Bicarbonate kinetics and predicted energy expenditure in critically ill children


ABSTRACT

Background: To determine nutrient requirements by the carbon oxidation techniques, it is necessary to know the fraction of carbon dioxide produced during the oxidative process but not excreted. This fraction has not been described in critically ill children. By measuring the dilution of $^{13}$C infused by metabolically produced carbon dioxide, the rates of carbon dioxide appearance can be estimated. Energy expenditure can be determined by bicarbonate dilution kinetics if the energy equivalents of carbon dioxide (food quotient) from the diet ingested are known.

Objective: We conducted a 6-h, primed, continuous tracer infusion of NaH$^{13}$CO$_3$ in critically ill children fed parenterally or enteraly or receiving only glucose and electrolytes, to determine bicarbonate fractional recovery, bicarbonate rates of appearance, and energy expenditure.

Design: Thirty-one critically ill children aged 1 mo–20 y who were admitted to a pediatric intensive care unit at a tertiary-care center were studied. Patients were stratified by age, BMI, and severity score (PRISM III).

Results: Fractional bicarbonate recovery was 0.69, 0.70, and 0.63, respectively, for the parenterally fed, enterally fed, and glucose-electrolyte groups, and it correlated with the severity of disease in the parenteral ($P < 0.01$) and glucose-electrolyte (< 0.05) groups. Rates of appearance varied between 0.17 and 0.19 mmol·kg$^{-1}$·h$^{-1}$ With these data and estimates of the energy equivalents of carbon dioxide (a surrogate for respiratory quotient), energy expenditure was determined.

Conclusions: The 2001 World Health Organization and Schofield predictive equations overestimated and underestimated, respectively, energy requirements compared with those obtained by bicarbonate dilution kinetics. Bicarbonate kinetics allows accurate determination of energy needs in critically ill children.


INTRODUCTION

Determination of amino acid requirements by carbon oxidation techniques requires knowledge of the fraction of carbon dioxide in blood or breath that was produced during the oxidative process. However, when bicarbonate labeled with stable or radioactive isotopes is infused, not all labeled carbon dioxide produced at the cellular level is excreted. Carbon dioxide produced during oxidative processes can be fixed in metabolic pools, such as urea formation and the conversion of pyruvate to oxaloacetate or to malate, and therefore is not recovered. Fixation of bicarbonate into slower-turnover pools, such as bone, also contributes to underrecovery of infused labeled bicarbonate. Thus, knowledge of the carbon dioxide recovery fraction is essential to accurately determine the rates of nutrient oxidation. The carbon dioxide recovery fraction can be determined by either compartmental or noncompartmental models by using a bolus or a tracer infusion of $[^{13}C]$-labeled bicarbonate (NaH$^{13}$CO$_3$) (1).

The fraction of $^{13}$CO$_2$ recovered has not been investigated in critically ill children receiving parenteral nutrition, enteral nutrition, or an infusion of only glucose and electrolytes. Critically ill pediatric patients present with pathophysiological conditions that may affect cardiac output, oxygen consumption ($V_{O2}$), and carbon dioxide production ($V_{CO2}$) rates. These patients often develop organ dysfunction and altered acid-base status, which may influence the fraction of $^{13}$CO$_2$ recovery. Therefore, data on the fractional recovery (FR) of $^{13}$CO$_2$ should be obtained under the experimental conditions for which this factor will be applied.

The isotopic dilution technique allows the $^{13}$C from infused labeled bicarbonate tracer to be diluted by metabolically produced carbon dioxide (2–7). By measurement of the extent of isotopic dilution in expired air or blood, $V_{CO2}$ rates can be estimated (3).

The production of carbon dioxide has been used as an index of substrate oxidation and energy expenditure (EE). Thus, bicarbonate kinetics have also been used to estimate EE rates (2, 4, 5, 8, 9). However, the assessment of EE must involve knowledge of the amount of energy released per liter of carbon dioxide produced, or the energy equivalents of carbon dioxide (EEq$CO_2$) (8), which constitutes the food quotient, and which, under conditions of nutrient balance (8), serves as a surrogate for respiratory quotient.

1 From the Critical Care Section, Department of Pediatrics, Texas Children’s Hospital, Baylor College of Medicine, Houston, TX (JS, AG, WEG, DG, JC-B, LJ, and LC); the Children’s Nutrition Research Center, US Department of Agriculture, Houston, TX (JS, WEG, WH, and LC); the Orthopedics Service, Boston Children’s Hospital, Boston, MA (DZ); and the Cleveland Clinic Lerner College of Medicine, Cleveland, OH (RMR).

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3 Reprints not available. Address correspondence to L Castillo, Children’s Nutrition Research Center, USDA, Room 805, 1100 Bates Street, Houston, TX 77030. E-mail: lcastill@bcm.edu. Received September 10, 2007. Accepted for publication April 25, 2008.
The objectives of the study were 1) to determine the fraction of \( ^{13} \text{CO}_2 \) recovered after an infusion of \( ^{13} \text{C} \)-bicarbonate in critically ill children receiving only glucose and electrolytes, those who were fed by total parenteral nutrition (TPN), or those who were fed by the enteral route; 2) to estimate EE from bicarbonate rates of appearance (Ra) and the EEqCO\(_2\); and 3) to compare rates of EE based on bicarbonate kinetics and EEqCO\(_2\) with the actual intakes received by critically ill children, the energy intakes recommended by the 2001 World Health Organization (WHO) publication (10), and those calculated with the use of the Schofield equations (11).

**SUBJECTS AND METHODS**

**Subjects**

Thirty-one critically ill children admitted to the Pediatric Intensive Care Unit (PICU) at Texas Children’s Hospital were studied. The major diagnoses were sepsis, pneumonia, and acute lung injury. All patients were studied when hemodynamically stable. Twelve children were studied in the TPN group, another 12 in the glucose-electrolytes group, and 7 in the enteral feedings group. Therefore, the glucose-electrolyte group was the closest possible representation of a fasting group. Drawing and infusing intravascular lines were placed in all patients. Patients with metabolic diseases or diabetes mellitus and those requiring renal replacement therapies or bicarbonate administration were excluded. The clinical characteristics of the patients are shown in Table 1.

All patients were supported on mechanical ventilation except 3 patients in the glucose-electrolytes group, who were breathing spontaneously. One patient in the TPN group received high-frequency oscillatory ventilation; all others remained on conventional ventilation. Almost all of the mechanically ventilated patients received continuous sedation with fentanyl and midazolam; 4 patients received morphine and midazolam. Four patients in the TPN group and 3 in the enteral group but none in the glucose-electrolytes group were given muscle-relaxant medication. Three patients in the glucose-electrolytes group who were breathing spontaneously received no sedation.

The mean (±SD) inspired oxygen concentration (FiO\(_2\)), mean airway pressure, and positive end-expiratory pressures among the groups were, respectively, 0.65 ± 38, 22 ± 5, and 9 ± 3 cm H\(_2\)O in the TPN group (12 patients); 0.44 ± 11, 15 ± 3, and 7 ± 2 cm H\(_2\)O in the enteral group (7 patients); and 0.40 ± 0.1, 10 ± 0.7, and 5 ± 3 cm H\(_2\)O in the 9 ventilated patients in the glucose-electrolytes group. The patients’ temperature fluctuated between 99.0 ± 1.984 ± 0.9, and 99.7 ± 1.2 °F in the TPN, enteral, and glucose-electrolytes groups, respectively. All patients had orders for temperature control by pharmacologic or physical (ie, cooling blanket) means. In the TPN group, 6 patients received dopamine and 3 patients received additional norepinephrine. In the enteral group, 1 patient received dopamine and 1 received milrinone. In the fasting group, 2 patients received dopamine and norepinephrine and 1 patient received dopamine, epinephrine, and vasopressin. Before entering the study, the patients had received TPN or enteral feedings for a mean of 5.5 ± 3.03 or 3.2 ± 2.5 d, respectively. The patients in the glucose-electrolytes group had received this solution for an average of 3.0 ± 2.9 d. All patients were assessed for severity of disease by using the Pediatric Risk Mortality (PRISM III) score, which predicts mortality rates in relation to acuity of disease (12), and all were studied within 72 h of PICU admission.

Written informed consent was obtained from the parents or guardians of all subjects. The study was approved by the Baylor College of Medicine Institutional Review Board.

**Diets**

Patients received TPN through a central venous catheter. Enteral feedings were provided through a nasojejunal tube placed for clinical indication, and the position of the tube was confirmed by X-ray. The glucose-electrolytes group received 5% dextrose and maintenance electrolytes. As shown in Table 2, the average intakes were 1.54 ± 0.96 and 2.02 ± 0.88 g protein · kg\(^{-1}\) · d\(^{-1}\) and 59.12 ± 20.59 and 45.99 ± 25.01 kcal · kg\(^{-1}\) · d\(^{-1}\) in the TPN and enteral fed groups, respectively. The glucose-electrolytes group had a minimal caloric intake of 10.82 ± 3.68 kcal · kg\(^{-1}\) · d\(^{-1}\). Protein and energy intakes of all groups were directed by the attending physician(s) as per standard clinical care, in collaboration with the Nutrition Service.

**Tracer study protocol**

On the day of the study, as shown in Figure 1, a 6-h intravenous tracer infusion of 99% enriched, sterile, and pyrogen-free NaH\(^{13}\)CO\(_3\) (Cambridge Isotope Laboratories, Andover, MA)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN (n = 12)</th>
<th>Enteral (n = 7)</th>
<th>Glucose-electrolytes (n = 12)</th>
<th>Overall</th>
<th>P(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>6:6</td>
<td>3:4</td>
<td>9:3</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Age (y)</td>
<td>7.8 ± 7.4(^2)</td>
<td>3.3 ± 4.1</td>
<td>6.3 ± 5.0</td>
<td></td>
<td>0.30</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>25.9 ± 21.8</td>
<td>13.0 ± 6.7</td>
<td>27.8 ± 22.6</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>18.8 ± 5.2</td>
<td>16.4 ± 3.5</td>
<td>18.7 ± 4.5</td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>pH</td>
<td>7.34 ± 0.08</td>
<td>7.33 ± 0.06</td>
<td>7.40 ± 0.08</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>PaCO(_2) (torr)(^3)</td>
<td>68.3 ± 17.2</td>
<td>67.0 ± 19.8</td>
<td>46.7 ± 14.2</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>PRISM III score</td>
<td>9.8 ± 2.6</td>
<td>8.0 ± 2.9</td>
<td>9.5 ± 7.1</td>
<td>0.72</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) TPN, total parenteral nutrition; PaCO\(_2\), arterial carbon dioxide tension; PRISM, Pediatric Risk Mortality. The chi-square test indicated no significant group differences with respect to sex.

\(^2\) ANOVA indicated no significant group differences according to the overall F test for age, weight, BMI, pH, or PRISM scores and no significant differences between any 2 groups on the basis of post hoc Tukey tests (P > 0.10 for all).

\(^3\) \(\bar{x} \pm \text{SD} \) (all such values).

\(^4\) PaCO\(_2\) production was significantly different in the TPN (P < 0.01) and enteral (P = 0.04) groups than in the glucose-electrolytes group.
Diego, CA). The tracer was prepared in a sterile physiologic saline solution by the Research Pharmacy at Texas Children’s Hospital and filtered through a 0.22-μm filter. Aliquots of the infused solution were collected at the end of the tracer study for measurement of infusate concentration.

At times −30 and 0 min, 2 baseline blood samples of 0.5 mL each were obtained; several samples were collected at 240, 300, 330, and 360 min. It was ensured that, during the blood transfer, air entered neither the blood-drawing nor the blood-collecting tube. Samples were transferred from the collection syringe into a 3-mL sodium heparin–coated, capped evacuated tube and maintained at room temperature. Samples were then processed as previously described (2). Blood samples were obtained from a preexisting intravascular catheter (arterial line) placed for clinical indication.

Measurement of carbon dioxide production rates

In the mechanically ventilated patients, the rates of VCO₂ (mL/min) were measured with a respiratory monitor (Cosmo; Respicont, Wallingworth, CT). The device was calibrated and directly connected to the endotracheal tube. Continuous measurements were obtained during the tracer study, and the average value was recorded. This respiratory monitor is routinely used per standard clinical practice in ventilated patients to adequately monitor pulmonary function; those readings displayed in the ventilator monitor may not be accurate, because of the plastic tubing compliance, dead space, etc. Three patients in the glucose-electrolytes group were breathing spontaneously. In these 3 patients, VCO₂ was measured by indirect calorimetry using a Vmax Encore calorimeter (Vyassis Healthcare, Yorbalinda CA) connected to a plastic canopy, which was placed over the head and chest of the patient. These patients were receiving FiO₂ ≤40%, and none of the 3 had air leaks through chest tubes.

Analyses

Analyses of blood samples for ¹³CO₂ enrichment were all conducted as previously described (13, 14). In brief, the carbon dioxide was liberated from the blood bicarbonate by adding 2 mL of 85% (by vol) phosphoric acid to the evacuated tube, and the contents of the tubes were mixed by vortex. The evacuated tube was then backfilled with nitrogen to bring it to atmospheric pressure, and then it was left to stand overnight. The liberated carbon dioxide was transferred to a plain, silicon-noncoated 15-mL tube (Venoject; Terumo Medical, Elkton, MD), which was subsequently backfilled with nitrogen to bring it to atmospheric pressure. The ¹³CO₂ enrichment was then measured by isotope ratio–mass spectrometry [Deltaplus XL Isotope Ratio Mass Spectrometer coupled with Gasbench-II; ThermoQuest Finnigan, Bremen, Germany (14)].

Calculations

Bicarbonate rates of appearance

The Ra of bicarbonate (μmol·kg⁻¹·h⁻¹) were calculated by using the standard isotope dilution, according to the following equation:

\[
Ra^{13}CO_2 = I \times \left[\frac{[Ei/EiCO_2]}{2} - 1\right]
\]

where \( I \) is the rate of NaH¹³CO₃ tracer infusion (μmol·kg⁻¹·h⁻¹), \( Ei \) is the enrichment of the NaH¹³CO₃ tracer (99%), and \( EiCO₂ \) is the mean isotopic enrichment of blood ¹³CO₂ at plateau during the tracer infusion (atom percent excess × 1000).

Fractional recovery of ¹³CO₂

The FR of NaH¹³CO₃ as blood ¹³CO₂ was estimated by using the following equation:

\[
FR^{13}CO_2 = \frac{(VCO_2 \times EiCO_2) / (I \times Ei)}{2}
\]

where \( VCO₂ \) measured in mL/min, was obtained by using a respiratory monitor or indirect calorimetry and converted to mmol/h by multiplying by 60 min and dividing by 22.4 (Avogadro’s number) to convert mL to mmol; \( I \) is expressed in mmol·kg⁻¹·h⁻¹, and \( Ei \) is the enrichment of the infusate (atom percent excess) (2).

### TABLE 2
Protein and energy intakes of study patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN (n = 12)</th>
<th>Enteral (n = 7)</th>
<th>Glucose-electrolytes (n = 12)</th>
<th>Overall P²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g·kg⁻¹·d⁻¹)</td>
<td>1.54 ± 0.96</td>
<td>2.02 ± 0.88</td>
<td>0 ± 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Energy (kcal·kg⁻¹·d⁻¹)</td>
<td>45.99 ± 25.01</td>
<td>59.12 ± 20.59</td>
<td>10.82 ± 3.68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1 TPN, total parenteral nutrition.

2 ANOVA indicated significant group differences according to the overall F test between the TPN and enteral feeding groups compared with the glucose-electrolytes group. \( P < 0.001 \) (post hoc Tukey test). No significant differences were found between the TPN and enteral groups for protein (\( P = 0.40 \)) or energy (\( P = 0.35 \)) intake.

3 \( \bar{x} \pm SD \) (all such values).

---

**FIGURE 1.** Experimental design for studies on bicarbonate kinetics in 31 critically ill children receiving enteral feedings (\( n = 7 \)), total parenteral nutrition (TPN) (\( n = 12 \)), or glucose and electrolytes (\( n = 12 \)).
**Predicted carbon dioxide production rates**

Predicted VCO2 rates (expressed in mmol·kg⁻¹·h⁻¹) were obtained by using the following equation:

\[
\text{Predicted } VCO2 \text{ rates } = \left( I \times \text{FR} \right) / \text{EEqCO2} \quad (3)
\]

where \( I \) is expressed in mmol·kg⁻¹·h⁻¹, and \( \text{FR} \) is the fractional recovery of NaH¹³CO₃ as blood ¹³CO₂.

**Energy equivalents of carbon dioxide**

The EECO₂ produced (kcal/L CO₂) (8) were assumed to be equal to those of the diet (EEqCO₂). The EEqCO₂ were calculated by using the following equation (8):

\[
\text{EEqCO₂ diet (kcal/L CO₂)} = 100 / \left[ \left( \%Eprot / \text{EEqCO₂ prot} \right) + \left( \%Ecarb / \text{EEqCO₂ carb} \right) + \left( \%Efat / \text{EEqCO₂ fat} \right) \right]
\]

where \( \%Eprot \), \( \%Ecarb \), and \( \%Efat \) represent the percentages of energy derived from the oxidation of protein, carbohydrate, and fat, respectively.

EEqCO₂ values for protein, carbohydrate, and fat were calculated by using the following equation (8):

\[
\text{EEqCO₂ prot (kcal/L CO₂)} = \left( \text{Prot} \times k \times 5.576 \right) + \left( \text{Carb} \times k \times 5.047 \right) + \left( \text{Fat} \times k \times 4.599 \right)
\]

where the caloric (kcal) fraction derived from protein, carbohydrate, or fat is multiplied by the respective EEqCO₂.

**Energy expenditure**

The predicted rates of EE (kcal·kg⁻¹·d⁻¹) were estimated from the RaCO₂ (equation 1) and from individual EEqCO₂ as shown in the following equation:

\[
\text{EE} = \text{RaCO₂} \times 22.4 \times \text{EEqCO₂} \times 24 \quad (6)
\]

where RaCO₂ is expressed as μmol·kg⁻¹·h⁻¹, 22.4 (Avogadro’s number) converts L CO₂/mol, and 24 is h/d (4).

**Statistical analysis**

All continuous data were tested for normality by using the Kolmogorov-Smirnov goodness-of-fit statistic; no significant departures were found. Analysis of covariance (ANCOVA) was used to compare mean fractional recovery between the 3 nutritional support groups (TPN, enteral feeding, and glucose-electrolytes) after control for the effects of continuous covariates (ie, age, BMI, and PRISM score) and categorical variables (ie, sex) (15). Differences between bicarbonate-predicted and measured rates of VCO₂ were analyzed by using paired \( t \) tests for each group. Repeated-measures analysis of variance (ANOVA), adjusted for covariates, was applied to evaluate differences in energy requirements as determined by using bicarbonate kinetics and equations of the WHO and Schofield for all 31 patients and each nutritional support group separately. The Tukey post hoc method was used to protect against an inflated type I error due to multiple group comparisons. In addition, the Bland-Altman method was used to assess agreement between 3 methods for determining energy requirements (ie, the WHO and Schofield equations and bicarbonate kinetics) and to construct 95% limits of agreement (16). This strategy was considered better for assessing agreement between paired measurements than were simple Pearson correlations. Mean bias (error) between methods and Bland-Altman plots was constructed on the basis of plotting the difference between the methods against the average. The relation between disease severity, as assessed by PRISM score, and the FR of bicarbonate was measured by using Pearson correlation coefficients (\( r \)). Statistical analyses were conducted by using SPSS software (version 15.1; SPSS Inc, Chicago, IL). Two-tailed values of \( P < 0.05 \) were considered significant.

**RESULTS**

The plasma isotopic enrichment of the bicarbonate tracer infused in the 3 groups is shown in Figure 2. Plateau enrichment was achieved by 240 min and maintained until the end of the tracer infusion. From this enrichment, the RaCO₂ were estimated. There were no significant differences (\( P > 0.05 \), ANOVA; \( P > 0.10 \), post hoc Tukey tests) between the groups with respect to age, weight, BMI, or the severity of disease as estimated by PRISM III scores. The glucose-electrolytes group had a higher pH and lower arterial carbon dioxide tension (\( P < 0.05 \); ANOVA and post hoc Tukey test) than did the TPN and enteral groups. There were no significant differences (ANOVA and post hoc Tukey test) in pH or arterial carbon dioxide tension between the TPN and enteral groups, but there was a significant

![FIGURE 2. Mean ± SEM plasma isotopic enrichment of blood ¹³CO₂ after a 6-h, primed, continuous tracer infusion of NaH¹³CO₃ in critically ill children.](image-url)
difference ($P < 0.05$; ANOVA and post hoc Tukey test) between those groups and the glucose-electrolytes group. Thus, the glucose-electrolytes group, although variable, appeared to have a better respiratory status than did the enteral and TPN groups. However, given the overall small sample size, a beta 2 error cannot be ruled out. As shown in Table 2, protein and energy intakes varied between the TPN and enteral groups. However, no significant differences were found between the TPN and enteral groups for protein ($P = 0.40$; ANOVA and post hoc Tukey test) or energy ($P = 0.35$; ANOVA and post hoc Tukey test) intakes. The glucose-electrolytes group, a surrogate for fasting state, received no protein and had a lower caloric intake, and, as expected, it differed significantly ($P < 0.001$; ANOVA and post hoc Tukey test) from the TPN and enteral groups. As shown in Table 3, the mean RaCO$_2$ varied between 0.17 ± 0.05 and 0.19 ± 0.07 μmol · kg$^{-1}$ · h$^{-1}$, and there was no significant difference among the groups ($P > 0.05$; ANOVA and post hoc Tukey test). The bicarbonate FR was 69.18%, 69.80%, and 62.87% in the TPN, enteral, and glucose-electrolytes groups, respectively, and there was no significant difference ($P > 0.05$; ANOVA and post hoc Tukey test) among the 3 groups. However, there was a positive and significant correlation between bicarbonate FR and the severity of disease, as estimated by the PRISM III score, in the TPN ($r = 0.73$, $P < 0.01$) and glucose-electrolytes ($r = 0.67$, $P = 0.02$) groups. No significant correlation was found in the enteral group, but the number of patients studied in this group was small.

The comparisons between measured and predicted VCO$_2$ rates among the 3 groups are also shown in Table 3. There was a close agreement ($R^2 = 0.99$, $P < 0.0001$; data not shown) between the predicted VCO$_2$ rates obtained by bicarbonate kinetics and both those measured with a respiratory monitoring device in the mechanically ventilation patients and those measured with indirect calorimetry in the 3 spontaneously breathing patients in the glucose-electrolytes group. This degree of agreement is not surprising, because of the mathematical interdependence between the estimates of VCO$_2$ rates and those of bicarbonate FR (16). There were no differences in VCO$_2$ rates among the 3 groups ($P > 0.05$; ANOVA and post hoc Tukey test).

The comparison in the 3 groups between energy requirements recommended by the 2001 WHO (10) and by the Schofield equations (11) in relation to those predicted by bicarbonate kinetics and EEqCO$_2$, after covariants were taken into account, is shown in Figure 3. For the TPN group, estimates of energy requirements were 81.3 ± 26.2, 52.2 ± 11.8, and 41.8 ± 12.6 kcal · kg$^{-1}$ · d$^{-1}$ according to the 2001 WHO recommendations, bicarbonate dilution kinetics, and the Schofield equations, respectively. Energy requirements based on the 2001 WHO recommendations were 55% higher than those obtained by bicarbonate kinetics ($P < 0.01$; ANOVA and post hoc Tukey test) and 95% higher than those obtained by the Schofield equations ($P < 0.0001$; ANOVA and post hoc Tukey test). Also in the TPN group, energy requirements predicted from bicarbonate kinetics were 20% higher ($P < 0.0001$; ANOVA and post hoc Tukey test) than those estimated by the Schofield equations.

In the enterally fed group, energy requirements were 86.4 ± 13.5, 60.7 ± 20, and 51.5 ± 9.1 kcal · kg$^{-1}$ · d$^{-1}$ according to the WHO recommendations, bicarbonate kinetics, and Schofield equations, respectively, whereas, in the glucose-electrolytes group, those requirements were 73.7 ± 19.8, 51.8 ± 18.0, and 44.1 ± 12.5 kcal · kg$^{-1}$ · d$^{-1}$, respectively. In both groups, the 2001 WHO estimates were significantly higher ($P < 0.0001$; ANOVA and post hoc Tukey test) than those obtained by bicarbonate kinetics and the Schofield equations, but there was no significant difference ($P > 0.5$; ANOVA and post hoc Tukey test) between the estimates obtained by bicarbonate kinetics and the Schofield equations. Hence, compared with bicarbonate kinetics and the Schofield equations, the WHO equations overestimated the energy requirements of critically ill children by ≈42% and ≈67%, respectively, in both the enteral and glucose-electrolytes groups.

To further assess whether the 3 methods to determine energy requirements were comparable, we used Bland-Altman analysis. The comparison between the 2001 WHO recommendations and those obtained from bicarbonate kinetics for the 31 patients showed a mean bias of 26 kcal · kg$^{-1}$ · d$^{-1}$ between methods. The variability between methods was 28.3 kcal · kg$^{-1}$ · d$^{-1}$, and the limits of agreement were between −31 and 83 kcal · kg$^{-1}$ · d$^{-1}$, which shows that the methods are not interchangeable. A comparison of the 2001 WHO recommendations and the Schofield equations found a mean bias of 34.6 kcal · kg$^{-1}$ · d$^{-1}$ and variability of 18 kcal · kg$^{-1}$ · d$^{-1}$. The limits of agreement were −1.4 to 70.6 kcal · kg$^{-1}$ · d$^{-1}$, which indicates, again, that the WHO recommendation and the Schofield equations are not comparable methods for estimating energy requirements in critically ill pediatric patients. Finally, the comparison between energy estimates predicted by bicarbonate kinetics and those estimated by the Schofield equations show a mean bias of 6.6 kcal · kg$^{-1}$ · d$^{-1}$ and variability of 13.7 kcal · kg$^{-1}$ · d$^{-1}$. The limits of agreement were −20.8 to 34 kcal · kg$^{-1}$ · d$^{-1}$, and thus the bicarbonate

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN ($n = 12$)</th>
<th>Enteral ($n = 7$)</th>
<th>Glucose-electrolytes ($n = 12$)</th>
<th>Overall $P^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RaCO$_2$ (μmol · kg$^{-1}$ · h$^{-1}$)</td>
<td>0.18 ± 0.04$^1$</td>
<td>0.17 ± 0.05</td>
<td>0.19 ± 0.07</td>
<td>0.78</td>
</tr>
<tr>
<td>Fractional $^{13}$CO$_2$ recovery (%)</td>
<td>69.18 ± 11.53</td>
<td>69.80 ± 20.50</td>
<td>62.87 ± 15.75</td>
<td>0.56</td>
</tr>
<tr>
<td>Predicted VCO$_2$ (mmol · kg$^{-1}$ · h$^{-1}$)</td>
<td>12.67 ± 2.48</td>
<td>12.01 ± 2.93</td>
<td>11.74 ± 2.54</td>
<td>0.71</td>
</tr>
<tr>
<td>Measured VCO$_2$ (mmol · kg$^{-1}$ · h$^{-1}$)</td>
<td>12.54 ± 2.46</td>
<td>12.18 ± 3.04</td>
<td>11.63 ± 2.52</td>
<td>0.72</td>
</tr>
</tbody>
</table>

$^1$ TPN, total parenteral nutrition.

$^2$ ANOVA indicated no significant group differences according to the overall $F$ test and no significant differences between any 2 groups according to post hoc Tukey tests ($P > 0.60$ for all).

$^3$ $\bar{x}$ ± SD (all such values).
kinetics and the Schofield equations also are not comparable methods for estimating energy requirements of critically ill pediatric patients.

Although energy intake recommendations in these patients were based on the WHO equations, the actual intake received by the TPN and enterally fed groups did not match the prescribed WHO-recommended intakes, which is not unusual in critically ill patients. Furthermore, when the actual intakes received by the patients were compared with the bicarbonate-predicted energy requirements, there was a clinically but not statistically significant difference. As shown in Figure 4, the actual individual intakes in the 3 groups of patients were higher or lower than those obtained by bicarbonate dilution kinetics. As expected, only the glucose-electrolytes group showed a significant difference ($P < 0.001$; ANOVA and post hoc Tukey test).

DISCUSSION

Changes in metabolic rates induced by feeding (17), exercise (18), or hormones (19) affect the rates of bicarbonate recovery. Thus, it is necessary to measure the bicarbonate FR under the same experimental conditions under which this factor will be used. In preparation for studies of amino acid requirements in critically ill children that used the carbon oxidative techniques, it was necessary to measure the bicarbonate FR in critically ill children under various metabolic conditions—ie, those fed parenterally or enterally and those receiving glucose and electrolytes. In contrast to data reported in healthy adults (2, 13), which show a clear difference in the fraction of bicarbonate recovered between the fasting and fed states, we did not observe a difference between the parenterally or enterally fed PICU patients and the glucose-electrolytes group, who served as a surrogate for fasting state. However, our “fasting” patients were never in a true fasting state, which could explain the present results. In addition, the sample size was limited, and a beta effect could potentially have occurred, which would prevent us from finding an effect of feeding on the fraction of bicarbonate recovered.

Neither the enteral nor parenteral route of nutrient administration affected the rates of bicarbonate recovery. This finding is in agreement with the data of others for preterm infants (20) and adults (17). Our values for the fraction of bicarbonate recovered were lower than values reported in mechanically ventilated adults (21), even though children have higher metabolic rates, and a higher bicarbonate recovery fraction would be expected. However, the adult study was conducted in 1993, and the standard care of critically ill patients has changed significantly since then. Better temperature regulation, pain control, and sedation protocols are now used; assisting ventilatory modes have considerably decreased the work of breathing. We found that patients with the highest acuity of disease had the greatest bicarbonate FR, which is consistent with the higher VCO₂ rates seen in sicker patients, although low VCO₂ rates can also be observed in terminal states.

Bicarbonate FR in the neonatal population has ranged from 72% to 119% in very-low-birth-weight babies (6) and from 69.6% to 83.5% in neonates with appropriate weight for gestational age (22). Higher values of bicarbonate FR in younger children with higher metabolic rates for body surface are expected.
Although the bicarbonate FR is affected by feeding, metabolic rate (V\textsubscript{CO\textsubscript{2}}), and severity of disease, the fractions of 0.69 and 0.70 obtained in our fed critically ill children are comparable to values of 0.70 obtained in 4 pilot studies conducted earlier in a similar population (23). Therefore this value is reproducible in our fed critically ill children are comparable to healthy adults against indirect calorimetry, the gold standard (2). These studies show reliable quantitative estimates of \text{}

Although \text{\textsubscript{VCO}}\text{\textsubscript{2}} rates are accurately measured by using a respiratory monitoring device attached to the mechanical ventilator, EE cannot be measured with these devices, and hence the need for indirect calorimetry, which is noninvasive and accurate. However, the use of indirect calorimetry to measured energy requirements is precluded in the sickest children, who require an FiO\text{\textsubscript{2}} > 0.6, or in those with air leaks via chest or endotracheal tubes. These conditions will render inaccurate measurements mainly of \text{\textsubscript{VO}}\text{\textsubscript{2}} and, therefore, of EE. It is precisely in this sickest population requiring a higher FiO\text{\textsubscript{2}} that adequate nutritional support is most necessary. However, because of the difficulties in obtaining accurate measurements in the sickest PICU patients, the estimates of EE and, consequently, the energy requirements in these patients are largely based on predictive equations derived from healthy populations. The WHO recommendations (10) and Schofield equations (11) are among the various methods frequently used in critically ill children.

In the present study population, we measured the Ra\text{\textsubscript{CO}}\text{\textsubscript{2}}, which varied between 0.17 and 0.19 \text{\textmu}mol \cdot \text{kg}^{-1} \cdot \text{h}^{-1}; by estimating the EEq\text{\textsubscript{CO}}\text{\textsubscript{2}} from the intakes received, we could determine energy requirements in critically ill children who were unfit for indirect calorimeter measurements. Our data showed that the WHO equations, compared with bicarbonate kinetics, overestimated energy requirements between 55% and 42% in critically ill pediatric patients, whether they were parenterally or enterally fed or were receiving only glucose and electrolytes. The comparison of the WHO estimates with those obtained by Schofield equations shows an even greater discrepancy, overestimating energy requirements by almost 2-fold in the parenterally fed patients and by \textless 67% in the enteral and glucose-electrolytes groups. In contrast, the Schofield equations, compared with bicarbonate dilution kinetics, significantly underestimated EE in the TPN but not in the enteral or glucose-electrolytes group. Nevertheless, the Bland-Altman analysis comparing bicarbonate-predicted and Schofield equations estimates in the 31 children show a substantial variability of 13.7 kcal \cdot \text{kg}^{-1} \cdot \text{d}^{-1}, and the limits of agreement varied from negative to positive numbers, which showed a considerable discrepancy. Hence, although there was not a statistically significant difference in mean values for energy requirements obtained by bicarbonate dilution kinetics and the Schofield equations in the enteral and glucose-electrolytes groups, there is a significant biological difference of -20.8 to 34 kcal \cdot \text{kg}^{-1} \cdot \text{d}^{-1}. The lack of significance could be related to our limited sample size. It has been consistently reported that predictive equations underestimate or overestimate energy requirements in critically ill children (24–27), and our data support this conclusion. The present study also showed that caloric recommendations were not necessarily matched by caloric intakes received by the patients, which illustrates the precarious nutritional support that critically ill children receive.

In summary, we measured the fraction of bicarbonate recovered after an infusion of Na\textsuperscript{13}CO\textsubscript{3} in critically ill children, parenterally or enterally fed or receiving glucose and electrolytes, and we observed that it correlates with severity of disease. We measured the Ra\text{\textsubscript{CO}}\text{\textsubscript{2}} derived from labeled bicarbonate infusion and observed that it is feasible to estimate energy requirements by bicarbonate dilution kinetics and EEq\text{\textsubscript{CO}}\text{\textsubscript{2}} in critically ill children.
ill pediatric patients under conditions in which indirect calorimetry would not be possible. The WHO recommendations and Schofield equations for measurement of EE overestimate and underestimate energy requirements in critically ill children.

The authors’ responsibilities were as follows—JS, AG, WEG, DG, JC-B, LJ, and LC: carried out the human phase of the experiments; DZ: conducted statistical evaluation of the data; JS and RMR: contributed to summarizing and calculating the raw data and revising the manuscript; WH: contributed to the experimental design and the manuscript; and LC: managed the overall project and wrote the manuscript. None of the authors had a personal or financial conflict of interest.

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