Metabolic response to stress

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Disclosures

• Speaker fees from Abbott, GE, Cosmed, B Braun, Baxter and Fresenius-Kabi
• Grants from Abbott, Baxter, B Braun and Fresenius-Kabi
Main messages

• Acute phase modifies energy expenditure and substrate utilization
• Anabolic resistance and protein breakdown are leading to significant muscle loss
• Persistent Inflammation-Immunosuppression Catabolism Syndrome (PICS) is secondary to significant nutritional changes
Stress: Trauma – Infection - Surgery

Epinephrine
Norepinephrine
Sympathetic drive

Cytokines
Inflammatory mediators

Uncontrolled catabolism

Adipokines

Anabolic resistance

GIT hormones?

Changes in: Energy expenditure   Body composition

Adapted from JC Preiser
Persistent Inflammation, Immunosuppression, and Catabolism: Evolution of Multiple Organ Dysfunction
Essential *versus* accessory aspects of cell death: recommendations of the NCCD 2015

Cell Death and Differentiation (2014), 1–16

![Diagram showing the relationship between ROS, ATP, and time in the context of cell death. The diagram illustrates the adaptive response, RCD initiation, and RCD execution phases.](image-url)
High ATP is associated with better outcome
Stress:
- Trauma
- Infection
- Surgery

Epinephrine
Norepinephrine
Sympathic drive

Cytokines
Inflammatory mediators

Uncontrolled catabolism

Adipokines

Anabolic resistance

Anabolic resistance

GIT hormones?

Changes in: Energy expenditure  Body composition

Adapted from JC Preiser
Phases of the response to injury: REE (Resting Energy Expenditure) is increased after the injury phase.

- **EBB Phase**: Energy, heat, O\(_2\) consumption increase.
- **FLOW Phase**: Hypermetabolic period, Energy consumption increase.
- **Injury Phase**: Turning point.
- **Anabolic Phase**: Catabolism.
- **Late Anabolism**: Energy consumption increase.

- **Elective surgery**: 10%
- **Trauma**: 25%
- **Peritonitis, sepsis**: 75%
- **Burn**: 100%

**Energy consumption increase**:

- Elective surgery: 10%  
- Trauma: 25%  
- Peritonitis, sepsis: 75%  
- Burn: 100%
Today the REE increase is less marked.
## Changes in the hypermetabolic period

<table>
<thead>
<tr>
<th>Hemodynamic</th>
<th>Hormonal</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO ↑</td>
<td>Cortisol ↑</td>
<td>Catabolism ↑</td>
<td>Gluconeogenesis ↑</td>
<td>Lypolysis ↑</td>
</tr>
<tr>
<td>SVR ↓</td>
<td>Glucagon ↑</td>
<td>Protein degradation ↑</td>
<td>Lactate ↑</td>
<td>Lipogenesis ↓</td>
</tr>
<tr>
<td>AV O₂ ↓</td>
<td>Insuline ↓</td>
<td>Liver acute phase protein synthesis ↑</td>
<td>Insulin resistance</td>
<td>Ketone bodies ↓</td>
</tr>
<tr>
<td></td>
<td>Adrenaline ↑</td>
<td>Urea ↑</td>
<td></td>
<td>FFA usage of myocard ↓</td>
</tr>
</tbody>
</table>
Stress response - Carbohydrate metabolism: Substrate endogenous production

- normal
- normal + endotoxin
- brief fasting
- sepsis
- burn
- burn + sepsis
- burn + sepsis + MOF

Splanchnic glucose production

Takala J. Baillieres Clin Endocrinol Metab 1997;11:617-27
Lipolysis during feeding is increased in injury or sepsis

Elwyn DH: Clin Nutr 1993
Muscle catabolism mechanisms

Critical illness:
Infections/Immobility/Mechanical ventilation

- Oxidative stress
- Inflammation / NF-κB
- Mechanical unloading

- Caspase
- Calpains

- Contractile proteins
- Ubiquitin proteasome
- Lysosomal autophagy
- Protein synthesis

Contractile protein dysfunction

Respiratory muscle weakness

Schellekens et al. Critical Care (2016) 20:103
(Surgical) trauma is accompanied by a negative nitrogen balance. Nitrogen balance is more negative than during pure fasting.
# Acute Skeletal Muscle Wasting in Critical Illness

Zudin A. Puthucheary, MRCP; Jaikitry Rawal, MRCS; Mark McPhail, PhD; Bronwen Connolly, BSc; Gamunu Ratnayake, MRCP; Pearl Chan, MBBS; Nicholas S. Hopkinson, PhD; Rahul Padhke, PhD; Tracy Dew, MSc; Paul S. Sidhu, PhD; Cristiano Velloso, PhD; John Seymour, PhD; Chibeza C. Agley, MSc; Anna Selby, PhD; Marie Limb, PhD; Lindsay M. Edwards, PhD; Kenneth Smith, PhD; Anthea Rowlerson, PhD; Michael John Rennie, PhD; John Moxham, PhD; Stephen D. R. Harridge, PhD; Nicholas Hart, PhD; Hugh E. Montgomery, MD

## Table. Baseline Characteristics of Patients

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 63)</th>
<th>Serial Muscle Biopsies and Ultrasound (n = 42)</th>
<th>Muscle Ultrasound Alone (n = 21)</th>
<th>Stable Isotope Incorporation (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>54.5 (50.0-59.1)</td>
<td>55.3 (49.4-61.1)</td>
<td>53.1 (45.4-60.1)</td>
<td>62.7 (50.1-75.4)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>37 (58.7)</td>
<td>30 (71.4)a</td>
<td>7 (31.3)</td>
<td>9 (81.8)a</td>
</tr>
<tr>
<td>Hospital length of stay prior to ICU admission, median (range), d</td>
<td>1 (1-45)</td>
<td>1 (1-6)</td>
<td>1 (1-45)</td>
<td>1 (1-6)</td>
</tr>
<tr>
<td>Period ventilated, median (range), d</td>
<td>10 (2-62)</td>
<td>8.5 (2-62)</td>
<td>10 (4-24)</td>
<td>12 (2-62)</td>
</tr>
<tr>
<td>ICU length of stay, median (range), d</td>
<td>16 (7-80)</td>
<td>15.5 (7-80)</td>
<td>17 (7-73)</td>
<td>18 (8-80)</td>
</tr>
<tr>
<td>Hospital length of stay, median (range), d</td>
<td>30 (11-334)</td>
<td>29.5 (11-212)</td>
<td>33 (13-334)</td>
<td>50 (17-212)</td>
</tr>
<tr>
<td>APACHE II score, mean (95% CI)</td>
<td>23.5 (21.9-25.2)</td>
<td>23.3 (21.3-25.3)</td>
<td>24 (20.1-27.2)</td>
<td>27 (22.9-31.3)</td>
</tr>
<tr>
<td>SAPS II score, mean (95% CI)</td>
<td>45.5 (41.8-49.3)</td>
<td>43.4 (39.2-47.6)</td>
<td>49.7 (42.0-57.4)</td>
<td>47 (39.6-54.4)</td>
</tr>
<tr>
<td>Survival, No. (%)</td>
<td>61 (97)</td>
<td>40 (95)</td>
<td>21 (100)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>ICU</td>
<td>56 (89)</td>
<td>37 (88)</td>
<td>19 (90)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Hospital</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal replacement therapy, No. (%)</td>
<td>19 (30.2)</td>
<td>13 (31.0)</td>
<td>6 (29.0)</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Use of neuromuscular blocking agents, median (range), d</td>
<td>0 (0-6)</td>
<td>0 (0-6)</td>
<td>0 (0-5)</td>
<td>0 (0-6)</td>
</tr>
<tr>
<td>Hydrocortisone dose, median (range), mgb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0 (0-800)</td>
<td>0 (0-800)</td>
<td>0 (0-400)</td>
<td>200 (0-800)</td>
</tr>
<tr>
<td>Total by day 10</td>
<td>0 (0-4533)</td>
<td>0 (0-4533)</td>
<td>0 (0-3360)</td>
<td>450 (0-4533)</td>
</tr>
</tbody>
</table>
From admission: loss of muscle mass in biopsy and Protein/DNA

A. Change in rectus femoris (RF) cross-sectional area (CSA) over 10 days.

B. Measures of muscle wasting in patients assessed by all 3 measures on both day 1 and day 7 (n = 28).

Breakdown > Synthesis

Tracers show an increase in synthesis and a higher increase in breakdown, leading to negative nitrogen balance.
The effects of bed rest...

Decrease in muscle mass
Long-Term Association Between Frailty and Health-Related Quality-of-Life Among Survivors of Critical Illness: A Prospective Multicenter Cohort Study

Sean M. Bagshaw, MD, MSc; H. Thomas Stelfox, MD, PhD; Jeffrey A. Johnson, PhD; Robert C. McDermid, MD; Darryl B. Rolfson, MD; Ross T. Tsuyuki, PharmD, MSc; Ouazi Ibrahim, MSc; Sumit R. Maiumdar, MD, MPH

6-months after ICU

<table>
<thead>
<tr>
<th>County</th>
<th>Not Frail</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Not Frail</td>
<td>90</td>
<td>70</td>
</tr>
<tr>
<td>Frail</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

12-months after ICU

<table>
<thead>
<tr>
<th>County</th>
<th>Not Frail</th>
<th>Frail</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>100</td>
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<td>70</td>
</tr>
<tr>
<td>Frail</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

p<0.001, for each
Autophagy cleans cell debris, but releases nutrients and is inhibited by feeding.
Substrate utilization
Weissman C, Crit Care Clinics 1999

Diagram showing the pathway of substrate utilization:
- Adipose tissue → Glycerol + Free Fatty Acids
- Muscle → Alanine → Liver
- Wound → Lactate → Glucose

Liver receives substrates from adipose tissue, muscle, and wound, processing them into glucose.
Qualitative Ultrasound in Acute Critical Illness Muscle Wasting

Zudin A. Puthucheary, PhD\textsuperscript{1,2,3}; Rahul Phadke, FRCPath\textsuperscript{4}; Jaikitry Rawal, MRCS\textsuperscript{1}; Mark J. W. McPhail, PhD\textsuperscript{5,6}; Paul S. Sidhu, FRCR\textsuperscript{7}; Anthea Rowlerson, PhD\textsuperscript{2}; John Moxham, MD\textsuperscript{8}; Stephen Harridge, PhD\textsuperscript{2}; Nicholas Hart, PhD\textsuperscript{9}; Hugh E. Montgomery, MD\textsuperscript{1}

Qualitative US can evaluate muscle wasting
CT Scan can evaluate fat mass and lean body mass of ICU patients
Phase angle obtained by bio-impedance is assessing malnutrition.
Phase angle is predictive of survival and malnutrition.

Table 2 Logistic regression multivariable analysis of factors associated with 28-day mortality (n = 895)

<table>
<thead>
<tr>
<th>Variables</th>
<th>aOR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.014</td>
<td>1.0016–1.0271</td>
<td>0.03</td>
</tr>
<tr>
<td>Day 1 phase angle</td>
<td>0.86</td>
<td>0.78–0.96</td>
<td>0.008</td>
</tr>
<tr>
<td>APACHE II</td>
<td>1.08</td>
<td>1.06–1.11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission diagnosis: surgery vs. medicine</td>
<td>0.51</td>
<td>0.33–0.79</td>
<td>0.002</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>0.39</td>
<td>0.21–0.72</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Area under the receiver operating characteristic curve = 0.79 [95% CI, 0.75–0.82]
Conclusions

• In the acute phase:
  – Energy expenditure is increased in a moderate way
  – mobilization of substrates to provide glucose,
  – obligatory lipolysis,
  – Obligatory proteolysis.

• In the stabilized phase, body composition should be preserved and nutritional support can be adapted to the patient’s needs to prevent from PICS.