 2;[11] Meyer et al A, B, and C;[12] and Mehta et al[13] (**Table I**; available at www.jpeds.com). In their respective studies, the authors compared predicted REE results with measured energy expenditure (MEE) values obtained with the Deltatrac II or the Vmax Encore instrument (Viasys Healthcare, Loma Linda, California), using the Bland-Altman limits of agreement (LoA) method.[24]

Predictive Equations to Estimate REE in Healthy Children and Adults

We tested the performance of predictive equations or tables developed for healthy children and frequently used in critically ill children: the equations of Schofield with weight and height (Schofield WH), Schofield with weight (Schofield W),[9] Henry with weight and height (Henry WH), Henry with weight (Henry W),[25] the World Health Organization,[10] Fleisch,[26] Harris-Benedict, and Harris-Benedict for infants,[27] and the tables of Talbot.[28] In 2012, the European Food Safety Authority[29] recommended the equations of Henry[25] and Schofield[9] in their guidelines for healthy children. The frequently used equations of Schofield are also presented in **Table I**. We also tested the equation of Harris-Benedict[27] developed in adults but widely used in critically ill children.[5]

Statistical Analyses

Traditionally, the Bland-Altman LoA methodology has been used to assess agreement between 2 methods of measurement.[24,30] However, when variances of the measurement errors of the 2 methods differ, the LoA method can be misleading.[31-34] Indeed, there are settings in which the regression line shows an upward or downward trend but there is no bias. In other cases, there is a bias despite a zero slope.[32] To avoid these deficiencies, we performed our statistical analyses using a recently proposed methodology to assess differential and proportional biases.[32]

Based on individual repeated indirect calorimetry measurements (MEE, in kcal/day), this proposed statistical methodology allowed us to compute the true REE value for each child.[32] Then the amount of the bias, which can be partitioned into a differential (α) and a proportional (β) bias of the 15 predictive equations, was calculated with the following equation: $bias = (\alpha + \beta \times true\_REE) - true\_REE$.[32] The differential bias is an additive bias that occurs when a new measurement method produces values that are systematically lower than or above the reference standard ($\alpha \neq 0$). The proportional bias is a multiplicative bias that occurs when the new measurement method produces values that are either lower or higher than the reference standard by an amount that depends on the level of the latent trait ($\beta \neq 1$). For each equation, the percentage of bias with its 95% CI was calculated and plotted on a graph for comparing the performance of the different equations. A bias ≤10% was considered clinically acceptable. This low cutoff was chosen to avoid the risk of underestimation or overestimation of REE using the different equations. For describing equations in more detail, bias plots showing the bias as a function of the true REE, as well as the amounts of differential and proportional biases, are provided online with individual data for MEE. To allow comparisons with the available literature, the Bland-Altman mean bias and LoA[24] (mean bias ± 1.96 SD) were calculated as well.

Characteristics of the population and MEE values are presented as median and IQR. Statistical analyses were