

# Influence of Fever on the Hypermetabolic Response in Burn-Injured Children

Dennis C. Gore, MD; David Chinkes, PhD; Arthur Sanford, MD; David W. Hart, MD; Steven E. Wolf, MD; David N. Herndon, MD

**Background:** Burn injury typically elicits a hypermetabolic response characterized by increased energy expenditure and muscle protein catabolism.

**Hypothesis:** Fever further increases energy expenditure and muscle loss in otherwise highly hypermetabolic burn patients.

**Design:** Retrospective analysis of experimental study.

**Setting:** University hospital.

**Patients:** Eighty-four children (aged 2-18 years) with burns covering 40% or more of total body surface area.

**Interventions:** None.

**Main Outcome Measures:** Simultaneous measurements of indirect calorimetry and leg net balance of phenylalanine (as an index of muscle protein catabolism) were obtained. Patients were stratified by their rectal temperature taken at the time of these metabolic measurements: afebrile (n=28; temperature, <39.0°C); mild fever (n=26;

temperature, 39.0°C-39.4°C); moderate fever (n=18; temperature, 39.5°C-39.9°C); or severe fever (n=12; temperature, ≥40.0°C).

**Results:** Febrile and afebrile patients were similar in age, body weight, and extent of burn area. Severe fever was associated with significantly increased resting energy expenditure (mean±SD resting energy expenditure–predicted basal, 1.38±0.39 for afebrile patients vs 1.68±0.30 for patients with severe fever;  $P<.05$ ) and a greater net loss of phenylalanine from the leg (net balance of phenylalanine,  $-6.0\pm 6.2$  mg/min per 100 mL of leg volume for afebrile patients vs  $-10.8\pm 7.2$  mg/min per 100 mL for patients with severe fever;  $P<.05$ ). Patient groups were similar in plasma glucose concentration and extent of leukocytosis.

**Conclusions:** These findings demonstrate the association of severe fever with further increase in energy expenditure and muscle protein catabolism in otherwise hypermetabolic burned children. This suggests a possible metabolic benefit in attenuating fever in such patients.

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**A** WOUND, ESPECIALLY from a severe burn injury, elicits a response characterized by an increase in energy expenditure, catabolism of lean body mass, glucose intolerance, and tachycardia.<sup>1</sup> Although the merits of mounting this hypermetabolic response are debated from a “teleological” perspective, each of these facets has detrimental consequences, and much effort, especially from a research standpoint, has been directed at minimizing these metabolic derangements. Often associated with this hypermetabolic response to injury is an increase in body temperature, which is especially pronounced in burned children.<sup>2</sup> Fever is associated with an increase in energy expenditure, muscle protein catabolism, and an increase in heart rate.<sup>3</sup> Theoretically, this increase in body temperature imparts an

adaptive value to the patient by augmenting the immune response and bacterial killing.<sup>4</sup> However, the “energy cost” to mount and sustain a fever may be substantial, especially in a burned patient who is already expending energy and catabolizing

## See Invited Critique at end of article

muscle at a vastly accelerated rate. Thus, the purpose of this study was to assess the effect of body temperature on the components of the hypermetabolic response in severely burned children and thus quantify this energy cost. If fever is associated with a significant, adjuvant increase in any or all facets of hypermetabolism, then measures to moderate body temperature in patients with large burn wounds may have clinical importance.

From the Department of Surgery–Trauma, The University of Texas Medical Branch (Dr Gore) and Shriners Hospitals for Children (Drs Chinkes, Sanford, Hart, Wolf, and Herndon), Galveston.

## METHODS

### SUBJECTS

From January 1, 1996, through June 30, 2000, indirect calorimetry and net balance of phenylalanine across the leg (ie, an index of muscle protein metabolism) were assessed in 84 burned children while they served as either nontreated or placebo-treated control subjects in a variety of investigations. All studies were approved by the institutional review board overseeing human subject research. All subjects had total body surface area (TBSA) burn in excess of 40% (mean  $\pm$  SD TBSA burn,  $60\% \pm 13\%$ ; TBSA full-thickness burn,  $46\% \pm 18\%$ ). Their ages ranged from 2 to 17 years (mean  $\pm$  SD,  $6.5 \pm 2.7$  years) and body weight ranged from 9 to 71 kg (mean  $\pm$  SD,  $24.0 \pm 13.7$  kg). Patients were cared for and underwent metabolic assessment in the Shriners Hospital for Children, Galveston, Tex.

A sizable variation was evident in the time from burn injury to the initiation of surgical care, because of delays of as much as 5 weeks in transporting many of the burn victims from Latin America. However, from the time of arrival on, these severely burned patients were cared for in a similar manner.<sup>5</sup> Surgical care consisted of early excision of the burn wound, autografting as much as possible, and covering any residual open wound with cadaveric skin. Patients were returned to the operating room when donor sites had sufficiently reepithelialized for repeated autografting, usually at weekly intervals. Donor sites were dressed with an ointment (Scarlet Red; Sherwood Medical Co, St Louis, Mo). At the time of metabolic assessment, feedings were exclusively enteral formula (Vivonex TEN; Sandoz Nutrition Corp, Minneapolis, Minn) and delivered continuously via either a nasojunal or nasogastric tube. For those less than 12 years of age, the feeding goal was 1800 kcal/m<sup>2</sup> of TBSA plus 1300 kcal/m<sup>2</sup> of TBSA burned. For subjects aged 12 years and older, the caloric goal was 1500 kcal/m<sup>2</sup> of TBSA plus 1500 kcal/m<sup>2</sup> of TBSA burned. All subjects, regardless of age, had a daily protein intake goal of 3 g/kg of body weight. Multiple broad-spectrum antibiotics were begun on admission to the burn hospital and continued until most of the wounds were healed.

### METABOLIC ASSESSMENT AND CALCULATIONS

Indirect calorimetry and phenylalanine net balance measurements were performed between the fifth and seventh days after a debridement and skin grafting procedure. All measurements were performed in the subjects' warmed hospital room. Indirect calorimetry was accomplished with a metabolic cart (SensorMedics 2900; SensorMedics, Yorba Linda, Calif), with measured values indexed to basal predicted values. Since phenylalanine is an essential amino acid that is neither oxidized nor deaminated peripherally, and since most protein metabolism within the leg is from muscle, the net balance of phenylalanine across the leg provides a measure of net muscle protein metabolism (ie, a negative net balance is indicative of net muscle protein catabolism).<sup>6</sup> Net balance was determined as follows:

$$NB = (C_{art} - C_{vein})LBF,$$

where *NB* indicates net balance of phenylalanine (micrograms per minute per 100 mL of leg volume); *C<sub>art</sub>* and *C<sub>vein</sub>*, plasma concentration of phenylalanine from femoral artery and vein sampling, respectively (milligrams per deciliter); and *LBF*, leg blood flow (milliliters per minute per 100 mL of leg volume).

The plasma concentration of phenylalanine was determined by means of high-performance liquid chroma-

tography (HPLC model 510; Waters Corp, Milford, Mass) or by measuring the plasma concentration from dilution of an infused stable isotope of phenylalanine (ie, internal standard technique).<sup>7</sup> Isotopic enrichment of phenylalanine in plasma was determined by gas chromatography and mass spectrometry after *N*-acetyl, *N*-propyl ester derivation (HP model 5989; Hewlett-Packard Co, Palo Alto, Calif).<sup>8</sup>

Leg blood flow was determined by infusion of indocyanine green dye (ICG) at 1 mg/mL for 20 minutes into the femoral artery with serial blood sampling from the femoral vein and central vein access.<sup>9</sup> The concentration of the ICG in these blood samples was analyzed spectrophotometrically (Spectromic 100; Bausch & Lomb, Rochester, NY) and leg blood flow was calculated as follows:

$$LBF = OD_{inf} (1 \text{ mL/min}) / [(OD_{fv} - OD_{cv})(1 - HCT)],$$

where *LBF* indicates leg blood flow (as above); 1 mL/min, infusion rate of ICG; *OD<sub>inf</sub>*, *OD<sub>fv</sub>*, and *OD<sub>cv</sub>*, optical density of ICG in the infusate, femoral vein, and central vein blood samples, respectively; and *HCT*, hematocrit (percentage).

Phenylalanine net balance and leg blood flow were indexed by the volume of the leg as determined by repeated measurements of leg circumference at prescribed anatomic points along the leg.<sup>10</sup> These circumference measurements and the measurements of distance between these anatomic landmarks were used to calculate leg volume. Vital signs and clinical laboratory values were recorded, stored, and subsequently retrieved by means of computerized hospital records (Sybase; Eclipsys Corp, Boca Raton, Fla). Dietary information, blood culture results, and notation of clinical sepsis, pneumonia, or wound infection were retrieved manually from review of the hospital records.

Subjects were stratified by their rectal temperature at the time of metabolic assessment. Rectal temperature of less than 39°C was considered afebrile. Post hoc tests for statistical significance were performed with Tukey test for multiple comparisons between groups, with *P* < .05 considered significant.

## RESULTS

The afebrile and mild, moderate, and severely febrile patient groups were similar in regard to age, weight, and TBSA burn (**Table 1**). Patient groups were also similar in their nutritional intake for both the calories and protein delivered (**Table 2**). Laboratory values for plasma creatinine, white blood cell count, and platelet count were also similar between groups (**Table 3**). There was a significantly elevated serum glucose concentration for patients with body temperatures between 39.5°C and 39.9°C compared with afebrile patients. However, patients with temperatures greater than or equal to 40.0°C had glucose values that were statistically similar to those of the afebrile patients and those with mild fever (Table 3). The other apparent difference in patient characteristics was a significantly faster average heart rate for the severely febrile patients in comparison with afebrile patients (**Table 4**). There was also no statistically significant dif-

**Table 1. Demographics\***

	Afebrile (n = 28)	Fever		
		Mild (n = 26)	Moderate (n = 18)	Severe (n = 12)
Age, y	6 ± 5	5 ± 4	10 ± 6	6 ± 3
TBSA burn, %	52 ± 17	63 ± 19	65 ± 17	62 ± 11
3rd-Degree burn, %	43 ± 21	46 ± 32	50 ± 23	50 ± 16
Weight, kg	23 ± 12	22 ± 12	28 ± 12	25 ± 16
Leg volume, 100 mL	31 ± 17	32 ± 26	48 ± 30	32 ± 21
Time of study after burn, d	14 ± 7	13 ± 7	11 ± 5	15 ± 7

Abbreviation: TBSA, total body surface area.

\*Values are mean ± SD.

**Table 2. Nutritional Intake\***

	Afebrile	Fever		
		Mild	Moderate	Severe
Carbohydrates, kcal/kg per day	60.7 ± 29	62.5 ± 25.9	70.3 ± 32.1	57.5 ± 20.0
Fats, kcal/kg per day	9.7 ± 5.3	12.7 ± 6.1	12.0 ± 9.2	10.6 ± 4.7
Protein, g/kg per day	4.2 ± 2.1	3.6 ± 1.3	4.1 ± 1.7	3.8 ± 1.1

\*Values are mean ± SD.

**Table 3. Laboratory Values\***

	Afebrile	Fever		
		Mild	Moderate	Severe
Glucose, mg/dL	123 ± 46	142 ± 40	170 ± 54†	140 ± 62
Potassium, mEq/L	3.8 ± 0.4	3.6 ± 0.4	3.5 ± 0.4	3.6 ± 0.5
Creatinine, mg/dL	0.33 ± 0.09	0.34 ± 0.09	0.47 ± 0.21	0.43 ± 0.25
WBCs, ×10 <sup>9</sup> /μL	12.1 ± 4.0	14.4 ± 4.8	11.0 ± 4.8	11.5 ± 4.7
Platelets, ×10 <sup>9</sup> /μL	335 ± 180	322 ± 138	279 ± 185	347 ± 172

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; glucose to millimoles per liter, by 0.0555.

\*Values are mean ± SD.

†P<.05 vs afebrile patients.

**Table 4. Temperature and Heart Rate\***

	Afebrile	Fever		
		Mild	Moderate	Severe
Mean temperature, °C/24 h	38.1 ± 0.4	38.8 ± 0.2	39.2 ± 0.3	39.3 ± 0.3†
Maximum temperature, °C	38.6 ± 0.4	39.3 ± 0.1	39.7 ± 0.1	40.2 ± 0.2†‡
Mean heart rate, beats/min per 24 h	149 ± 19	161 ± 14	155 ± 21	164 ± 18§
Maximum heart rate, beats/min	189 ± 41	189 ± 27	187 ± 39	215 ± 47

\*Values are mean ± SD.

†P<.01 vs afebrile and mild groups.

‡P<.05 vs moderate group.

§P<.05 vs afebrile group.

ference between groups in regard to infectious complications or subsequent mortality (**Table 5**).

In regard to indirect calorimetry, there was an apparent trend toward increases in oxygen consumption and energy expenditure with increasing body temperature (**Table 6**). When indexed as a percentage of each

subject's predicted basal value, the resting energy expenditure for the severely febrile patients was significantly elevated in comparison with afebrile subjects and those with body temperatures less than 39.5°C.

For phenylalanine balance measurements, the concentration of phenylalanine within the femoral ar-

**Table 5. Infectious Complications and Mortality\***

	Afebrile, No. (%)	Fever, No. (%)		
		Mild	Moderate	Severe
Septic	8 (28.6)	6 (23.1)	2 (11.1)	5 (41.7)
Pneumonia	4 (14.3)	6 (23.1)	4 (22.2)	4 (33.3)
Wound infection	2 (7.1)	0	2 (11.1)	1 (8.3)
Positive blood culture	0	0	0	1 (8.3)
Mortality	1 (3.6)	1 (3.8)	0	0

\*No significant difference, analysis by  $\chi^2$ .

**Table 6. Energy Expenditure\***

	Afebrile	Fever		
		Mild	Moderate	Severe
REE, kcal/kg per day	57.7 ± 23.2	60.9 ± 17.7	62.6 ± 20.7	66.8 ± 20.7
REE/predicted BEE, %	138 ± 39	138 ± 38	142 ± 49	168 ± 30†
VO <sub>2</sub> , mL · min <sup>-1</sup> · kg <sup>-1</sup>	7.8 ± 3.0	8.5 ± 4.3	8.7 ± 4.2	9.2 ± 3.0
VCO <sub>2</sub> , mL · min <sup>-1</sup> · kg <sup>-1</sup>	7.3 ± 3.3	8.4 ± 3.1	8.5 ± 3.1	8.9 ± 2.6

Abbreviations: BEE, basal energy expenditure; REE, resting energy expenditure; VCO<sub>2</sub>, carbon dioxide consumption; VO<sub>2</sub>, oxygen consumption.

\*Values are mean ± SD.

† $P < .05$  vs afebrile and mild fever groups.

**Table 7. Phenylalanine Flux\***

	Afebrile	Fever		
		Mild	Moderate	Severe
C <sub>art</sub> , mg/dL	1.22 ± 0.38	1.42 ± 0.38	1.78 ± 0.48†	1.75 ± 0.53†
C <sub>vein</sub> , mg/dL	1.27 ± 0.40	1.47 ± 0.41	1.83 ± 0.48†	1.83 ± 0.56†
LBF, mL/min per 100 mL of leg volume	12.0 ± 7.8	11.2 ± 6.2	10.5 ± 6.1	13.5 ± 7.6
Net balance, µg/min per 100 mL of leg volume	-6.0 ± 6.2	-5.6 ± 7.4	-5.3 ± 10.7	-10.8 ± 7.2†

Abbreviations: C<sub>art</sub> and C<sub>vein</sub>, phenylalanine concentration in femoral artery and vein, respectively; LBF, leg blood flow.

SI conversion factor: To convert C<sub>art</sub> and C<sub>vein</sub> to micromoles per liter, multiply by 60.54.

\*Values are mean ± SD.

† $P < .05$  vs afebrile patients.

tery and venous blood increased with progressive elevations in body temperature, becoming statistically significant when moderately and severely febrile patients were compared with afebrile subjects (**Table 7**). Net balance measurements demonstrated a significantly greater efflux of phenylalanine from the leg in the severely febrile group compared with afebrile patients.

#### COMMENT

In this study, patients with burns encompassing more than 40% of their TBSA and with relatively normal body temperatures had resting energy expenditures of about 38% above their basal predicted values. Patients with comparable burn size yet with temperatures greater than or equal to 40.0°C had an additional 30% increase in resting energy expenditure over their afebrile counterparts. While this difference was statistically significant, it amounted to only slightly more than 9 kcal/kg per day in energy expenditure. With the average body weight of these study subjects being 25 kg, this 1.5°C increase in

body temperature imparted only a 228-kcal/d caloric deficit. Extrapolating from recent evidence in septic adults, studies by Plank et al<sup>11</sup> noted that discrepancies between caloric support and energy expenditure largely influenced the body's fat mass, while protein loss continued unabated regardless of caloric intake. Recently, Hart et al<sup>12</sup> found this also to be evident in burn patients in whom caloric supply affected fat mass, yet failed to alter the erosion of lean body mass. Since there appears to be no clinical utility in maintenance of fat mass, and acknowledging the ravages of overfeeding, such as hepatic steatosis and increased ventilatory requirements,<sup>13</sup> then, this fever-related caloric deficit of 9 kcal/kg per day is apparently of minimal clinical importance. Furthermore, even the very high fever had only minimal influence on hemodynamics; for example, a statistically insignificant 15% increase in leg blood flow and only a 10% increase in heart rate were evident in patients with fever equal to or in excess of 40.0°C. Likewise, laboratory values were largely similar between the severely febrile and afebrile burn patients, further discounting any major re-

relationship between fever and multiple organ dysfunction.

Fever did significantly influence muscle protein catabolism. This was evident both by the increase in phenylalanine concentration in the femoral artery and vein, presumably from an increase in muscle protein breakdown, and as measured more directly from the phenylalanine net balance from the leg. Hall-Angeras et al<sup>14</sup> showed, by using an in vitro experiment with rat muscle, that elevating the incubation temperature from 37°C to 40°C increased muscle protein breakdown without a compensatory change in the rate of muscle protein synthesis. In another in vitro experiment using rat muscle, Baracos et al<sup>15</sup> demonstrated a significant increase in proteolysis from muscle incubated at 37°C with human leukocyte pyrogen (interleukin 1) added to the medium and from muscle incubated at 39°C without pyrogen.<sup>15</sup> The combination of leukocyte pyrogen and the increase to 39°C resulted in an even greater increase in muscle protein breakdown. Baracos et al suggested that their results demonstrated a direct effect of cytokines to mediate muscle protein catabolism, an effect that is augmented with fever. The findings of this human in vivo study further support this notion that the rate of muscle protein loss may be accelerated by an increase of body temperature.

Using the single amino acid phenylalanine as an index, this 1.5-°C increase in body temperature correlated to a greater than doubling in the rate of muscle protein catabolism. Biolo et al<sup>16</sup> previously showed that the concentration of phenylalanine in skeletal muscle from the leg of healthy volunteers is approximately 233 nmol/mg.<sup>16</sup> Assuming that with fever there was no selectivity in the release of amino acids from muscle, a sustained increase in body temperature to 40°C or more for 24 hours would result in an additional loss of muscle over and above that measured in the hypermetabolic yet afebrile burn patients, of 229 mg/100 mL of leg volume. With the average leg volume of the study participants being 3500 g, approximately 8 g of muscle per leg per day is lost with a sustained fever. Assuming that approximately 40% of body weight is skeletal muscle, of which approximately one third of all skeletal muscle resides in each leg, then a very high fever corresponds to a net loss of skeletal muscle mass of 0.3%/d. The clinical significance of this 0.3%/d increase of muscle loss is uncertain. Since this value is far less than the 10% to 15% loss of lean body mass shown to correspond to significant increases in infections and marked delays in wound healing,<sup>17</sup> and since fever of this magnitude is rarely sustained for a continuous 24 hours, it seems unlikely that fever has a major clinical impact on outcome in severely burned children. However, as an alternative view, biochemical markers of cellular proliferation and inflammatory response have been shown to be impaired after only 7 days of protein restriction following injury<sup>18</sup> and, in conjunction with the already accelerated muscle protein catabolism in burn patients, this more than doubling in the rate of phenylalanine release may have a significant adjuvant effect on catabolism.

Unfortunately, a cause-and-effect relationship between fever and muscle protein catabolism cannot be deduced on the basis of this study. Relying on laboratory

markers and clinical impression, there is no apparent relationship between increases in body temperature and sepsis or infection rate in these burned children. In another investigation examining fever in burned children, Parish et al<sup>19</sup> found that for children with more than 20% TBSA burn, a body temperature greater than 38.2°C was of no value in differentiating those with infection. These researchers thus concluded that fever in burned children had no predictive value for identifying the presence of infection. While the study by Parish et al and the present study differ in the body temperature categorization of fever and the extent of burn for subject inclusion, both reports demonstrate that elevations in body temperature in burned children do not connote sepsis. Yet, if not an infection, then what is underlying the generation of fever in burned children and why do these variations in body temperature accelerate muscle protein catabolism? One possibility would be that the febrile children were shivering and that those muscle contractions contributed to protein breakdown. Unfortunately, notations of shivering or activity by the study subjects in either the hospital records or study documents were rare and sporadic.

There are 2 other failings of this study. One is that the study does not address the best method for reducing fever or even whether normalizing the body temperature in these burn patients will reduce muscle protein catabolism. Previous work by Wilmore et al<sup>20</sup> demonstrated that placing burned adults in a progressively cooler environment increased resting energy expenditure and plasma catecholamine levels. This would imply that cooling methods to reduce fever, such as using cooling blankets and cold rooms, would heighten metabolic stress of the patient and be detrimental. In contrast, recent work by Mantous et al<sup>21</sup> noted that using cooling blankets on febrile, critically ill patients decreased their cardiorespiratory work as measured by decreases in oxygen consumption, oxygen extraction, and cardiac output. A common maneuver to reduce fever is to administer an antipyretic medicine, most often a prostaglandin inhibitor such as acetaminophen. Unfortunately, the metabolic effects of such medications have yet to be extensively addressed in severely burn-injured children. The value of the present study suggests that the best index to gauge the efficacy of any method to reduce fever is not necessarily to measure only energy expenditure or oxygen consumption, but to quantify changes in muscle protein metabolism and/or inflammatory response. Another shortcoming of this study is the absence of any measure of immune function other than quantifying the white blood cell count. Since a heightened immunologic response is the presumed benefit of the increase in body temperature, any evaluation of fever should incorporate measures of both the benefits and drawbacks of a physiological manipulation. Thus, any future study should index the alterations in body temperature to direct measures of muscle protein catabolism accompanied by measures of immune function.

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*Corresponding author and reprints: Dennis C. Gore, MD, Department of Surgery-Trauma, The University of*

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## Invited Critique

Greene and his colleagues have performed an elegant study on febrile children with burn wounds. They studied the effects of fever on the metabolic response in these patients and have prepared an excellent article. The study was designed to define the energy "cost" of fever in these patients by using indirect calorimetry and the net flux of phenylalanine across the leg as an index of muscle catabolism. Febrile patients, as expected, exhibited increases in heart rate, serum glucose level, oxygen consumption, and energy expenditure. Indeed, febrile patients also exhibited a significantly greater efflux of phenylalanine from the leg compared with patients without fever, indicating an increase in muscle catabolism with fever.

The authors point out the most significant problems with their own study. First, there can be no cause-and-effect relationship established between the presence of fever and an increase in muscle catabolism. If the authors had administered antipyretic agents and reexamined the same patients after normalization of their core body temperature, they might have been able to make such a statement. Second, the measurement of some other set of variables might have led to a more compelling set of conclusions. The authors hypothesized that the increase in fever seen in burned patients may in some way be protective to the host against the development of infection, yet no immune function was measured other than to quantify the white blood cell count. Perhaps more extensive measurements of immune function, both during fever and after antipyretic therapy, along with the metabolic studies that were so beautifully performed, would shed more light on this important issue.

Mark Silen, MD, MBA  
Portland, Ore