Acute Skeletal Muscle Wasting
in the Critically Ill

Z A Puthucheary
on behalf of the UK-MUSCLE Investigators
• “Death, morbidity and economics are the only endpoints for trials” Koretz 2005

<table>
<thead>
<tr>
<th>Year of admission</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of admissions</td>
<td>83,116</td>
<td>90,761</td>
<td>77,394</td>
<td>106,479</td>
</tr>
<tr>
<td>Critical care unit length of stay (hours), median (IQR) [N]</td>
<td>50 (23, 120)</td>
<td>51 (24, 125)</td>
<td>52 (24, 124)</td>
<td>54 (24, 125)</td>
</tr>
<tr>
<td>Total acute hospital length of stay (days)*, median (IQR) [N]</td>
<td>13 (6, 28)</td>
<td>13 (6, 28)</td>
<td>13 (6, 27)</td>
<td>13 (6, 27)</td>
</tr>
<tr>
<td>Critical care unit mortality, deaths (%) [N]</td>
<td>14,904 (17.9)</td>
<td>15,806 (17.4)</td>
<td>13,136 (17.0)</td>
<td>17,520 (16.5)</td>
</tr>
<tr>
<td>Acute hospital mortality*, deaths (%) [N]</td>
<td>21,189 (27.1)</td>
<td>22,299 (26.1)</td>
<td>18,491 (25.4)</td>
<td>24,620 (24.4)</td>
</tr>
<tr>
<td>Duration of advanced respiratory support (calendar days), median (IQR) [N]</td>
<td>1 (0, 3)</td>
<td>1 (0, 3)</td>
<td>1 (0, 3)</td>
<td>0 (0, 2)</td>
</tr>
<tr>
<td>Age, mean (SD) median (IQR) [N]</td>
<td>60.1 (18.8)</td>
<td>60.3 (18.7)</td>
<td>60.5 (18.5)</td>
<td>60.7 (18.4)</td>
</tr>
<tr>
<td>APACHE II score†, mean (SD) median (IQR) [N]</td>
<td>16.7 (7.4)</td>
<td>16.3 (7.1)</td>
<td>16.2 (7.1)</td>
<td>16.0 (7.0)</td>
</tr>
</tbody>
</table>

*Excluding readmissions to the critical care unit during the hospital stay
†Excluding admissions aged less than 16 years
IQR: interquartile range; N: number of admissions; SD: standard deviation
• “Muscle weakness is the most common physical problem faced by patients following critical illness”
  – ICUSteps. Registered Charity No. 1117033

• “All patients reported poor function and attributed this to the loss of muscle bulk, proximal weakness and fatigue”
  – Herridge et al New England of Medicine 2003
• “Survivorship will be the defining challenge of critical care in the 21st century”
  — Iwashyna Ann Int Med 2010

<table>
<thead>
<tr>
<th>Condition</th>
<th>Highest Incidence</th>
<th>Lowest Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU-AW</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>VAP</td>
<td>25%</td>
<td>10%</td>
</tr>
<tr>
<td>DVT</td>
<td>30%</td>
<td>4%</td>
</tr>
<tr>
<td>CVC infection</td>
<td>0.058%</td>
<td>0.001%</td>
</tr>
</tbody>
</table>

• “The lack of detailed understanding of the pathophysiology of the muscle wasting needs to be addressed”
  — National Institute of Clinical Excellence 2009

De Jonghe JAMA 2002
ATS AUCCCM 2005
Boddi JTN 2010
Provonost NEJM 2006
FACTORS INFLUENCING SKELETAL MUSCLE MASS & FUNCTION DURING CRITICAL ILLNESS

MUSCLE MASS

TIME

HEALTH

CRITICAL ILLNESS

FUNCTIONAL LIMITATION

SURVIVORS

RECOVERY

Puthucheary et al J Physiol 2010
Musculoskeletal Ultrasound Study in Critical Illness: Longitudinal Evaluation

MUSCLE: NCT01106300

1. Describe changes in muscle mass and quality
2. Determine role of altered protein homeostasis
3. Investigate clinical correlates
STUDY RECRUITMENT

363 Patients screened

213 did not meet criteria

150 met entry and exclusion criteria

59 refused

91 gave assent

4 Withdrew
2 Transfer to another hospital
12 Died
10 ICU stay less than 7 days

63 patients studied
PATIENT CHARACTERISTICS

• 54.5 ± 18 years, 58.7% male
• Apache II 23.5 ± 6.5

• Ventilated 10 days (2-62)
• ICU Stay 16 days (7-80)
• ICU survival 97%
• hospital survival 89%
1. MUSCLE MASS AND QUALITY

RECTUS FEMORIS ULTRASOUND

MUSCLE BIOPSY

PROTEIN/DNA RATIO

SEYMOUR THORAX 2009
COAKLEY CLIN SCI 1986
DUBOWITZ 1985
7 day loss (n=28)

- RF_{CSA}
- Fibre_{CSA}
- Protein/DNA ratio

p=0.31
MUSCLE QUALITY DECLINED

>50% demonstrated patchy necrosis (20/37)
No other myopathic changes
2. MUSCLE PROTEIN HOMEOSTASIS

Diagram showing the balance between muscle protein synthesis (MPS) and breakdown (MPB) over time. The graph illustrates the net gain or loss of muscle protein at various time points (0, 4, and 8 hours) with arrows indicating the direction of these changes.
STABLE ISOTOPE INFUSIONS

DAYS: 1 3 7 10

[1,2 $^{13}$C$_2$] Leucine

D$_3$-Phenylalanine

Enriched

Millward Nature 1973
Rennie Proc Nutr Soc 1984
SIGNALLING IN MUSCLE PROTEIN HOMEOSTASIS

MYOSTATIN

ACTIVIN

IGF1-R

PTEN

SMAD2,3

AKT

mTOR

GSK3β

P70s6K

4EBP-1

EEF2

eIF4B

eIF4e

RPS6

Nucleus

FOXO

NFκβ

MURF-1

MAFBx

UBIQUITINISATION

INITIATION

ELONGATION

TERMINATION

FOLDING

PROTEIN SYNTHESIS

PROTEIN BREAKDOWN
PROTEIN HOMEOSTASIS (n=11)

LIMB PROTEIN BALANCE

μmol phe/min/kgBW*100

Days from admission

1

7

Breakdown
Synthesis
Balance

p=0.05*
p<0.01*
PROTEIN HOMEOSTASIS (n=11)

Muscle protein synthesis

FSR %/hr

patients (n=11)

controls (n=8)

p=0.57

DAYS FROM ADMISSION
INTRACELLULAR SIGNALLING DATA

Principle Component Analysis was performed

Intracellular signalling vs Limb Protein Synthesis

Intracellular signalling vs Limb Protein Breakdown

\[ r = -0.69 \]
\[ p = 0.04^* \]

\[ r = -0.83 \]
\[ p < 0.01^* \]
## 3. Clinical Correlates of Muscle Wasting

<table>
<thead>
<tr>
<th>Muscle Wasting</th>
<th>$r^2=0.51$, $p&lt;0.001$</th>
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<tr>
<td><strong>Inverse Association</strong></td>
<td></td>
</tr>
<tr>
<td>PaO$_2$/FiO$_2$</td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td></td>
</tr>
<tr>
<td>Admission haemoglobin</td>
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<td><strong>Association</strong></td>
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</tr>
<tr>
<td>C-Reactive Protein</td>
<td></td>
</tr>
<tr>
<td>Total Protein delivered</td>
<td></td>
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<th>10% Muscle Wasting (AUROC=0.9,$p&lt;0.001$)</th>
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<td><strong>Association</strong></td>
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<tr>
<td>Age</td>
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</table>
HYPOTHESIS

Severity of acute lung injury is causally associated with acute muscle loss
3. CLINICAL CORRELATES OF MUSCLE WASTING

MUSCLE WASTING

\[ r^2 = 0.51, \ p < 0.001 \]

**INVERSE ASSOCIATION**

- \( \text{PaO}_2/\text{FiO}_2 \)
- Bicarbonate
- Admission haemoglobin

**ASSOCIATION**

- C-Reactive Protein
- Total Protein delivered

10% MUSCLE WASTING

(AUROC = 0.9, \( p < 0.001 \))

**INVERSE ASSOCIATION**

- \( \text{PaO}_2/\text{FiO}_2 \)
- Bicarbonate

**ASSOCIATION**

- Age
THE MUSCLE FULL EFFECT

• Muscle protein synthesis returns to baseline after 90 minutes


Early vs Late Parenteral Nutrition in Critically ill adults- Casear NEJM 2011
Optimisation of energy provision with supplemental parenteral nutrition- Heidigger Lancet 2013
Early Parenteral nutrition in critically patients with short term relative contraindications to enteral nutrition- Doig JAMA 2013


Millward Clin Sci 1995
Conclusions

1. Critical illness muscle wasting
   - Occurs rapidly and early during the first week
   - Is most pronounced in multi-organ failure
   - Results from decreased muscle protein synthesis and a net catabolic state
   - Is associated with age, acute lung injury and systemic acidosis

2. Muscle necrosis with macrophage infiltration is common
RELEVANCE

• Description of acute muscle wasting
• Framework of testing interventions
Critical Care PROMS

SF-36 Forms

Physical Activity
UK-MUSCLE 2013-14: The Bench
2015-Back to the Bedside

MUSCLE II (GET-RIP’D)
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  • London Respiratory Muscle Group (KCL, Imperial)
  • Centre for Human and Aerospace Physiological Sciences, KCL
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