Relative association of fever and injury with hypermetabolism in critically ill patients

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The purpose of this study was to determine the association of injury type (trauma, surgery, medical disease), systemic inflammatory response syndrome (SIRS) and fever with the degree of hypermetabolism in critically ill patients. Medical records of 204 critically ill, mechanically ventilated injured, surgical and medical patients were reviewed for indirect calorimetry and associated data. Analysis of variance and covariance was used to test the effects of injury, fever and SIRS on the degree of hypermetabolism. All injury types were found to be hypermetabolic. Analysis of variance of hypermetabolism with injury type and presence of fever as main effects revealed a significant increase in hypermetabolic response from fever, of similar magnitude across all injury types. Subjects with SIRS were significantly more hypermetabolic than subjects without SIRS. However, analysis of variance indicated no effect for SIRS but a significant effect for fever in increasing the hypermetabolic response. It is concluded that fever portends a magnification of the hypermetabolic response, being similar across injury types. SIRS does not identify hypermetabolic patients independent of fever. The host response to injury, not the injury itself, determines metabolic rate in critically ill patients. Neither SIRS nor injury type should be used to classify hypermetabolic states without stratifying for presence of fever. © 1997 Elsevier Science Ltd. All rights reserved.


Introduction

Hypermetabolism (resting energy expenditure and oxygen consumption greater than 115 per cent of basal rate) has been described in critically ill patients, but the degree of hypermetabolism reported from study to study is variable. Furthermore, patient classifications have usually been based on degree or type of injury (e.g. burns, brain injury, multiple trauma, surgery, pancreatitis), with trauma usually being the most hypermetabolic condition. For example, recent reports of resting energy expenditure in trauma patients indicate an elevation of 50–60 per cent$–5$, compared with 10–30 per cent for major surgery$–10$. The discrepancy may lead to the conclusion that degree of injury is responsible for the difference in resting energy expenditure among different patient types. However, an association between fever and hypermetabolism has long been recognized$–1$, and recently the systemic inflammatory response syndrome (SIRS) has offered a framework for classification of hypermetabolic states because it is, in theory, a non-specific host response to a number of stimuli (e.g. trauma, major surgery, cancer, pancreatitis, infection, prolonged hypoperfusion)$–1$. Thus, one can reason that if SIRS is elicited, a similar hypermetabolic response would result no matter what underlying event caused the SIRS. Epidemiological studies have validated SIRS as a clinical entity$–1$. However, SIRS has not been well described in terms of effects on metabolism.

The purpose of the current study was to determine which of several factors are associated with hypermetabolism in critically ill patients. Factors evaluated included injury type (trauma, major surgery, medical disease) and host response as determined by the presence or absence of SIRS or fever. The hypothesis was that host response rather than injury type would best describe hypermetabolism in a varied population of critically ill patients.

Materials and methods

A database was assembled from clinical records of patients undergoing indirect calorimetry while admitted to the surgical and medical intensive care units of a University Hospital. Inclusive study dates were May 1992 to May 1995. The hospital is a tertiary referral centre and includes a Level I Trauma Centre. The project was approved by the University Clinical Investigations Committee. Informed consent requirements were waived by the Committee.

Indirect calorimetry studies were included in the current study if the following conditions were met:
(1) Measurements were made within 14 days of admission to the intensive care unit;
(2) The patient was haemodynamically stable (not in shock);
(3) The patient was mechanically ventilated with FIO2 < 0.6 and no air leak; and
(4) The patient was measured under resting conditions.

Rest was defined as a 5 min period in which the patient's room was quiet, the patient was not moving or disturbed by hospital personnel, and the coefficients of variation for oxygen consumption, carbon dioxide production and minute ventilation were ≤5 per cent. Nutrient infusions were not stopped during the measurement. No changes in ventilator mode were made for at least 30 min before the indirect calorimetry study.

Indirect calorimetry was performed with an open circuit indirect calorimeter (Cybermedic Metascope II, Cybermedic, Denver, Colorado). The calorimetry device used for the current study was validated in vitro by an ethanol burn test conducted at our institution. Energy expenditure was calculated from oxygen consumption and carbon dioxide production using Weir's modified calculation, ignoring the adjustment for protein oxidation.

Injury classification
Patients were classified into three types of underlying injury: trauma, major surgery and medical disease. Injury Severity Score (ISS) was computed for all trauma patients.

The Acute Physiology and Chronic Health Evaluation (APACHE) III Major Disease Category system and the Acute Physiology Score (APS) were used to describe patients within the overall trauma, major surgery and medical disease classifications.

Host response to injury
Patients were assessed for presence of systemic inflammatory response syndrome (SIRS) using established criteria of the presence of at least two of the following:
(1) Maximum body temperature > 38.0°C or < 36.0°C.
(2) Leucocyte count > 12.0 10⁹/1 or < 4.0 10⁹/1, or band count > 10 per cent.
(3) Heart rate > 90 beats/min.
(4) Respiratory rate > 20 breaths/min.

For the current study, criterion four could not be considered because all patients were mechanically ventilated.

Severe SIRS was determined to be present if, in addition to meeting the SIRS definition, at least two organ systems displayed signs of dysfunction:
(1) Cardiovascular – dopamine infusion > 5µg/kg/min or use of any other inotropic agent required to maintain blood pressure.
(2) Pulmonary – PaO₂/FIO₂ ratio ≤ 150.
(3) Renal – serum creatinine ≥ 2.0 mg/dl (177 µmol/l) with no history of chronic renal failure.

(4) Hepatic – serum albumin < 2.8 g/dl (28 g/l) and serum total bilirubin > 2.5 mg/dl (43 µmol/l).

As a simplified measure of host response, patients were stratified as febrile or afebrile using a maximum body temperature of 38°C to define fever.

Anthropometric assessment
All patients underwent standardized clinical assessment of body size prior to indirect calorimetry measurement. Height and estimated or reported normal weight were recorded. Estimated or reported normal weight was compared to ideal weight calculated from the Hamwi equation:

\[
\text{Adjusted wt} (\text{kg}) = 0.25(\text{dry wt} - \text{ideal wt}) + \text{ideal wt}
\]

Standard basal energy expenditure and definition of hypermetabolism
In order to relate the resting energy expenditure data of patients with various body sizes, ages and sex to a familiar standard reference point, basal energy expenditure was calculated from the Harris–Benedict equations:

\[
\text{Male} - 66 + (13.7 \times \text{wt}) + (5.0 \times \text{ht}) - (6.8 \times \text{age})
\]
\[
\text{Female} - 665 + (9.7 \times \text{wt}) + (1.8 \times \text{ht}) - (4.7 \times \text{age})
\]

where wt is weight in kg, ht is height in cm and age is in years. Estimated or reported dry weight was used in the calculation of basal energy expenditure if patient weight was ≤ 125 per cent of ideal. Adjusted weight was used if patient weight was ≥ 125 per cent of ideal, since in obese patients use of estimated or reported dry weight would result in overestimation of basal energy expenditure.

Degree of variability in predicted basal energy expenditure may be ± 15 per cent. Therefore, hypermetabolism was defined as a resting energy expenditure > 115 per cent of predicted basal energy expenditure.

Statistics
Data were stratified by injury type (trauma, major surgery, medical), fever status (febrile, afebrile) and SIRS status (SIRS, non-SIRS). Degree of hypermetabolism (resting energy expenditure/basal energy expenditure ratio) was analysed using a general linear model to perform analysis of variance for main effects and interactions. The resulting factor means were adjusted for the other factor.
One way analysis of variance was used to analyse the differences in clinical variables among the injury types. Tukey's method of multiple simultaneous comparisons was used to test for statistically significant differences among groups. The overall family error rate was set at \( p < 0.05 \). Correlation and regression analysis were used to determine the degree of linear association among variables. Non-categorical data were displayed as means ± standard deviations. All statistical tests were performed with Minitab Release 8.0 (Minitab Corp., State College, Pennsylvania).

### Results

In total 204 patients met the criteria for inclusion in the current analysis. The study sample was 61 per cent male with a mean age of 53 ± 20 years. Eighty-three per cent of all subjects were hypermetabolic (resting energy expenditure > 115 per cent of basal energy expenditure). Eighty-eight per cent of all subjects were receiving nutritional support during the indirect calorimetry test. The mortality rate was 24 per cent.

#### Injury type

The study sample consisted of 90 trauma (mean Injury Severity Score = 28 ± 13), 66 major surgery and 48 medical intensive care patients. The trauma group was composed of three isolated brain injury patients, 34 patients with multiple trauma including brain injury and 53 patients with multiple trauma without brain injury. The major surgery group consisted of 12 vascular, 47 gastrointestinal and seven neurological surgery patients. The medical group included 10 cardiovascular, 21 respiratory, eight sepsis, two neurological and five miscellaneous patients. Relevant clinical and physiologic data are shown in Table I. The trauma group was younger and had lower APACHE III and APS results compared to the major surgery and medical groups.

Resting energy expenditure was elevated in all three injury types (Table II). Unadjusted mean metabolic rate was 139 ± 22 per cent of basal in trauma, 134 ± 21 per cent of basal in major surgery and 132 ± 22 per cent of basal in the medical group \( (p = 0.058, \text{trauma vs. medical}) \). The proportion of subjects with hypermetabolism was similar among the trauma (90 per cent), major surgery (92 per cent) and medical groups (85 per cent), and the degree of hypermetabolism among these subjects was similar \( (144 ± 19 \text{ per cent in trauma}, 139 ± 19 \text{ per cent in major surgery and } 139 ± 19 \text{ per cent in medical}) \). Neither the APACHE III score nor the APS was associated with resting energy expenditure \( (R^2 = 0.03 \text{ and } 0.004, \text{respectively}) \).

In the trauma group, there was no correlation between Injury Severity Score and degree of hypermetabolism \( (R^2 = 0.01) \).

#### Host response

**Fever.** Significantly fewer medical patients were febrile (50 per cent) than either trauma (74 per cent) or major surgery patients (70 per cent) \( (p < 0.05) \). Fever had a statistically significant effect on degree of hypermetabolism among the three injury groups (Table II). No significant injury type × fever status interaction occurred. Analysis of injury types with body temperature entered into the model as a covariant revealed almost no difference among the groups: 137 ± 21 per cent of basal in trauma, 135 ± 20 per cent of basal in major surgery and 135 ± 21 per cent of basal in medical. The correlation between maximum body temperature and resting energy expenditure was mild but statistically significant \( (R^2 = 0.18, p < 0.0001) \).

#### Systemic inflammatory response syndrome

Of the 204 subjects in the current study, 157 met the criteria for SIRS (77 per cent). Of the 157 SIRS subjects, 127 were febrile (81 per cent). Thirty SIRS patients (19 per cent) had evidence of severe SIRS \( (i.e. \text{SIRS with evidence of multiple organ dysfunction}) \). The mean level of hypermetabolism among all SIRS subjects was 138 ± 21 per cent of basal; significantly greater than the mean for all non-SIRS subjects \( (128 ± 18 \text{ per cent of basal}) \). There was no significant difference in degree of hypermetabolism between SIRS and severe SIRS \( (143 ± 22 \text{ per cent vs. } 135 ± 23 \text{ per cent of basal}; p > 0.05) \).

### Table I. Clinical and physiological variables in the trauma, major surgery and medical groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Trauma (n = 90)</th>
<th>Major surgery (n = 66)</th>
<th>Medical (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44 ± 20</td>
<td>61 ± 16</td>
<td>58 ± 19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ± 18</td>
<td>83 ± 26</td>
<td>75 ± 22</td>
</tr>
<tr>
<td>Metabolically active wt (kg)</td>
<td>74 ± 12</td>
<td>73 ± 16</td>
<td>67 ± 15</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>47 ± 19</td>
<td>69 ± 27</td>
<td>66 ± 23</td>
</tr>
<tr>
<td>APS</td>
<td>43 ± 16</td>
<td>58 ± 27</td>
<td>54 ± 22</td>
</tr>
<tr>
<td>ICU day</td>
<td>5 ± 3</td>
<td>7 ± 4</td>
<td>7 ± 4</td>
</tr>
<tr>
<td>Maximum body temperature (°C)</td>
<td>38.5 ± 0.7</td>
<td>38.3 ± 0.7</td>
<td>38.1 ± 0.9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>104 ± 21</td>
<td>102 ± 19</td>
<td>99 ± 20</td>
</tr>
<tr>
<td>Leucocyte count (10⁹/L)</td>
<td>11.8 ± 5.2</td>
<td>14.9 ± 7.4</td>
<td>14.3 ± 8.2</td>
</tr>
<tr>
<td>Minute ventilation (l/min)</td>
<td>11.8 ± 2.8</td>
<td>12.1 ± 3.7</td>
<td>12.2 ± 4.0</td>
</tr>
</tbody>
</table>

\( p < 0.05 \) (family error rate) vs. all other groups; \( p < 0.05 \) (family error rate) vs. major surgery.

### Table II. Analysis of variance of degree of hypermetabolism (per cent of basal energy expenditure) for injury type, fever status and injury × fever interactions (adjusted means)

<table>
<thead>
<tr>
<th>Injury type</th>
<th>Febrile Mean</th>
<th>Afebrile Mean</th>
<th>Injury type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>145 ± 22</td>
<td>123 ± 14</td>
<td>134 ± 23</td>
</tr>
<tr>
<td>Major surgery</td>
<td>138 ± 22</td>
<td>125 ± 14</td>
<td>132 ± 22</td>
</tr>
<tr>
<td>Medical</td>
<td>139 ± 20</td>
<td>125 ± 20</td>
<td>132 ± 20</td>
</tr>
<tr>
<td>Fever status means</td>
<td>141 ± 24</td>
<td>124 ± 17</td>
<td></td>
</tr>
</tbody>
</table>

\( p \) values - main effects: injury type, 0.831 and fever status, 0.0001; injury × fever interaction, 0.351.
Table III. Analysis of variance of degree of hypermetabolism (per cent basal energy expenditure) for SIRS status, fever status and SIRS × fever interactions

<table>
<thead>
<tr>
<th>SIRS status</th>
<th>Fever status</th>
<th>SIRS status means</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIRS</td>
<td>Non-SIRS</td>
</tr>
<tr>
<td></td>
<td>Febrile</td>
<td>Afebrile</td>
</tr>
<tr>
<td>SIRS</td>
<td>141 ± 23</td>
<td>123 ± 17</td>
</tr>
<tr>
<td>Non-SIRS</td>
<td>149 ± 20</td>
<td>125 ± 24</td>
</tr>
<tr>
<td>Fever status means</td>
<td>145 ± 34</td>
<td>124 ± 21</td>
</tr>
</tbody>
</table>

p values – main effects: SIRS status, 0.284 and fever status, 0.0001; SIRS × fever interaction, 0.495.

Analysis of variance of degree of hypermetabolism for the main effects, SIRS status and fever status (Table III), revealed no statistically significant effect for SIRS, but a significant effect for fever. No significant SIRS status × fever status interaction effect occurred. Addition of injury type to the model (as a covariate) did not change the results.

Discussion

Wide and often conflicting variation in resting energy expenditure among groups of apparently similar patient types has been reported. For example, studies in trauma patients have reported mean levels of hypermetabolism of 116–158 per cent of basal energy expenditure.\(^\text{3-22}\). In the current study, trauma patients had an overall unadjusted mean increase in energy expenditure of 139 per cent of basal. In non-trauma surgical patients, the range of reported mean elevation in metabolic rate is 100–134 per cent of basal.\(^\text{10}\). Similar to our reported overall unadjusted mean rate of 134 per cent of basal.

Few studies of metabolic rate have been published for critically ill medical patients. It is often assumed that medical patients are not significantly hypermetabolic. In one study, resting energy expenditure was reported as 107–112 per cent above basal energy expenditure\(^\text{26}\) (within the 115 per cent of basal limit for defining hypermetabolism). However, in a different study, focusing on medical patients with sepsis or sepsis syndrome, the mean elevation of resting energy expenditure was 155 per cent of basal.\(^\text{27}\). In the current study, the medical patients had an overall unadjusted mean elevation in resting energy expenditure of 132 per cent of basal.

In the current study, fever was a better marker of hypermetabolism than was injury type. Once stratified for fever (by two-way analysis of variance and by covariance analysis), there were only small and statistically insignificant differences in per cent elevation in energy expenditure among the trauma, surgical and medical patients.

Febrile trauma patients developed a degree of hypermetabolism similar to that of febrile surgical and febrile medical patients. Likewise, afebrile trauma, surgical and medical patients had similar levels of hypermetabolism, these being significantly lower than their febrile counterparts. This suggests that the host response to injury and not the injury per se determines the elevation in metabolic rate. Furthermore, failure to stratify subjects for presence of fever could explain the conflicting reports in the literature regarding the hypermetabolic response among and within various injury types.

Certainly, fever does not explain all of the increase in resting energy expenditure during critical illness. Even the afebrile subjects were hypermetabolic (mean resting energy expenditure 24 per cent above basal levels). However, development of fever portends an increase in the hypermetabolic response above that of the injury itself, with energy expenditure being on average 41 per cent above basal across all injury types.

It is not particularly surprising that fever was associated with hypermetabolism in the current study. The correlation between body temperature and metabolic rate has been known since the studies of DuBois.\(^\text{11}\). The surprising aspect of the current study was the lack of difference in metabolic rate between groups with markedly different levels of injury (trauma, surgery, medical disease) once presence of fever was controlled for. In other words, fever rather than the marked difference in severity of injury between trauma, surgery and medical disease is the more important factor associated with the degree of hypermetabolism in critically ill patients.

Although SIRS has been described as the host response to injury or infection\(^\text{12}\), data from the current study demonstrated that fever, independent of SIRS, determined increased hypermetabolism. Febrile SIRS patients were significantly more hypermetabolic than afebrile SIRS patients (141 vs. 123 per cent of basal). In fact, afebrile SIRS patients were no more hypermetabolic than afebrile non-SIRS patients (125 per cent of basal).

One difficulty which arose in the current study was how to treat the tachypnoea criterion of SIRS, since all subjects were mechanically ventilated and, therefore, were not controlling their own respiratory rates. One of two approaches to this problem could have been taken: (1) ignore the tachypnoea criterion; or (2) assume all subjects would have been tachypnoeic had they not been receiving mechanical ventilation. The first approach was taken for the current study. Acknowledging that this approach might fail to identify subjects as having SIRS, another analysis of subjects was undertaken in which the tachypnoea criterion was assumed present in all subjects. Thus, the presence of any one of the other SIRS criteria would qualify the subject as having SIRS. Three subjects categories arose: febrile SIRS, afebrile SIRS and non-SIRS. Resting energy expenditure in febrile SIRS (141 ± 23 per cent of basal) was significantly greater than in afebrile SIRS (123 ± 17 per cent of basal), with no significant difference between afebrile SIRS and non-SIRS (125 ± 24 per cent of basal). Thus, whether the tachypnoea criterion was included or excluded from the SIRS definition, fever was found to be an independent marker of increased hypermetabolism.
Conclusions

(1) Hypermetabolism is a common but variable condition in critically ill patients.
(2) Febrile critically ill patients have an increase in hypermetabolism over afebrile critically ill patients. The magnitude of increase in metabolic rate is similar among patients experiencing trauma, major surgery and medical disease.
(3) Host response to injury, not the degree of injury per se, determines the extent of hypermetabolism in the critically ill. Fever rather than SIRS seems to be the marker of host response most associated with elevation of metabolic rate.

References

2 Hwang T. L., Huang S. L. and Chen M. F. The use of indirect calorimetry in critically ill patients - the relationship of measured energy expenditure to injury severity score, septic severity score, and APACHE II score. J Trauma 1993; 34: 247.

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