Longitudinal evaluation of energy expenditure in preterm infants with birth weight less than 1000 g

Jacqueline Bauer1*, Kathrin Maier 2, Gerald Hellstern 1 and Otwin Linderkamp 1

1Division of Neonatology, Department of Pediatrics, University of Heidelberg, Germany
2Department of Paediatrics, University of Freiburg, Germany

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The aim of the present study was to obtain serial values of O2 consumption (\(V_O_2\)), CO2 production (\(V_CO_2\)) and energy expenditure (EE) in healthy but extremely-low-birth-weight infants (birth weight <1000 g), during the first 5 weeks after birth. A total of seventeen spontaneously breathing and appropriate-for-gestational-age (birth weight and body length above the 10th and below the 90th percentile) preterm infants with gestational age 25–28 weeks and birth weight 590–990 g were enrolled in the study. Calorimetry was performed using an open-circuit calorimeter on days 6, 12, 18, 24, 30 and 36 of postnatal life. During the 5 weeks of observation, \(V_O_2\) increased from 4·7 (SD 0·5) to 9·1 (SD 1·0) ml/kg per min, \(V_CO_2\) from 4·5 (SD 0·4) to 8·3 (SD 0·6) ml/kg per min and EE from 115 (SD 12) to 310 (SD 71) kJ/kg per d. The energy intake was always higher than EE, even at days 6 and 12. The RER decreased from 0·99 (SD 0·09) at day 12 to 0·91 (SD 0·05) at day 30. On all study days, there were highly significant positive correlations between energy intake and weight gain, EE and weight gain, and EE and energy intake (\(P<0·05\)). Multiple regression analysis showed that on most study days EE was more affected by energy intake than by weight gain. We conclude that in healthy preterm infants with birth weight <1000 g, EE increases by about 150% in the first 5 weeks after birth, and that the EE values are related to energy intake and weight gain independent of postnatal age.

Energy expenditure: Growth: Preterm: Oxygen consumption

The substantial improvement of the survival rate in extremely-low-birth-weight (ELBW) infants (birth weight <1000 g) has changed the focus towards prevention of long-term morbidity. Adequate nutrition is an important prerequisite for intact survival of ELBW infants (Lucas, 1987; Lucas et al. 2001). Determinations of energy requirements are usually based on calculation of the energy balance (= energy intake (EI) – energy loss via faeces and urine – energy expenditure (EE)). Energy loss via faeces and urine is about 10% EI, independent of postnatal age and EI in preterm infants (Sauer et al. 1984a). However, EE tends to increase with increasing age. Chessex et al. (1981) suggested that EE increases with age of preterm infants due to increasing EI. Their assumption was based on only three serial studies in preterm infants with a mean birth weight of 1155 (SD 39) g. Leitch & Denne (2000) summarised published EE values measured in seventy-five preterm infants with birth weight <1000 g v. postnatal age, and found an increase of EE from 209 kJ/kg per d at birth to 272 kJ/kg per d at 5 weeks of age. However, thirty-five of the seventy-five infants were small-for-gestational-age with a mean postnatal age of 6–0 weeks, whereas forty infants had birth weights appropriate for gestational age and mean postnatal age of 2.5 weeks. Thus, the apparent increase in EE with age may be due in part to higher EE of small-for-gestational-age infants (Boehler et al. 1999).

Recommendations for EI and dietary intakes are usually based on the assumption that postnatal growth should be similar to that in utero to achieve intrauterine growth rates. Preterm infants need an EI of 419–503 kJ (100–120 kcal)/kg per d (Cooke & Embleton, 2000). However, preterm infants usually receive only about 100–120 kJ/kg on the first day after birth. EI is then increased by about 35 kJ/kg per d for 4–5 weeks until the recommended EI is reached. Cooke & Embleton (2000) calculated that 5 weeks after birth, ELBW infants have a cumulative deficit of energy of 3349 kJ (800 kcal)/kg. Reasons for this severe undernutrition include medical complications, assumed and actual feeding intolerance and concerns about necrotising enterocolitis.

Abbreviations: EE, energy expenditure; EI, energy intake; ELBW, extremely-low-birth-weight; \(V_CO_2\), carbon dioxide production; \(V_O_2\), oxygen consumption.

* Corresponding author: Dr Jacqueline Bauer, fax +49 6221 565602, email Jacqueline_Bauer@med.uni-heidelberg.de
No study on serial determinations of EE in ELBW infants has been found in the literature. The aim of our present study was to obtain serial values for EE in healthy preterm infants with birth weight <1000 g, by measuring O2 consumption (VO2) and CO2 production (VCO2) by indirect calorimetry.

Patients and methods
Seventeen spontaneously breathing preterm infants with mean gestational age of 26·6 (sd 1) (range 25–28, median value 27·0) weeks and mean birth weight of 836 (sd 101) (range 590–990, median value 820) g were enrolled in the study. Informed consent was obtained from the parents of each infant studied. The study had been approved by the Ethics Committee of the University of Heidelberg Medical Centre. Infants were free of major malformations, sepsicaemia, and pulmonary or circulatory compromise, and did not receive supplemental O2 during the study period. Because infants with intrauterine growth retardation may show increased EE (Picaud et al. 1994; Boehler et al. 1999), only appropriate-for-gestational-age infants (10th to 90th birth-weight percentile according to Munich growth charts; Riegel & Linderkamp, 1991) were included. Infants with hyperirritability were excluded, since EE increases with increasing physical activity (Billeaud et al. 1993). All infants were treated with caffeine for apnoea (Bauer et al. 2001). Serum concentrations of caffeine ranged from 10 to 15 μg/ml. No other stimulatory drugs were given during the study period. None of the infants received sedative or analgesic drugs.

Nutrition and body weight
Parenteral nutrition (glucose, amino acids and electrolytes) was started immediately after birth. Gastric nutrition (small amounts of preterm formula milk) was started on the first day of birth. On the first study day (day 6), infants received approximately 50% total EI parenterally and 50% enterally via a gastric tube. At 12–36 d, all infants were fed preterm formula milk exclusively. The preterm formula milk was given every 2 h via gastric tubes as a bolus. The formula contained 24 g protein, 78 g carbohydrate, 44 g fat and 3350 kJ/litre (Prematil®; Milupa, Friedrichsdorf, Germany). The same formula was used in all infants. Body weight was measured daily at 08.00 hours using a calibrated electronic scale with a resolution of 1 g. The weight gain was calculated as the mean value from six consecutive days around the calorimetric measurements (e.g. calorimetry at day 12, weight gain from day 10 to 15). The modified Atwater factor (Livesey, 2001) was used to estimate the energy content.

Monitoring and behavioural state
Heart rate, respiratory rate and O2 saturation were monitored continuously. Skin (lower leg) and rectal temperatures (Exacon 4000; Exacon, Roskilde, Denmark) were measured continuously for 2 h before, during and after indirect calorimetry. Skin temperature was kept constant at 34·5–35·8°C and rectal temperature was 36·5–37·5°C.

All infants were studied only during sleep (according to Freymond et al. 1986).

Indirect calorimetry
In seventeen infants, measurements of VO2 and VCO2 were performed by means of a portable open-circuit continuous indirect calorimetry device, the Deltatrac II Metabolic Monitor (Datex-Ohmeda, Instrumentarium Corp., Helsinki, Finland). Details of the technique, the precision of the VO2/measurement device and its validation for indirect calorimetry in neonates were as previously described (Bauer et al. 1996, 2002). The accuracy of the device was tested as a mean experimental error for VO2 measurements of 2 (sd 2) % (Bauer et al. 1997). This transportable device consists of a fast differential paramagnetic O2 sensor and an infrared CO2 sensor attached to a silicon face mask that was continuously ventilated by a constant-flow generator. The device does not measure inspiratory and expiratory O2 concentration separately, but measures O2 differences of 0·1 ml/l as a 1 min average very accurately. Calibration of the device was performed before each measurement with a standard calibration gas (O2–CO2, 5:95). The analyser was set at zero according to room air. Calibration gases were prepared to an accuracy of ±0·03 % and certified gravimetrically. A silicon face mask and a sampling flow of 3 litres/min were used. The Deltatrac II monitor stores each minute-to-minute value of VO2 and VCO2 electronically. At the end of the measurements the values were transmitted to a personal computer and processed using SAS for Windows (SAS Institute Inc., Cary, NC, USA). The non-protein EE was calculated as: EE (kJ/kg per d) = 5·50 VO2 (kJ/kg per d) + 1·76 VCO2 (kJ/kg per d) (Weir, 1949). Marks et al. (1987) and Bauer et al. (1997, 1998) showed that a face mask gives more reliable results in very-low-birth-weight infants (<1500 g) than a hood, and offers the advantage of ready access to the infant. Errors in VO2 and VCO2 measurements may result from incomplete breath sampling, inaccurate flow measurement and rapid changes of physiological variables such as increasing activity or changing body temperature. The relatively low flow rate of 3 litres/min used in our present study, and in those of other authors, on preterm infants has been shown to be accurate up to a tidal volume of 15 ml (Bauer et al. 1997, 1998). The flow is accurately delivered by the device (Perring et al. 2000). Infants in our present study were continuously observed by the principal investigator (J. B.). Rectal and skin temperature remained constant throughout each study period. The five-minute-to-five-minute variability of the VO2 and VCO2 measurements was studied in ten preterm infants during one study period. Variability averaged 1·2 (sd 0·7) %.

Study protocol
If inclusion criteria were fulfilled, measurements of VO2 and VCO2 were started on day 6 of postnatal life. The measurements were repeated in all seventeen infants on days 12, 18, 24, 30 and 36. Calorimetry was started at 15.00 to 16.00 hours and lasted for 4 h. Because VO2 and VCO2 are strongly influenced by feeding, each period of
indirect calorimetry began 45 min after feeding, according to published recommendations (Stothers & Warner, 1979). Measurements were started after an equilibration time of 15 min as described by the manufacturer. Therefore, each period of calorimetry began 60 min after feeding and lasted for 60 min to minimise effects of postprandial thermogenesis on the results. Four periods of measurements were done to obtain 4 h of calorimetry. The four mean values of \( V_O \) and \( V_{CO_2} \) were used for calculation of individual EE values. Measurements were not interrupted by nursing routine. Indirect calorimetry and temperature measurements were done in a double-walled, air temperature-controlled incubator (model 8000; Draeger AG, Lübeck, Germany) at thermoneutral temperatures (31–37°C) and humidity of 60–75 %, in accordance with the recommendations of Sauer et al. (1984a,b). All infants were treated in the same type of incubator.

**Results**

The values of \( V_O \) and \( V_{CO_2} \) increased 2-0-fold, and EE 2.5-fold, during the observation period of 5 weeks (Tables 1 and 2). EI was always greater than EE and reached a maximum value of 495 kJ/kg per d on day 36. Due to an early loss of 10 % body weight, the mean weight gain was negative during the first week of birth. Birth weight was regained during the second or third week, at a mean value of 14 d after birth.

On each study day there were highly significant correlations between EE and EI, EE and weight gain, and EI and weight gain (Table 3; \( P<0.001 \)).

The correlation coefficients indicate that both EI and weight gain increased EE. To assess the relative contributions of EI and weight gain, multiple regression analysis, using EE as dependent variable and EI and weight gain as independent variables, was done separately for each study day from day 12 to 36. On days 12, 18 and 30, EI contributed about two-thirds and body weight one-third to each unit increase of EE. At day 24, only EI contributed significantly (\( P<0.05 \)), and at day 36 only weight gain contributed to increases in EE.

**Discussion**

Our present investigation was designed to study the effect of postnatal age on EE in ELBW infants during the first 5 weeks after birth. Serial studies on EE and other nutritional results have not been published previously for ELBW infants with birth weight <1000 g. Leitch & Denne (2000) summarised results from twelve reports on EE in ELBW infants and calculated a rise of EE from 209 kJ/kg per d during the initial days to 272 kJ/kg per d at 5 weeks of postnatal age. Gudinchet et al. (1982) studied EE in three infants with birth weight <1000 g. Two were studied at 1 and 4 weeks of age and one infant was studied at 2, 3, 5 and 6 weeks of age. At 1 week of age, EE averaged 163 kJ/kg and at 4 weeks 253 kJ/kg. We found a much more pronounced rise of EE from 115 (SD 12) kJ/kg per d at day 6 to 310 (SD 71) kJ/kg per d at day 36 (Table 2). The greater initial values measured in previous studies may be explained by the inclusion of infants with severe respiratory disease and mechanical ventilation (Wahlig et al., 1994), whereas the infants in the present study were free of respiratory and other complications. Moreover, our present infants were nursed in double-walled incubators to minimise heat loss, whereas some of the previous investigators used open incubators, thereby increasing the heat loss greatly (Sauer et al., 1984b). In the study of Gudinchet et al. (1982), EI at 1 week of age averaged 299 kJ/kg per d. The higher EI may have increased EE in their infants.

We found a positive energy balance during the entire observation period. In two previous studies on EI and EE in ELBW infants with postnatal age <7 d, EI was only 126 and 155 kJ/kg per d and the EE was 205 and 230 kJ/kg per d, thus resulting in a highly negative energy balance (Samiec et al., 1994; Wahlig et al., 1994). Gudinchet et al. (1982) found a positive energy balance in two preterm infants with birth weight <1000 g of 140 kJ/kg per d at 7 d of age. Infants in their study were without major medical problems, as in our present study.

We found highly significant relationships between EE and EI and between EE and weight gain at each study day. The results of multivariant analysis showed that EI had a stronger effect on EE than weight gain on most study days. This suggests that the increase in EE with postnatal age is not causally related to increasing age, but due to the increase in EI and weight gain.

From their overall relationship between EE and weight gain, Chessex et al. (1981) calculated a minimum EE (without weight gain) of 232 kJ/kg per d. The minimum EE in our present infants was much less, in particular

<table>
<thead>
<tr>
<th>Postnatal age (d)</th>
<th>Body weight (g)</th>
<th>Body length (m)</th>
<th>( V_O ) (ml/kg per min)</th>
<th>( V_{CO_2} ) (ml/kg per min)</th>
<th>RER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
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<td>4.5 0.4</td>
<td>0.95 0.05</td>
</tr>
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<td>819 204</td>
<td>0.34 0.012</td>
<td>5.6 0.5</td>
<td>5.6 0.5</td>
<td>0.99 0.09</td>
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<td>7.0 0.3</td>
<td>6.9 0.4</td>
<td>0.98 0.03</td>
</tr>
<tr>
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<td>956 103</td>
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<td>7.6 0.6</td>
<td>7.3 0.5</td>
<td>0.98 0.05</td>
</tr>
<tr>
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<td>8.8 0.6</td>
<td>8.0 0.3</td>
<td>0.91 0.05</td>
</tr>
<tr>
<td>36</td>
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<td>0.39 0.019</td>
<td>9.1 1.0</td>
<td>8.3 0.6</td>
<td>0.91 0.04</td>
</tr>
</tbody>
</table>

* For details of subjects and procedures, see p. 534.
Table 2. Serial values of energy balance and daily weight-gain values in preterm infants*

<table>
<thead>
<tr>
<th>Postnatal age (d)</th>
<th>Energy intake (kJ/kg per d)</th>
<th>Energy expenditure (kJ/kg per d)</th>
<th>Weight gain (g/kg per d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
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<tr>
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<td>60</td>
<td>277</td>
</tr>
<tr>
<td>36</td>
<td>495</td>
<td>91</td>
<td>310</td>
</tr>
</tbody>
</table>

* For details of subjects and procedures, see p. 534.

Table 3. Relationships between energy expenditure, energy intake and weight gain in preterm infants*

<table>
<thead>
<tr>
<th>Age (d)</th>
<th>EE v. EI†</th>
<th>EE v. WG†</th>
<th>EI v. WG†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression equation</td>
<td>r²</td>
<td>Regression equation</td>
</tr>
<tr>
<td>6</td>
<td>EE=0·38EI+10·51</td>
<td>0·77</td>
<td>–</td>
</tr>
<tr>
<td>12</td>
<td>EE=0·45EI+1·06</td>
<td>0·78</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>EE=0·47EI+15·21</td>
<td>0·93</td>
<td>EE=8·84WG+67·4</td>
</tr>
<tr>
<td>24</td>
<td>EE=0·78EI−92·14</td>
<td>0·88</td>
<td>EE=7·75WG+149·5</td>
</tr>
<tr>
<td>30</td>
<td>EE=0·64EI−37·79</td>
<td>0·88</td>
<td>EE=7·75WG+157·7</td>
</tr>
<tr>
<td>36</td>
<td>EE=0·73EI−56·10</td>
<td>0·88</td>
<td>–</td>
</tr>
</tbody>
</table>

EE, energy expenditure; EI, energy intake; WG, weight gain.
* For details of subjects and procedures, see p. 534.
† EE was expressed as kJ/kg per d, EI as kJ/kg per d and WG as g/kg per d.

during the first 18 d after birth (39·1–67·4 kJ/kg per d), but increased to 149·5 kJ/kg per d on day 30 (Table 3). Chessex et al. (1981) do not report whether the infants in their study suffered from respiratory distress or whether they were nursed in closed or open incubators.

EE per g weight gain, calculated from regression analysis, decreased from 10·5 kJ/kg per d at day 12 to 7·8 kJ/kg per d at days 30 and 36. From the regression equation EE = weight gain × b + a, the minimum EI without weight gain (a) and the EI per g weight gain (b) can be calculated. The wide range of energy storage per g weight gain can be calculated. Values were 18·6, 14·8, 10·6, 12·2 and 9·7 kJ/g on days 12, 18, 24, 30 and 36 of postnatal age respectively. A postnatal decrease in energy storage per g weight gain can also be derived from results in literature reviewed by Leitch & Denne (2000). A postnatal decrease in the energy storage per g weight gain could be explained by decreasing fat:protein ratio in newly formed tissues, since the energy value of fat (38·75 kJ/g) is greater than that of protein (23·67 kJ/g) (Ziegler et al. 1976).

We conclude that extremely small but healthy preterm infants expend relatively little energy during the first 2 weeks after birth. They increase their EE during the first weeks of postnatal age by 150 %, due to rising EI and weight gain. The evidence suggests that the energy stored per g weight gain decreases during the first 3 weeks due to decreasing fat:protein ratios in new tissue. Longitudinal measurements of energy, protein and fat intakes, losses via faeces and urine, EE and weight gain in healthy extremely small preterm infants are necessary to assess this further.

References

Bauer J, Sontheimer D, Fischer Ch & Linderkamp O (1996) Metabolic rate and energy balance in very low birth weight


