0031-3998/07/6102-0228
PEDIATRIC RESEARCH

Vol. 61, No. 2, 2007
Printed in U.S.A.

Oxidation of Intravenous Lipid in Infants and Children With Systemic Inflammatory Response Syndrome and Sepsis

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ABSTRACT: During sepsis in adults, fat becomes a preferred fuel; however, oxidation may be impaired relative to the circulating fatty acid levels. Little is known about the ability of infants and children to oxidize lipids during systemic inflammation (SIRS) and sepsis. The aim of this study was to examine the oxidation of exogenous lipid in these patients. Sixteen patients with SIRS/sepsis and eight controls with no evidence of sepsis were studied by indirect calorimetry during an i.v. lipid utilization test (1 h of 0.3 g/kg/h glucose followed by 3 h of 0.1 g/kg/h glucose plus 0.15 g/kg/h lipid). The respiratory quotient (RQ) (1.0 for carbohydrate utilization and 0.7 for fat utilization) was measured. Results were compared by repeated-measures analysis of variance (ANOVA), paired or unpaired *t* tests. There was no difference in baseline RQ between controls and patients with SIRS/sepsis (mean ± SD; 0.82 ± 0.08 *versus* 0.82 ± 0.04). The RQ of controls dropped significantly to 0.78 ± 0.08 at 240 min ($p < 0.001$). The RQ of patients with SIRS/sepsis also fell to 0.78 ± 0.06 ($p < 0.01$). Infants and children with SIRS/sepsis are able to oxidize i.v. lipid. **(*Pediatr Res* 61: 228–232, 2007)**

Optimal nutrition of critically ill infants and children remains an unsolved problem, particularly during sepsis. During sepsis in adults, fat becomes a preferred fuel for oxidation (1,2), which together with increased gluconeogenesis (3) can contribute to hyperglycemia (4). However, fat mobilization greatly exceeds oxidation under these conditions, resulting in considerable cycling (5,6). This could be due to inhibition of lipoprotein lipase (7–9), an increase in very low density lipoprotein production (10), decreased low-density lipoprotein clearance (11), or decreased oxidation of fatty acids (12). Proinflammatory cytokines increase adipose tissue lipolysis (13) and hepatic triglyceride (TG) release (14) but can impair lipoprotein lipase activity (15) and fatty acid oxidation (16,17). Thus, the overall effects of systemic inflammation and sepsis on oxidative metabolism of exogenous fat are difficult to predict. However, the fact that individual effects on different stages of fatty acid oxidation observed in clinical sepsis are similar to those exerted by proinflammatory cytokines suggests that the overall effects of SIRS and sepsis on lipid oxidation may well be similar.

There is little information on the ability of infants and children to oxidize fat during sepsis or critical illness. Some authors have suggested that hypermetabolic critically ill infants preferentially oxidize fat (18), whereas in a study of infants and children with SIRS and sepsis, we could find no difference in the RQ between critically ill and control patients (19). Studies performed on septic premature neonates suggested impaired fat oxidation (20,21).

Although lipids form an important component of parenteral nutrition, excess lipid administration can result in hypertriglyceridemia, impairment of leukocyte and platelet function, impaired pulmonary function, and other metabolic disturbances including an increase in serum free fatty acids. Studies in premature neonates have shown an increase in plasma TG levels during sepsis (20,21). Lipid administration during total parenteral nutrition has been linked to an increase in lipid peroxidation and to how much lipid is used (22). Impairment of lipid oxidation during sepsis could also therefore contribute to free radical production. In addition, administration of lipid itself is a risk factor for infection (23). Hence, although not evidence based, most centers introduce lipid gradually with close monitoring of TG levels (24). Whether lipid provision needs to be altered during SIRS or sepsis in infants and children is unknown.

The aim of this study was to determine whether SIRS and sepsis affect oxidation of i.v. lipid in infants and children.

METHODS

Patients. Studies were performed in 16 critically ill patients with sepsis or SIRS requiring intensive care in Great Ormond Street Hospital for Children, London, UK, and Catholic University of Rome, Italy. SIRS was defined as the systemic inflammatory response to a variety of severe clinical insults and sepsis as the systemic response to a documented infection (19,25) (Table 1). The diagnoses of the SIRS/sepsis patients are shown in Table 2; patients were studied within 36 h after admission. A control group of eight stable infants and children was also studied. Six of them were surgical patients studied >48 h after surgery; one patient had chronic colitis and one patient an intracranial hemorrhage. Patients with chronic lung disease or congenital metabolic abnormalities were excluded. All critically ill patients and four control patients were mechanically ventilated, and the remaining patients were spontaneously breathing without oxygen supplement.

Respiratory gas exchange measurement. Mechanically ventilated patients were enrolled in the study only if ventilated with Servo Ventilator (SV 300, SV 900, or Servo C; Siemens, Elema, Sweden) receiving <50% O_2. Respiratory gas exchange was measured by an indirect calorimeter (Datex Deltratrac II, Helsinki, Finland) as previously described in ventilated infants (26)

Received May 23, 2006; accepted September 14, 2006.

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DOI: 10.1203/01.pdr.0000252441.91671.e5

Abbreviations: MDA, malondialdehyde; **NEFAs,** nonesterified fatty acids; **REE,** resting energy expenditure; **SIRS,** systemic inflammatory response syndrome; **TG,** triglyceride; **VCO_2,** carbon dioxide production; **VO_2,** oxygen consumption

Table 1. *Current definitions of SIRS/sepsis recommended for children*

SIRS defined as two or more of the following:
Hyper- or hypothermia: T ≥38°C or <36°C
Tachycardia: infant HR >160 bpm; child HR >150 bpm; adolescent HR >90 bpm
Tachypnea: infant RR >60 bpm; child RR 50 bpm; adolescent RR >20 bpm
Pathologic WBCs: >15,000 cells/μL, <4000 cells/μL or >10% immature (band) forms

Sepsis: SIRS with proven infective cause; HR, heart rate; T, temperature; bpm, beats per minute; WBCs, white blood cells.

and children (19). Inspired and expired O_2 and CO_2 were analyzed to calculate the RQ ($RQ = VCO_2/VO_2$) (carbon dioxide production/oxygen consumption) (27). The RQ is influenced by the type of substrate used with an RQ approaching 0.7 for fat oxidation, an RQ of 1.0 for glucose oxidation, and an RQ >1.0 for lipogenesis (28). We did not examine urinary nitrogen excretion as we assumed that the component of the RQ due to protein oxidation would not change during the study (*i.e.* glucose and fat infusion). This assumption is supported by studies indicating no effect of glucose or fat intake on protein metabolism (29,30). We have previously validated RQ measurements in both modes using this indirect calorimeter, and the error in the RQ less than ±3% (19,31).

Intravenous fat utilization test. During 4 h of indirect calorimetry, while other nutrition was discontinued, the capacity to oxidize fat was tested using an i.v. fat utilization test previously described in infants (32). During the first hour, patients received 0.3 g/kg/h glucose. During the following 3 h, the glucose infusion was decreased to 0.1 g/kg/h (to avoid hypoglycemia) and i.v. fat (Intralipid 30%; Pharmacia & Upjohn, Milton Keynes, Bucks, UK) at 0.15 g/kg/h, well below the recommended dose in infants and children and one sixth of the daily dose usually given in our hospital during i.v. feeding. RQ values were averaged over 30 min, excluding periods of crying or movement. Blood samples (ethylenediamine tetraacetic acid tubes) for measurement of plasma MDA, TG, and nonesterified fatty acids (NEFAs) were taken at the beginning and the end of the protocol, where an arterial or venous line was available and therefore no additional venipuncture was required, as this was a requirement of our ethical approval.

Plasma samples. Plasma malondialdehyde (MDA), a measure of lipid peroxidation, was measured by high-performance liquid chromatography (33). Plasma TGs were measured spectrophotometrically (Sigma Chemical Co.) and nonesterified fatty acids (NEFAs) were measured by a spectrophotometric kit (Wako Chemical Company).

Statistical evaluations. Data were normally distributed and are expressed as mean ± SD. Comparisons were made using a *t* test for comparisons between groups and by repeated-measures ANOVA to analyze the drop in the RQ over time. Instat v3.0 was used for comparisons.

The study protocol was approved by the Great Ormond Street Hospital for Children and Institute of Child Health Research Ethics Committee. Informed parental consent was obtained for each patient.

RESULTS

Patient demographics. Patients with SIRS/sepsis ($n = 16$) were of a median age of 21.8 (range, 3.3–202) months, which was similar to the age of controls [20.7 (range, 0.3–96) months; $n = 8$] at the time of study.

Intravenous fat utilization test. The baseline RQ was 0.82 ± 0.08 in control patients ($n = 8$). As expected, there was a significant drop in the RQ after lipid infusion was initiated, reflecting a switch from carbohydrate to fat oxidation (Fig. 1*A*). The RQ was significantly lower compared with baseline at 180, 210, and 240 min (all $p < 0.001$). The baseline RQ was 0.82 ± 0.04 in patients with SIRS or sepsis ($n = 16$), and there was similarly a significant drop in the RQ in these patients (Fig. 1*B*), such that the RQ was significantly lower than baseline at 210 and 240 min ($p < 0.01$). There was no significant difference in the RQ at any time between the control and SIRS/sepsis patients.

TG and nonesterified fatty acid analysis. Blood samples were available from four of eight control patients and 12 of 16 SIRS/sepsis patients. Plasma TG levels before lipid infusion were significantly higher (1.35 ± 0.64 mmol/L) in SIRS/sepsis patients than in controls (0.91 ± 0.25 mmol/L, $p = 0.03$). Lipid infusion would be expected to increase plasma TG levels. This was indeed shown to be the case; in all patients, there was a significant increase in plasma TGs after Intralipid infusion compared with before lipid infusion. This increase took place in both SIRS and sepsis patients (Fig. 2*B*, preIntralipid, 1.35 ± 0.57 mmol/L, postinfusion 2.09 ± 0.82, $p < 0.0001$ on paired *t* test) and controls (Fig. 2*A*), although samples were only available in four control patients so statistical evaluation was not possible.

Action of lipoprotein lipase on plasma TGs makes NEFAs available for tissue uptake. Lipid infusion would therefore be expected to increase NEFA levels, provided lipoprotein lipase is not inhibited. NEFA levels before lipid infusion were greater in SIRS/sepsis patients (0.70 ± 0.37 mmol/L) than in controls (0.19 ± 0.08 mmol/L). The NEFA levels in most patients, both controls and SIRS/sepsis patients, increased in response to lipid infusion (Fig. 2 *C*, *D*).

There is normally a positive linear relationship between circulating TGs and NEFAs. We therefore analyzed whether such a relationship persisted in SIRS/septic patients. There was a strong correlation between TGs and NEFAs in control patients ($r^2 = 0.71$, $p = 0.009$) but not in SIRS/sepsis patients considered as a whole group ($r^2 = 0.09$, $p =$ not significant) (Fig. 3).

Lipid peroxidation in plasma. As lipid peroxidation occurs during parenteral nutrition (34) and has specifically been linked to the amount of infused and oxidized fat (22,35), we wanted to determine whether short-term lipid infusion at a

Table 2. *Clinical diagnoses of patients with systemic inflammatory response syndrome and sepsis*

	No. of patients	Intubation status	PRISM score	Positive blood culture
Meningococcal septicemia	4	4/4	10,15,16,20	4/4
Streptococcus A sepsis	2	2/2	16,23	2/2
Pneumococcal sepsis	1	1/1	20	1/1
Pneumococcal meningitis	1	1/1	23	1/1
Septic shock	1	1/1	36	0/1
Pneumonia	4	4/4	12,15,17,18	0/4
Behçet syndrome with respiratory failure	1	1/1	10	0/1
Bronchiolitis with suspected infection	1	1/1	20	0/1
Postoperative SIRS	1	1/1	23	0/1

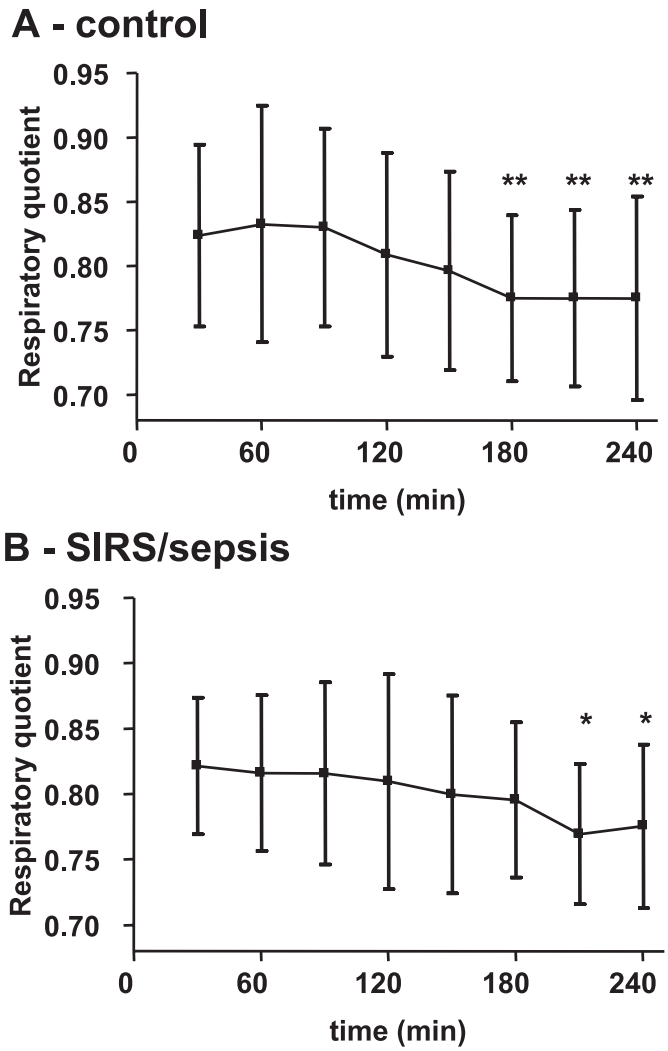

Figure 1. Changes in the RQ over time in control patients ($n = 8$) (*A*) and patients with SIRS or sepsis ($n = 16$) (*B*). Results were compared with baseline (30-min time point) by repeated-measures ANOVA. *$p < 0.01$ *vs* baseline; **$p < 0.001$ *vs* baseline.

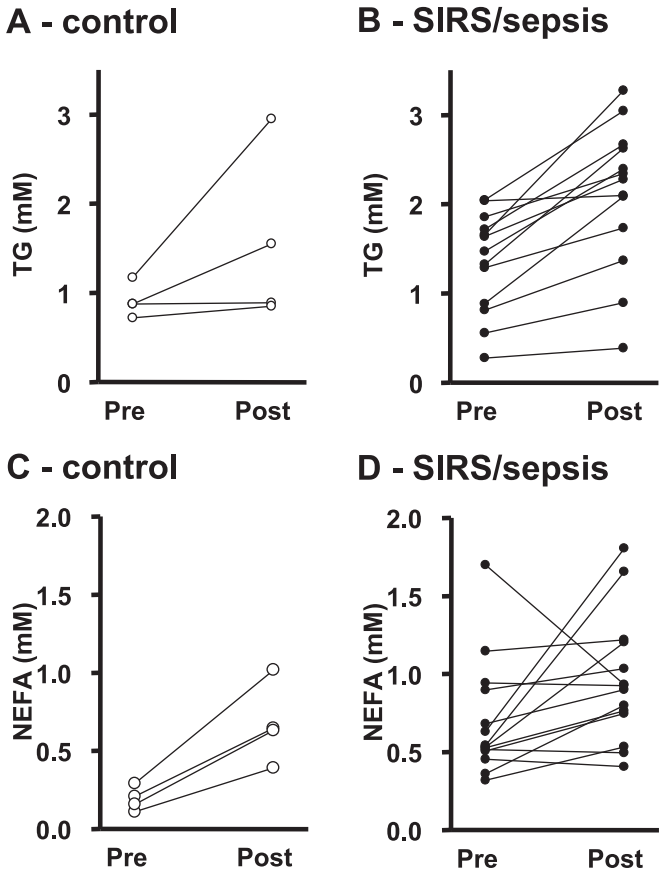

Figure 2. Plasma triglyceride (*A*, *B*) and NEFA (*C*, *D*) concentration in patients before and after lipid infusion in control patients ($n = 4$) (*A*, *C*) and patients with SIRS/sepsis ($n = 13$) (*B*, *D*).

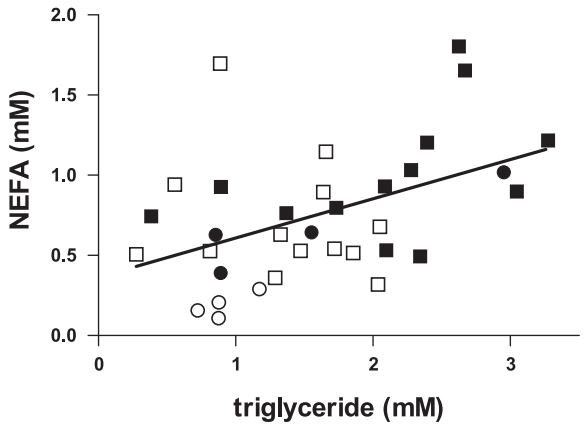

Figure 3. Relationship between NEFA and TG concentrations in control patients (*circles*, $n = 3$–4) and SIRS/sepsis patients (*squares*, $n = 13$). *Open symbols*, before lipid infusion; *closed symbols*, after lipid infusion. The linear regression line refers to all patients. $r^2 = 0.21$, $p = 0.006$.

relatively high infusion rate led to an increase in lipid peroxidation. Measurement of plasma malondialdehyde (MDA) as a marker of lipid peroxidation indicated that lipid infusion over 3 h did not lead to an increase in lipid peroxidation; there was no significant difference in plasma MDA between pre- and post–lipid infusion samples in SIRS/sepsis patients ($p = 0.88$) or in controls (Fig. 4 *A*, *B*).

DISCUSSION

Malnutrition is common in critically ill children and is associated with increased physiologic instability and increased quantity of care (36). The common belief that critically ill children would be hypermetabolic has not been confirmed (19,37); on the contrary, they are more frequently hypometabolic (38). The patterns of energy expenditure, the nature of fuel utilization, and whether manipulation of these or other factors can affect patient outcome represent an important research field.

Several tests have been used to estimate ability to tolerate or metabolize i.v. lipid. Many of these examine plasma lipid clearance (39,40), but this does not reflect oxidation (41). Oxidation of i.v. lipid can be followed by oxidation of isotopically labeled lipid to CO_2 (41). However, for such tests to be clinically relevant, they require isotopically labeled lipid emulsions otherwise identical to those used clinically, and these are not available. The indirect calorimetry i.v. fat utilization test (32) relies on the fact that fat has an RQ of 0.7, whereas carbohydrate has an RQ of 1.0. A baseline RQ is measured in the absence of exogenous lipid, lipid infusion is

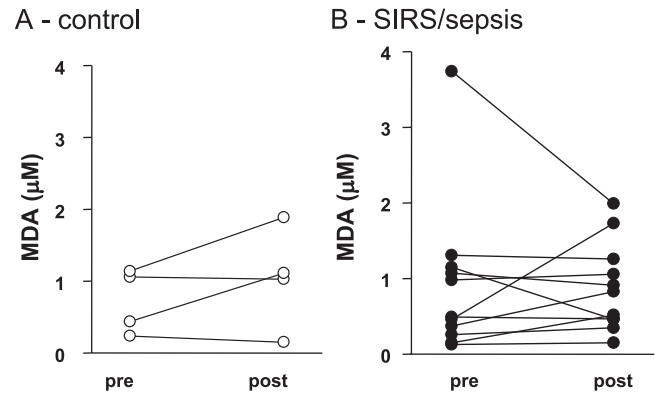

Figure 4. Plasma MDA before and after lipid infusion in control patients ($n = 4$) (*A*) and patients with SIRS/sepsis ($n = 12$) (*B*).

initiated, and if fat is oxidized, a drop in RQ is observed. Although this test has the advantages that it measures oxidation of a clinically relevant lipid emulsion, it does have some limitations: First, as with any indirect calorimetry-based method, only net effects are observed. However, it is unlikely that significant lipogenesis occurred during our study, as glucose administration was low. Measurement of VCO_2 by indirect calorimetry assumes that the bicarbonate pool is constant and so should be performed under steady-state conditions. Alteration of substrate oxidation will alter the metabolic VCO_2 rate and therefore the size and kinetics of the bicarbonate pool. Hence, there is a delay before breath CO_2 reflects changes in metabolism, and in the lipid utilization test, time must be allowed to reach a new steady state, which was achieved in both control and SIRS/sepsis patients in our study. The lag time before a fall in the RQ is observed therefore reflects the time to initiate lipid oxidation plus time to re-equilibrate the bicarbonate pool. Although both spontaneously breathing and ventilated patients were included in the control group, the aim of this study was to evaluate the ability of patients to decrease their RQ in response to fat infusion rather than to compare absolute values of the RQ or REE between the groups. As described in the Materials and Methods section, measurement of the RQ has been validated in each measurement mode.

In the current study, we have shown that infants and children with SIRS or sepsis were able to oxidize i.v. lipid, as shown by a drop in the RQ similar to that in controls. Lipid peroxidation has been reported to be associated with fat infusion in infancy (42), and it is possible that lipid infusion therefore exposes the infant to free radical stress. However, we have previously shown that, provided carbohydrate infusion is limited, lipid is oxidized for fuel rather than peroxidized (22), so our finding that MDA production was not altered by lipid infusion is consistent with lipid oxidation. Although the SIRS/sepsis patients whom we studied were able to oxidize fat, this could be related to the timing of the study—patients were studied early in their intensive care unit admission, and impairment in fat oxidation could be acquired later. Although only a few patients were studied in the control group, the use of repeated-measures ANOVA meant that each patient was effectively acting as his or her own control, and thus this enabled us to detect a significant drop in the RQ. Unfortunately, blood samples were only available from a few patients in the control group for ethical reasons.

Interestingly, four of the patients in the SIRS/sepsis group had meningococcal septicemia, and a separate analysis of these patients suggests that were not able to decrease their RQ in response to lipid infusion, and their plasma NEFA levels did not decrease (results not shown). This suggests that patients with meningococcal septicemia may not be able to oxidize lipids, possibly due to inhibition at the level of lipoprotein lipase, but this needs verification in a larger number of patients.

Patients with SIRS/sepsis were able to oxidize 0.15 g/kg/h of lipid, which would correspond to 3.6 g/kg if lipid infusion was continued for 24 h. This suggests that despite the caution shown by many centers in administering lipids to septic infants and children, most are able to oxidize considerable amounts of lipid. There may be advantages to maintaining lipid infusion in SIRS/sepsis, as decreasing metabolic VCO_2 could decrease respiratory load. In the present study, we infused lipid at a relatively high rate, with a low rate of glucose administration. It is likely that lower amounts of lipid would also be adequately oxidized provided that carbohydrate administration is not excessive. Another note of caution is that even in the absence of exogenous lipid, the baseline TG levels of SIRS/sepsis patients was significantly higher than those of controls. Monitoring of TGs during lipid infusion in patients with SIRS/sepsis is probably even more important than in other infants and children. Because of the short-term nature of the test used, we are only able to measure the ability of infants and children to oxidize lipid when challenged with a sudden increase. Adaptation may well take place when lipids are administered for longer, but lipid administration over a longer period could conversely potentially lead to lipid intolerance.

In this study, we examined only oxidation of i.v. lipid rather than utilization for other purposes. Lipid storage or utilization in other metabolic pathways could be impaired in septic infants and children, but this would best be measured by stable isotopic methods. Another shortcoming of our study is the large interpatient variability; we tried to overcome this by using paired statistics (*i.e.* repeated-measures ANOVA or paired *t* tests). There could, however, be other important differences, for example, differing responses according to age, which would become apparent if more patients were studied from matched groups.

In conclusion, we have demonstrated that infants and children with SIRS and sepsis are able to oxidize exogenous lipid at clinically relevant infusion rates.

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