Effect of Sepsis Syndrome on Neonatal Oxygen Consumption and Energy Expenditure

Jacqueline Bauer, MD*; Roland Hentschel, MD†; and Otwin Linderkamp, MD*

ABSTRACT. Objective. To evaluate oxygen consumption (VO\textsubscript{2}), carbon dioxide production, and energy expenditure (EE) in full-term neonates with early-onset neonatal sepsis daily for 7 days beginning at the day of clinical diagnosis of sepsis.

Methods. A total of 17 spontaneously breathing full-term neonates, 10 with clinical signs of sepsis and 7 healthy neonates (control group), were enrolled in the study. Age at first study day was 3 ± 0.9 days in both groups. Sepsis syndrome was defined as a systemic response to a bacterial infection with clinical signs of infection, elevated values of interleukins 6 and 8 and C-reactive protein, and abnormal white blood cell count and positive blood cultures (9 group B streptococci, 1 Escherichia coli). Measurements of VO\textsubscript{2} and carbon dioxide production were performed daily for 7 days by means of indirect calorimetry.

Results. In the septic infants, VO\textsubscript{2} and EE were increased by about 20% at days 1 to 3 and by 15% at day 4 when compared with the controls. From days 1 to 3, EE averaged 57 ± 3 kcal/kg/d in the neonates and 47 ± 2 kcal/kg/d in the controls. At day 4, EE was 55 ± 2 and 47 ± 2 kcal/kg/d, respectively. Energy intake was about the same in both groups, whereas weight gain during the 7 study days was significantly lower in the sick patients than in the control group (19 ± 2 g/d vs 33 ± 9 g/d and 5.4 ± 0.5 g/kg/d vs 9.4 ± 2.6 g/kg/d, respectively). Increased EE was associated with increased heart rate (126 ± 4 vs 112 ± 4 min\textsuperscript{-1} at day 1) and respiratory rate (56 ± 6 vs 40 ± 4 min\textsuperscript{-1} at day 1). There were no differences in rectal temperature (37.3 ± 0.4 °C vs 37.4 ± 0.2 °C), skin temperature (36.5 ± 0.4 °C vs 36.6 ± 0.3 °C), and oxygen saturation (96 ± 3% vs 96 ± 3% between the 2 groups.

Conclusions. Neonates with sepsis syndrome have elevated VO\textsubscript{2} and EE values that could explain impaired growth during the illness period and may make the infants vulnerable to insufficient calorie supply during the acute phase of septic disease. Pediatrics 2002;110(6). URL: http://www.pediatrics.org/cgi/content/full/110/6/e69; oxygen consumption, energy expenditure, sepsis, newborn.

ABBREVIATIONS. VO\textsubscript{2}, oxygen consumption; V\textsubscript{CO\textsubscript{2}}, carbon dioxide production; EE, energy expenditure; SNAP, score for neonatal acute physiology (SNAP); IL, interleukin; CRP, C-reactive protein.

From the *Division of Neonatology, Department of Pediatrics, University of Heidelberg, Heidelberg, Germany; and †Division of Pediatrics, University of Freiburg, Freiburg, Germany.Received for publication Apr 29, 2002; accepted Aug 6, 2002.

Reprint requests to (J.B.) Division of Neonatology, Department of Pediatrics, University of Heidelberg, Im Neuenheimer Feld 150, D-69120 Heidelberg, Germany. E-mail: jacqueline.bauer@med.uni-heidelberg.de

PEDIATRICS (ISSN 0031-4005). Copyright © 2002 by the American Academy of Pediatrics.

http://www.pediatrics.org/cgi/content/full/110/6/e69

T

The sepsis syndrome in adults is associated with hypermetabolism characterized by increased oxygen consumption (VO\textsubscript{2}), increased carbon dioxide production (V\textsubscript{CO\textsubscript{2}}), and increased resting energy expenditure (EE). Increments in EE by 20% to 90% have been reported in adults with sepsis as a result of trauma, peritonitis, pancreatitis, or various underlying diseases. In septic adults, EE was increased for up to 3 weeks after the beginning of the disease.

Little is known about VO\textsubscript{2} and EE in septic neonates. Turi et al studied EE in 15 septic infants and children with ages ranging from 3 days to 7 years. The values were not different from those of controls. Mrozek et al determined VO\textsubscript{2} in 7 newborn infants with sepsis syndrome (gestational age, 34–41 weeks) and compared the results with those in sick infants with presumed but without proven septicemia. They observed a positive correlation between VO\textsubscript{2} and the degree of illness (score for neonatal acute physiology [SNAP]) but no significant difference between the 2 groups. The VO\textsubscript{2} values did not change at recovery from sepsis. Necrotizing enterocolitis in neonates with gestational age ranging from 28 to 40 weeks and postnatal age of 6 to 47 days was not associated with increased VO\textsubscript{2} and EE.

Because VO\textsubscript{2} and EE are strongly affected by the gestational and postnatal age, the wide range of gestational and postnatal ages in previous studies may have hidden effects of neonatal sepsis on VO\textsubscript{2} and EE. The present investigation was designed to study VO\textsubscript{2}, V\textsubscript{CO\textsubscript{2}}, and EE in term infants with early-onset sepsis (ie, beginning within the first 5 days of postnatal life) daily during the first 7 days of the septic illness.

METHODS

Patients

Seventeen full-term neonates with gestational age of 38 to 40 weeks (mean ± standard deviation: 39 ± 1 week) and birth weight of 3100 to 4000 g (3518 ± 277 g) were enrolled in the study (Table 1). The 17 infants were born and treated in the Perinatal Center of the University of Freiburg or in the Perinatal Center of the University of Heidelberg. All infants were spontaneously breathing without supplemental oxygen. Ten had clinical signs of sepsis, and 7 were healthy neonates. Infants with malformations, chromosomal anomalies, erythroblastosis, diabetic mothers, perinatal asphyxia (pH <7.20), or intrauterine growth retardation were excluded. Maternal risk factors of premature rupture of the membranes, maternal fever, and maternal colonization with group B streptococci were present in 5 infants in the sepsis group. Sepsis syndrome was defined as a systemic response to a bacterial infection with clinical signs of infection, elevated interleukins (ILs) 6 and 8 (IL-6 >6 pg/mL, IL-8 >35 pg/mL), increased C-reactive
indicators (eg, adoption).

Table 1. Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Sepsis Group (n=10)</th>
<th>Control Group (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>3490 + 314</td>
<td>3547 + 230</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>39 + 0.9</td>
<td>39 + 0.9</td>
</tr>
<tr>
<td>Age at first study day (d)</td>
<td>3 + 0.9</td>
<td>3 + 0.9</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>150 + 50</td>
<td>0</td>
</tr>
<tr>
<td>Leukocyte count (cells/µL)</td>
<td>28.184 + 4732</td>
<td>0</td>
</tr>
<tr>
<td>SNAP score</td>
<td>4.4 + 1.0</td>
<td>0 + 0</td>
</tr>
<tr>
<td>Arterial pH at first study day</td>
<td>7.29 + 0.1</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation (SD).

protein (CRP; ≥50 mg/L), and abnormal neutrophil count. Neutropenia (<2.5 × 10^9/L) and neutrophilia (>8.7 × 10^9/L) were defined according to a reference range for healthy neonates studied at 3 days after birth. Two infants with presumed sepsis showed neutropenia, and 8 infants had neutrophilia. Sepsis was clinically diagnosed when 2 or more of the following conditions were present: abdominal distension, feeding intolerance, lethargy, irritability, temperature instability, hepatomegaly and jaundice, tachycardia or bradycardia, and respiratory rate >50 breaths/min. In all newborns investigated for neonatal infection, blood samples were collected for blood cell counts, CRP, and ILs. Blood, urine, and surface swabs were obtained for cultures. Six patients showed positive blood cultures, clinical symptoms of sepsis, and laboratory signs of infection and 4 infants showed clinical symptoms and elevated CRP, IL levels and positive surface swab, or urine cultures but negative blood cultures. Nine of the 10 infants had group B streptococci cultured in blood and/or surface swabs, and 1 neonate had Escherichia coli in blood culture and surface swabs. Cerebrospinal fluid was obtained from 3 patients with negative culture results. Calorimetry in infants with presumed sepsis was done 1 to 2 hours after the time of diagnosis (ie, before culture results were available), when IL-6, IL-8, and CRP were elevated, and the blood picture was abnormal, and clinical signs of sepsis were present. Two infants met all of these criteria, but no bacteria grew in any of the cultures. These 2 infants were retrospectively excluded from the study. In all infants with presumed sepsis, chest radiographs were done. Pneumonia was diagnosed in 2 of the 10 infants. The 10 infants with proven or presumed diagnosis of sepsis were treated for 7 days with antibiotics (pipercillin, 200 mg/kg/d, and netilmicin, 5 mg/kg/d). No catecholamines, methylyxanthines, sedatives, or analgesics were given during the study period. The degree of illness severity on day 1 was measured using the SNAP. All infants with laboratory and clinical signs of sepsis and born in the year 2000–2001 were studied prospectively. Altogether, 17 infants met the inclusion criteria. However, parents of 3 infants refused to participate and 4 were admitted at a time when the principal investigator (J.B.) was not available for calorimetry. Seven healthy full-term infants matched for birth weight and gestational age served as control group. Healthy infants were admitted to the hospital because of maternal indications (eg, adoption).

### Nutrition and Weight

During the whole study period, all infants were fed every 4 hours with an infant formula. The formula contained 1.8 g of protein, 8.1 g of carbohydrate, 3.7 g of fat, and 72 kcal/mL. Both groups had comparable calorie and fluid intake during the study period. Body weight was measured shortly after admittance to the hospital and then daily at 8 AM by using a scale with a resolution of 5 g. Weight gain was calculated as difference of the weight of the study day and the weight of the previous day.

### Monitoring and Behavioral State

Heart rate, respiratory rate, and oxygen saturation (Marquette Hellige, Freiburg, Germany) were monitored, and periodic breathing and event data (apneas, bradycardias, oxygen desaturation) were recorded continuously on a computer. Skin (lower leg) and rectal temperatures (Exacon 4000, Roskilde, Denmark) were measured continuously 2 hours before, during, and 2 hours after indirect calorimetry. Measurements of indirect calorimetry were done in a temperature-controlled incubator (Draeger AG, Lübeck, Germany) at thermoneutral temperature according to published recommendations. All of the infants were treated in the same type of incubator.

The behavioral states of all infants were recorded throughout the measurement period, based on the modified Freymond Behavioral State Scale. Four different behavioral states were distinguished: 0, eyes open or closed, regular respiration, no movements; 1, small movements; 2, vigorous movements; and 3, crying. All the infants were studied only during sleep (state 0–1).

### Indirect Calorimetry

Measurements of VO_2 and VCO_2 were performed by means of a portable open-circuit continuous indirect calorimetry device, the Deltatrac II Metabolic Monitor (Datex-Ohmeda, Instrumentarium Corp, Helsinki, Finland) by 1 investigator (J.B.). Details of the technique and the precision of the VO_2 measurement device and its validation for indirect calorimetry in neonates were as previously described. The device consists of a differential paramagnetic oxygen sensor and an infrared carbon dioxide sensor attached to a transparent hood that is continuously ventilated by a constant-flow generator, thus offering the advantage of ready access to the infant. The device measures differences between inspiratory and expiratory oxygen concentrations with an accuracy of 0.01% (vol). Thus, at a Deltatrac II flow constant of 3 L/min (room air and expiration air of the patient), the accuracy in VO_2 measurements is ±0.3 ml/min. Differential measurement is based on repeated automatic zeroing (every 4 minutes) during the measuring sequence. The calibration of the device was performed before each measurement by a standard calibration gas (5% CO_2 and 95% O_2). The analyzer was set at 0 according to room air. Calibration gases were prepared to an accuracy of ±0.05% and certified gravimetrically. The Deltatrac II stores each minute-to-minute value of VO_2 and VCO_2 electronically. At the end of the measurements, the values were transmitted to a personal computer and processed using SAS for Windows (SAS Institute, Cary, NC). Energy expenditure was calculated as EE = 5.50 VO_2 + 1.76 VCO_2 (in kilocalories per kilogram per day).

### Study Protocol

Informed consent was obtained from the parents of each infant studied before the first calorimetric measurement. When inclusion criteria were fulfilled, a total period of 6-hour measurements of VO_2 and VCO_2 was started within 12 hours of admittance to the hospital for clinical signs of sepsis. Because VO_2 and VCO_2 are influenced strongly by feeding, each period of indirect calorimetry began 45 minutes after feeding and lasted for 195 minutes. Measurements were started after an equilibrium time of 15 minutes as recommended by the manufacturer. Measurements were not interrupted by nursing routine. After the next feeding and nursing routine, a second measurement period was repeated under identical conditions. The measurements were repeated daily under identical conditions for 7 days.

### Statistical Analysis

Data were expressed as group means and standard deviation of the mean. Groups mean values were compared using a t test. P < .05 was considered significant.

### RESULTS

The septic newborn infants showed higher heart rate and respiratory rate (P < .005) during the first 2 observation days compared with the control group (Table 2). There were no differences in rectal temperature (37.3 ± 0.4°C vs 37.4 ± 0.2°C), skin temperature (36.5 ± 0.4°C vs 36.6 ± 0.3°C), and oxygen saturation (96 ± 3% vs 96 ± 3%) between the 2 groups. Weight gain during the 7 study days was significantly (P < .005) lower in the sick patients than in the control group (19 ± 2 g/d vs 33 ± 9 g/d or 5.4 ± 0.5 g/kg/d vs 9.4 ± 2.6 g/kg/d). In the septic infants, no significant weight gain occurred from day 1 to day 2 and from day 2 to day 3 (Table 2). SNAP scores obtained on day 1 of the study were 4.4 ± 1.0 in the septic infants and 0 ± 0 in the controls.
in both groups. EE in the infant with balance was positive during the entire study period infants correlated with EE (kcal/kg/d on days 1, 2, and 3, respectively). More–in the range of the other septic infants (58, 56, and 54 kcal/kg/d). Therefore, we had to stop calorimetry in these 3 infants and intake a marked reduction of the energy stored (energy 1). Three infants showed pe-

tations of sepsis.

All 17 infants spent the entire time during calorimetry in sleep (states 0–1). Three infants showed periods with activity states >1 during the study. Because Vo2 and EE could be obtained only in states 0 to 1, we had to stop calorimetry in these 3 infants and the investigation was repeated successfully 4 hours later.

In the septic infants, Vo2 and EE were increased by approximately 20% at days 1 to 3 and by 15% at day 4 when compared with the controls. From day 5 to 7, no differences were observed (Table 3). Because energy intake was approximately the same in both groups, increased EE in the septic group resulted in a marked reduction of the energy stored (energy intake – EE) during the first 3 days (Table 3). Energy balance was positive during the entire study period in both groups. EE in the infant with E coli sepsis was in the range of the other septic infants (58, 56, and 54 kcal/kg/d) on days 1, 2, and 3, respectively. Moreover, there were no differences in EE between infants with neutropenia and neutrophilia.

The SNAP score calculated on day 1 for the septic infants correlated with EE (r = 0.54) and Vo2 (r = 0.54) on day 1, although infants were not ventilated, did not require supplemental oxygen or inotropic support, and showed only mild clinical manifestations of sepsis.

DISCUSSION

In the present investigation, full-term neonates with septicemia showed an increase in Vo2 and EE by approximately 20% during the first days of their illness when compared with healthy controls. In adults with septicemia, Vo2 and EE were found to increase by 20% to 90% when compared with adult controls.1–7 Kreymann et al2 observed that the basal metabolic rates were more increased in adults with uncomplicated sepsis (+55%) than in adults with sepsis syndrome (+24%) and septic shock (+2%). Uncomplicated sepsis was classified when clinical signs of fever, tachycardia, and tachypnea were present but no signs of altered organ function or perfusion were found.2 The clinical findings in the septic infants of our study corresponded to the criteria defined by Kreymann et al2 for adults with uncomplicated sepsis. Thus, different degrees of septic illness may explain that in contrast to our results, other authors found no change in Vo2 and EE in neonates with sepsis or necrotizing enterocolitis.9,10 Neonates in the previous studies were more se-

| TABLE 2. Physiological Parameters in 10 Septic Neonates and 7 Control Infants |
|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                 | 1              | 2              | 3              | 4              | 5              | 6              | 7              |
| Heart rate (min⁻¹) |
| Septic          | 126 ± 4*       | 124 ± 3*       | 122 ± 3*       | 114 ± 6       | 109 ± 4       | 108 ± 3       | 102 ± 4       |
| Control         | 112 ± 4        | 113 ± 7        | 110 ± 8        | 108 ± 7       | 109 ± 5       | 106 ± 4       | 110 ± 5       |
| Respiratory rate (min⁻¹) |
| Septic          | 56 ± 6*        | 52 ± 3*        | 42 ± 4         | 37 ± 2        | 38 ± 2        | 38 ± 2        | 40 ± 3        |
| Control         | 40 ± 4         | 36 ± 2         | 40 ± 3         | 37 ± 2        | 39 ± 1        | 38 ± 3        | 39 ± 2        |
| Body weight (g) |
| Septic          | 3353 ± 292     | 3358 ± 295     | 3362 ± 288     | 3385 ± 293    | 3415 ± 291    | 3450 ± 275    | 3488 ± 292    |
| Control         | 3488 ± 189     | 3508 ± 182     | 3535 ± 180     | 3570 ± 185    | 3603 ± 187    | 3647 ± 186    | 3722 ± 199    |

Data are mean ± SD.
* P < .005 compared with control group.

| TABLE 3. Serial Values of Energy Balance in 10 Neonates With Sepsis (S) and 7 Healthy Newborns (C) |
|-----------------|-----------------|-----------------|----------------|-----------------|-----------------|-----------------|-----------------|
|                 | 1              | 2              | 3              | 4              | 5              | 6              | 7              |
| Vo2 (mL/kg/min) |
| Sepsis          | 8.1 ± 0.5†     | 8.2 ± 0.4†     | 8.1 ± 0.2†     | 7.7 ± 0.3†     | 7.1 ± 0.3      | 7.0 ± 0.3      | 7.2 ± 0.4      |
| Control         | 6.7 ± 0.6      | 6.7 ± 0.4      | 6.7 ± 0.2      | 6.7 ± 0.3      | 6.9 ± 0.5      | 6.8 ± 0.3      | 7.1 ± 0.4      |
| Vco2 (mL/kg/min) |
| Sepsis          | 7.6 ± 2.4†     | 7.3 ± 1.9†     | 7.1 ± 1.5†     | 7.1 ± 1.1†     | 6.7 ± 0.7      | 7.0 ± 0.5      | 7.0 ± 0.3      |
| Control         | 6.3 ± 0.4      | 6.0 ± 0.3      | 6.1 ± 0.3      | 6.1 ± 0.3      | 6.6 ± 0.5      | 6.6 ± 0.4      | 6.9 ± 0.2      |
| RQ              |
| Sepsis          | 0.93 ± 0.04    | 0.88 ± 0.03    | 0.86 ± 0.04‡   | 0.91 ± 0.04    | 0.94 ± 0.05    | 0.98 ± 0.06    | 0.96 ± 0.05    |
| Control         | 0.94 ± 0.05    | 0.89 ± 0.04    | 0.91 ± 0.03    | 0.92 ± 0.04    | 0.94 ± 0.03    | 0.99 ± 0.03    | 0.97 ± 0.04    |
| EE (kcal/kg/d)  |
| Sepsis          | 58 ± 3†        | 58 ± 3†        | 56 ± 3†        | 55 ± 2†        | 49 ± 2         | 50 ± 2         | 51 ± 2         |
| Control         | 47 ± 4         | 47 ± 2         | 47 ± 1         | 47 ± 2         | 49 ± 3         | 49 ± 2         | 51 ± 2         |
| Energy intake (kcal/kg/d) |
| Sepsis          | 75 ± 2         | 78 ± 3         | 79 ± 4         | 89 ± 3         | 95 ± 4         | 108 ± 6        | 118 ± 2        |
| Control         | 74 ± 2         | 79 ± 3         | 83 ± 5         | 88 ± 4         | 98 ± 2         | 105 ± 6        | 119 ± 2        |
| Energy intake-EE (kcal/kg/d) |
| Sepsis          | 17 ± 2†        | 22 ± 4†        | 32 ± 4         | 37 ± 4         | 46 ± 3         | 55 ± 6         | 67 ± 3         |
| Control         | 26 ± 5         | 32 ± 4         | 36 ± 4         | 41 ± 5         | 48 ± 5         | 56 ± 7         | 68 ± 4         |

Data are mean ± SD.
* P < .05.
† P < .005 compared with control group.
verely ill than infants in our study, and most of them required mechanical ventilation, whereas infants in the present study did not receive mechanical ventilation or continuous positive airway pressure. Mechanical ventilation decreases the work of breathing as well as heat loss through the respiratory tract, thereby decreasing EE. Sedation and muscle relaxation decrease VO2 and EE by reducing activity. Moreover, neonates in the previous investigations had a wide range of gestational and postnatal ages. Values of VO2 and EE decrease with rising gestational age and increase with rising postnatal age. All infants in our study were full term, and their postnatal age was <5 days at the beginning of the study period.

In septic adults, increased VO2 and EE have been explained as response to bacterial toxins, mediators as interleukin-1, tumor necrosis factor, prostanoids, hormones, and radicals. Endotoxin has been shown to trigger hypermetabolic response mainly in splanchic organs. Tumor necrosis factor can induce a similar metabolic response as endotoxin. Stress hormones such as cortisol, glucagon, and catecholamines are released during sepsis. These hormones may impair glucose utilization and increase fat and protein oxidation, resulting in a catabolic state and increased VO2 and EE. Despite increased EE, the septic infants showed a positive energy balance of approximately 20 kcal/kg/d during the first 2 observation days (Table 3).

Moreover, VO2 and EE may increase in septic patients as a result of tachycardia, tachypnea, and fever. Pierro et al determined the relationship between heart rate and energy expenditure in newborn infants and found that each beat resulted in a rise in EE by 0.2 kcal/kg. In the septic neonates of our study, heart rate was increased by 12 minutes during the first 3 observation days. This increase in heart rate may have caused an increase in EE by 2.5 kcal/kg/d. In preterm infants with bronchopulmonary dysplasia, increase in respiratory rate was associated with a rise of EE by 0.7 kcal/kg/d per breath. Thus, the increase in respiratory rate by 16 minutes at days 1 and 2 may have increased EE by 11 kcal/kg/d in the septic neonates. The septic neonates in our study had normal rectal temperatures and were studied in a thermoneutral environment. It is therefore unlikely that EE for thermoregulation was increased in the septic neonates.

CONCLUSION

Full-term neonates with uncomplicated sepsis syndrome have elevated VO2 and EE values during the first 4 days of the disease. The rise in EE may be explained by increased heart rate and respiratory rate.

REFERENCES

Effect of Sepsis Syndrome on Neonatal Oxygen Consumption and Energy Expenditure
Jacqueline Bauer, Roland Hentschel and Otwin Linderkamp
Pediatrics 2002;110;e69
DOI: 10.1542/peds.110.6.e69

Updated Information & Services
Updated Information & Services including high resolution figures, can be found at:
/content/110/6/e69.full.html

References
This article cites 23 articles, 3 of which can be accessed free at:
/content/110/6/e69.full.html#ref-list-1

Citations
This article has been cited by 3 HighWire-hosted articles:
/content/110/6/e69.full.html#related-urls

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Infectious Disease
/cgi/collection/infectious_diseases_sub
Pulmonology
/cgi/collection/pulmonology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Effect of Sepsis Syndrome on Neonatal Oxygen Consumption and Energy Expenditure
Jacqueline Bauer, Roland Hentschel and Otwin Linderkamp
*Pediatrics* 2002;110;e69
DOI: 10.1542/peds.110.6.e69

The online version of this article, along with updated information and services, is located on the World Wide Web at:
/content/110/6/e69.full.html