INTERNATIONAL EARLY MOBILIZATION NETWORK 2014
2nd European Conference on Weaning & Rehabilitation in Critically Ill Patients Programme

ICU-AW: FROM BENCH TO BEDSIDE ASSESSMENT
Bridging the Gap Between Science and Clinical Medicine

Nicholas Hart
Reader in Respiratory & Critical Care Medicine
Division of Asthma, Allergy & Lung Biology
Kings College London

Clinical & Academic Director
Lane Fox Respiratory Unit
St Thomas’ Hospital
London UK
Muscle-UK Critical Care Programme

Musculoskeletal Ultrasound Study in Critical Care: A Longitudinal Evaluation (MUSCLE)

Clinicians
Dr Ronan Astin (University College London)
Dr Bronwen Connolly (King’s College London/Kings College Hospital/ St Thomas’ Hospital)*
Dr Nicholas Hart (King’s College London/St Thomas’ Hospital)
Dr Nicholas Hopkinson (Imperial College/Royal Brompton Hospital)
Dr Mark McPhail (Imperial College/Kings College Hospital)
Prof Hugh Montgomery (University College London/Whittington Hospital)
Dr Mike Polkey (Imperial College/Royal Brompton Hospital)
Dr Zudin Puthucheary (University College London/King’s College London)**
Prof John Moxham (King’s College London/Kings College Hospital)
Dr Ged Rafferty (King’s College London/Kings College Hospital)
Kanak Roberts (King’s College London/St Thomas’ Hospital)

Scientists
Dr Lindsay Edwards (King’s College London)
Prof Paul Greenhaf (University of Nottingham)
Prof Steve Harridge (King’s College London)
Dr Angela McNelly (University College London)
Prof Mike Rennie (University of Nottingham)
Dr Anthea Rowlerson (King’s College London)
Dr Kenneth Smith (University of Nottingham)
Dr Cristina Velloso (King’s College London)

PEER-REVIEWED AWARDS
*ATS Critical Care Assembly Abstract Award 2013
*ATS Critical Care Assembly Abstract Award 2012
**ESICM Young Investigator’s Award 2010
**BTS Early Career Investigators Award 2012
**Commendation for ICS Gold Medal 2012
**European Society of Anaesthesiology Anaesthesia and Intensive Care Award for Publication of Significant Clinical Relevance 2014
How is all started?
It is always assumed that the first thing in any illness is to put the patient to bed. Hospital accommodation is always numbered in beds. Illness is measured by the length of time in bed. Doctors are assessed by their bedside manner. Bed is

**Muscles and Joints.**—The contraction of some muscles and the stretching of others are complications of rest which may cause considerable crippling. Foot-drop is of course the commonest, and stiffness and flexion of the knee-joints probably the next. The weakness and wasting of the general skeletal musculature and the restriction of the excursion of the joints are often manifest in the hobbling, painful gait of the convalescent patient.

**Bones.**—When bones are not used the calcium drains from them, and this disuse osteoporosis can be a serious matter, especially in the elderly. Fractures for that reason may take longer to heal, and the absence of weight-bearing is another reason for delayed union. This is shown by George Perkins's recently published cases where the broken ends of bone, when splinted by a metal plate, did not heal until the plate accidentally broke and the resulting increase in weight-bearing led to rapid bony union. The advantages of the Smith-Petersen pin over older methods of managing intracapsular fractures of the femur are largely due to the shorter time in bed.

**Mental Changes.**—Lastly, consider the mental changes, the demoralizing effects of staying in bed. At the start it may produce fussiness, pettiness, and irritability. The patient may acquire an exaggerated idea of the seriousness of his illness and think, “Surely I must be very ill if I am kept in bed?” At a later stage a dismal lethargy overcomes the victim. He loses the desire to get up and even resents any efforts to extract him from his supine stupor. The end result can be a comatose, vegetable existence in which, like a useless but carefully tended plant, the patient lies permanently in tranquil torpidity.

Even the insomnia and nocturnal restlessness so common in hospital patients may be related to the abuse of rest. Too much sleep during the day means too little sleep at night. You may notice that many patients who disturb the ward at night are flat on their backs snoring during the day. They lie in bed with nothing much to do, and we cannot blame them for taking frequent cat naps. I am sure that many hours of half-sleeping and dozing are less beneficial than a few hours of deep sleep, and I believe they encourage a certain confusion of mind.
over 50 years later...

‘The recovery process may present serious physical, psychological, and social problems for both patients and their families, and these may last for months or years’

ABC of Intensive Care: Recovery from Intensive Care
BMJ 1999
Richard D Griffith and Christina Jones
‘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

‘The lack of detailed understanding of the pathophysiology of the muscle wasting needs to be addressed’

National Institute of Clinical Excellence 2009

‘Survivorship will be the defining challenge of critical care in the 21st century’

Iwashyna Ann Int Med 2010
...and along came the revolution...

COMPARATIVE INCIDENCE OF ICU-ACQUIRED WEAKNESS

<table>
<thead>
<tr>
<th></th>
<th>ICU-AW</th>
<th>VAP</th>
<th>DVT</th>
<th>CVC infection</th>
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<tbody>
<tr>
<td>highest incidence</td>
<td>50%</td>
<td>25%</td>
<td>30%</td>
<td>0.058%</td>
</tr>
<tr>
<td>Lowest incidence</td>
<td>25%</td>
<td>10%</td>
<td>4%</td>
<td>0.001%</td>
</tr>
</tbody>
</table>
A Critical Role for Muscle Ring Finger-1 in Acute Lung Injury–associated Skeletal Muscle Wasting

Am J Respir Crit Care Med Vol 185, Iss. 8, pp 825-834, Apr 15, 2012

D. Clark Files1,2, Franco R. D’Alessio1, Laura F. Johnston1, Priya Kesari1, Neil R. Aggarwal1,
Brian T. Garibaldi1, Jason R. Mock1, Jessica L. Simmers3, Antonio DeGorordo1, Jared Murdoch1,
Monte S. Willis4, Cam Patterson4, Clarke G. Tankersley5, Maria L. Messi6, Chun Liu2,
Osvaldo Delbono6, J. David Furlow7,8, Sue C. Bodine7,8, Ronald D. Cohn3, Landon S. King1,
and Michael T. Crow1
A Critical Role for Muscle Ring Finger-1 in Acute Lung Injury–Associated Skeletal Muscle Wasting

Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane

Jeffrey Bierbrauer, MD; Susanne Koch, MD; Claudio Olbricht, MD; Jida Hamati; Dörte Lodka; Joanna Schneider, MD; Anja Luther-Schröder; Christian Kleber, MD; Katharina Faust, MD; Solveigh Wiesener, MD; Claudia D. Spies, MD; Joachim Spranger, MD; Simone Spuler, MD; Jens Fielitz, MD; Steffen Weber-Carstens, MD
A Critical Role for Muscle Ring Finger-1 in Acute Lung Injury–associated Skeletal Muscle Wasting

Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane

Novel events in the molecular regulation of muscle mass in critically ill patients

Despina Constantin¹, Justine McCullough², Ravi P. Mahajan² and Paul L. Greenhaff¹
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Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane

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Critical Care
Mechanisms underlying intensive care unit muscle wasting and effects of passive mechanical loading

A Critical Role for Muscle Ring Finger-1 in Acute Lung Injury–associated Skeletal Muscle Wasting

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Early type II fiber atrophy in intensive care unit patients with nonexcitable muscle membrane

Jeffr
Joan
Solv
Jens

Novel events in the molecular regulation of muscle mass in critically ill patients


Despite

Critical Care

Mechanisms underlying

Critical Care

Monica Llano
Guillaume
Magnus André
Humberto Gonzales
Nicola
Henrik
Rebecca
Konstantin
Jonas
Lars

The Lancet Respiratory Medicine

Volume 1, Issue 8, October 2013, Pages 621–629

Articles

Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial

Greet Hermans, MD⁴, Michael P Casaer, MD⁵, Beatrix Clercx, PT⁶, Fabian Güiza, PhD⁷, Tine Vanhullebusch, PT⁸, Sarah Derde, PhD⁹, Philippe Meerssman, MD⁴, Inge Derese, BSc⁴, Dieter Mesotten, MD⁴, Pieter J Wouters, MSc⁴, Sophie Van Cromphaut, MD⁴, Yves Debaveye, MD⁴, Rik Gosselink, PhD⁴, Jan Gunst, MD⁴, Alexander Wilmer, MD⁴, Greet Van den Berghe, Dr MD⁴, Ilse Vanhorebeek, PhD⁴

¹ Medical Intensive-Care Unit, Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium
² Department of Intensive Care Medicine, University Hospitals Leuven, Leuven, Belgium
³ Laboratory of Intensive-Care Medicine, Division of Cellular and Molecular Medicine, KU Leuven, Leuven, Belgium
⁴ Department of Rehabilitation Sciences, KU Leuven, Leuven, Belgium
So in 2006...

Muscle-UK Critical Care Programme

Translational Science Programme: From Bench to Bedside
TO DEFEAT ICU-ACQUIRED WASTING

Understand the mechanisms of the wasting and the catabolic and anabolic drivers contributing to the loss of muscle mass

TOPICAL REVIEWS

Structure to function: muscle failure in critically ill patients
Zudin Puthucheary¹, Hugh Montgomery², John Moxham³, Stephen Harridge⁴ and Nicholas Hart⁵

Skeletal muscle dysfunction in critical care: Wasting, weakness, and rehabilitation strategies
Zudin Puthucheary, MRCP; Stephen Harridge, PhD; Nicholas Hart, PhD
Crit Care Med 2010 Vol. 38, No. 10 (Suppl)
WASTING

MUSCLE STRUCTURE → MUSCLE FUNCTION → FUNCTIONAL OUTCOME → CLINICAL OUTCOME

WEAKNESS
WASTING

- WEAKNESS
- INACTIVITY

MUSCLE STRUCTURE → MUSCLE FUNCTION → FUNCTIONAL OUTCOME → CLINICAL OUTCOME
WASTING → WEAKNESS → INACTIVITY

ICU LOS
Hospital LOS
HRQL
Mortality
Rapid change in fracture risk in patients with acute lung injury
Crit Care Med Puthucheary et al. Under Review

Preservation of Mitochondrial Oxidative Capacity in Critically Ill Patients Balances Reduction in Mitochondrial Biogenesis
Astin et al. In Preparation

Use of ultrasound for the assessment of peripheral skeletal muscle architecture in critical illness: a systematic review
Crit Care Med Connolly et al. In Press

Connolly et al Crit Care 2013 17: R229
Critical Care Clinical Predictive Value of Manual Muscle Strength Testing During Critical Illness

BMJ Open 2014:4 e004963 Connolly et al.
A UK survey of rehabilitation following critical illness: implementation of NICE Clinical Guidance 83 (CG83) following hospital discharge

The Human and Financial Cost of Surviving Critical Illness: Physical Activity, Health-Related Quality of Life and Health Economics
Crit Care Med McNelly et al. Under Review

MUSCLE STRUCTURE → MUSCLE FUNCTION → FUNCTIONAL OUTCOME → CLINICAL OUTCOME

ACUTE MUSCLE WASTING → ACUTE MUSCLE WEAKNESS → PHYSICAL ACTIVITY → CLINICAL & COST EFFECTIVENESS
Translational Science: From Bench to Bedside
How Can We Assess Wasting?

How Can We Assess Strength?

How Can We Assess Function?
1. Quantify Skeletal Muscle Mass
2. Assess Muscle Quality
3. Measure Skeletal Muscle Contractility
5. Supervised Exercise Capacity
6. Unsupervised Physical Activity

Acute Critical Illness
Unable to Follow Commands

Post Critical Illness
Recovery
Self-Initiation of Activity
1. Quantify Skeletal Muscle Mass
‘Comprehensive study to characterize skeletal muscle wasting and define the pathogenic roles of altered protein synthesis and breakdown’
Ultrasound Measurement of Rectus Femoris Cross-Sectional Area and the Relationship to Quadriceps Strength in Chronic Obstructive Pulmonary Disease

\[ T_{wQ} (\text{kg}) \]

\[ R_{FCSA} (\text{mm}^2) \]

\[ \% \text{ of Day 1 value} \]

Day of ICU admission

Seymour et al Thorax 2009
Ultrasound Measurement of Rectus Femoris Cross-Sectional Area and the Relationship to Quadriceps Strength in Chronic Obstructive Pulmonary Disease

Mean Reduction in $RF_{CSA}$ of 18.7% at 10 days

*Seymour et al Thorax 2009*
Muscle wasting was significantly greater in the sickest patients:
- 7% loss in $\text{RF}_{\text{CSA}}$ with 1 organ failure
- 20% loss in $\text{RF}_{\text{CSA}}$ with > 2 organ failure
- 26% loss in $\text{RF}_{\text{CSA}}$ with > 4 organ failure

*Puthucheary et al. JAMA 2013*
1. Quantify Skeletal Muscle Mass

2. Assess Muscle Quality

Acute Critical Illness
Unable to Follow Commands

Post Critical Illness
Recovery
Self-Initiation of Activity
Female
24 Year
Septic Shock
Multi-Organ Failure
10% reduction in RF$_{\text{CSA}}$
Haematoxylin & Eosin Stain

Puthucheary et al. JAMA 2013
Female
24 Year
Septic Shock
Multi-Organ Failure
10% reduction in RF
CSA
Haematoxylin & Eosin

Day 1

Day 7

> 50% demonstrated patchy necrosis

Puthucheary et al  JAMA 2013
1. Quantify Skeletal Muscle Mass
2. Assess Muscle Quality
3. Measure Skeletal Muscle Contractility

Non-Volitional Measurements of Skeletal Muscle Performance

Acute Critical Illness
Unable to Follow Commands

Post Critical Illness
Recovery
Self-Initiation of Activity
Watson et al, Crit Care Med 2001 29: 1325-1331
Harris et al, Am J Respir Crit Care Med 2000; 162: 240-245
Swallow et al, J Appl Physiol 103: 739-746 2007
1. Quantify Skeletal Muscle Mass
2. Assess Muscle Quality
3. Measure Skeletal Muscle Contractility
Only moderate agreement for diagnosis of ICU-AW at awakening. Inter-observer agreement for diagnosis of ICU-AW is a consequence of patient rather than clinician variability. Clinical value of MMT and MRC-SS is limited at awakening.

- 74% diagnosed as ICU-AW at awakening
- No relationship between MRC-SS and ICU mortality and hospital mortality
- Relationships between MRC-SS and ICU LOS ($p=0.004$) and hospital LOS ($p=0.04$)
MRC-SS < 48, indicative of ICU-AW: Limited predictive value for ICU LOS > 14 days or hospital LOS > 28 days

MRC-SS ≥ 48 at awakening: Predictive of an ICU LOS ≤ 14 days and a hospital LOS ≤ 28 days

Table 3 Clinical predictive value of medical research council sum-score <48 at awakening

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<tr>
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<tr>
<td></td>
<td>%</td>
<td>95% CI</td>
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</tr>
<tr>
<td>Sensitivity</td>
<td>92.9</td>
<td>76.5-99.1</td>
<td>84.2</td>
<td>68.7-94.0</td>
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<td>Specificity</td>
<td>40.5</td>
<td>24.8-57.9</td>
<td>40.7</td>
<td>22.4-61.2</td>
</tr>
<tr>
<td>PPV</td>
<td>54.2</td>
<td>39.2-68.6</td>
<td>66.7</td>
<td>51.6-79.6</td>
</tr>
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<td>NPV</td>
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MRC-SS < 48, indicative of ICU-AW: Limited predictive value for ICU LOS >14 days or hospital LOS >28 days

MRC-SS ≥ 48 at awakening: Predictive of an ICU LOS ≤ 14 days and a hospital LOS ≤ 28 days
1. Quantify Skeletal Muscle Mass

2. Assess Muscle Quality

3. Measure Skeletal Muscle Contractility


5. Supervised Exercise Capacity

Acute Critical Illness
Unable to Follow Commands

Post Critical Illness
Recovery
Self-Initiation of Activity
<table>
<thead>
<tr>
<th></th>
<th>Activity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Nothing (lying in bed)</td>
</tr>
<tr>
<td>1</td>
<td>Sitting in bed, exercises in bed</td>
</tr>
<tr>
<td>2</td>
<td>Passively moved to chair (no standing)</td>
</tr>
<tr>
<td>3</td>
<td>Sitting over edge of bed</td>
</tr>
<tr>
<td>4</td>
<td>Standing</td>
</tr>
<tr>
<td>5</td>
<td>Transferring bed to chair</td>
</tr>
<tr>
<td>6</td>
<td>Marching on spot (at bedside)</td>
</tr>
<tr>
<td>7</td>
<td>Walking with assistance of 2 or more people</td>
</tr>
<tr>
<td>8</td>
<td>Walking with assistance of 1 person</td>
</tr>
<tr>
<td>9</td>
<td>Walking independently with a gait aid</td>
</tr>
<tr>
<td>10</td>
<td>Walking independently without a gait aid</td>
</tr>
</tbody>
</table>
• Intensive care unit mobility practices
• 38 Australian and New Zealand ICUs
• 514 patients (498 complete datasets)
• 45% mechanically ventilated
• Mobilisation activities
  – 28% completed an in-bed exercise regimen
  – 19% sat over the side of the bed
  – 37% sat out of bed
  – 25% stood
  – 18% walked
  – No patient requiring mechanical ventilation sat out of bed or walked
• Patient mobilisation was low in patients requiring mechanical ventilation

Berney et al Crit Care Resusc. 2013
• Intensive care unit mobility practices
• 116 German ICUs
• 783 patients
• Mobilisation activities
  – 24% of mechanically ventilated patients were mobilised out of bed (sitting on the edge of the bed or higher level of mobilisation)
  – 8% with an endotracheal tube were mobilised out of bed
  – 38% with a tracheostomy tube were mobilised out of bed
• Patient mobilisation was shown to be low in patients requiring mechanical ventilation

*Nydahl et al Crit Care Med. 2014*
<table>
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### Acute Critical Illness
Unable to Follow Commands

### Post Critical Illness
Recovery
Self-Initiation of Activity
What is the effect of critical Illness on skeletal muscle?

What is the effect of the treatments of critical illness on skeletal muscle?
MUSCLE MASS
First Week in ICU

10.3 ± 10.9%

17.5 ± 30.2%

29.5 ± 41.5%

p=0.31

p=0.03

Puthucheary et al  JAMA 2013
MUSCLE MASS REGULATION

MUSCLE PROTEIN HOMEOSTASIS

DAY 1  3  7  10

STABLE ISOTOPE INFUSIONS

[1,2-\(^{13}\)C\(_2\)] Leucine

\[\text{CH}_3\text{C}^\text{\scriptsize{13}}\text{C}^\text{\scriptsize{13}} \text{COOH}\]

D\(_2\)-Phenylalanine

\[\text{H}_2\text{C}-\text{C}^\text{\scriptsize{2D}}\text{C}^\text{\scriptsize{2D}}\text{N}\text{H}_2\]

GC-MS

SKELETAL MUSCLE BIOPSY
Muscle Signalling Pathways
Muscle Protein Breakdown Signals

- AKT-FOXO-E3 Ligase Axis

Muscle Protein Synthesis Signals

- AKT-mTOR-P70S Axis

Muscle Wasting
MUSCLE PROTEIN BREAKDOWN PATHWAYS

Autophagosome Pathway

Ubiquitin Proteosome Pathway

Cytosolic Protease Pathway

ATP-dependant intracellular protein breakdown pathway
Lecker et al, 1999; Cahill et al, 2011; Novak et al, 2011; Lecker et al, 2004

ATP-independent Cytosolic proteases e.g. calpains for calcium activated proteolysis
Lecker et al, 1999

Control extracellular & membrane surface protein turnover
Lecker et al, 1999
Mitch and Goldberg, 1996

Final common proteolysis pathway
Signalling in Muscle Protein Homeostasis

- MYOSTATIN
- ACTIVIN Receptor Ilb
- IGF1-R
- TNFR-1

- AKT
- SMAD2,3

- eIF4B
- eIF4e
- mTOR
- 4EBP-1
- GSK3β
- P70s6K
- EEF2
- RPS6

- FOXO
- NFκβ
- MURF-1
- MAFBx

- UBIQUITINISATION
- Nucleus

- PROTEIN SYNTHESIS
- PROTEIN BREAKDOWN
Principle Component Analysis demonstrated the relationship between anabolic and catabolic pathways and real time measures of protein turnover.

Puthucheary et al JAMA 2013
What Happens to Muscle Protein Turnover?
PROTEIN HOMEOSTASIS (n=11)

MUSCLE PROTEIN SYNTHESIS

MPS rates at day 1 were depressed to levels observed in fasted healthy controls

Significant Increase in MPS from day 1 to day 7

MPS rates at day 7 recovered to similar levels of healthy fed controls
PROTEIN HOMEOSTASIS (n=11)

MUSCLE PROTEIN SYNTHESIS

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PROTEIN HOMEOSTASIS (n=11)

MUSCLE PROTEIN SYNTHESIS

MPS rates at day 1 were depressed to levels observed in fasted healthy controls. Significant increase in MPS from day 1 to day 7. MPS rates at day 7 recovered to similar levels of healthy fed controls.
PROTEIN HOMEOSTASIS (n=11)

LIMB PROTEIN BALANCE

μmol phe/min/kgIBW*100

DAYS FROM ADMISSION

Breakdown
Synthesis
Balance

Protein Turnover (% normal)
7 Weeks Long Leg Cast Immobilisation

Gibson et al 1987

Normal
Immobilised
PROTEIN HOMEOSTASIS (n=11)

LIMB PROTEIN BALANCE

µmol phe/min/kgIBW*100

DAYS FROM ADMISSION

0 5 10 15

0 1 7

Breakdown
Synthesis
Balance

Protein Turnover (% normal)

0 30 60 90 120 150

Normal Immobilised

7 Weeks Long Leg Cast Immobilisation

Gibson et al 1987
PROTEIN HOMEOSTASIS (n=11)

LIMB PROTEIN BALANCE

μmol phe/min/kgIBW*100

DAYS FROM ADMISSION

Breakdown
Synthesis
Balance

Protein Turnover (% normal)

7 Weeks Long Leg Cast Immobilisation

Gibson et al 1987
Are there clinical correlates with muscle wasting?
Greater severity of acute lung injury was associated with acute muscle loss. Higher total protein delivered was associated with greater muscle wasting.
**CLINICAL CORRELATES**

<table>
<thead>
<tr>
<th>MUSCLE WASTING</th>
<th>10% MUSCLE WASTING</th>
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<tr>
<td>$r^2=0.51$; $p&lt;0.001$</td>
<td>AUROC = 0.9; $p&lt;0.001$</td>
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### INVERSE CORRELATION
- $\frac{PaO_2}{FiO_2}$
- Bicarbonate
- Admission haemoglobin

### DIRECT CORRELATION
- C-Reactive Protein
- Total Protein delivered

### INVERSE CORRELATION
- $\frac{PaO_2}{FiO_2}$
- Bicarbonate

### DIRECT CORRELATION
- Age

Greater severity of acute lung injury was associated with acute muscle loss.

Higher total protein delivered was associated with greater muscle wasting.
**CLINICAL CORRELATES**

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<td>Admission haemoglobin</td>
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<td>C-Reactive Protein</td>
<td>Age</td>
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<tr>
<td>Total Protein delivered</td>
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Greater severity of acute lung injury was associated with acute muscle loss.

Higher total protein delivered was associated with greater muscle wasting.
Muscle protein synthesis returns to baseline after 1.5 (E) to 2 hours (P)

Parenteral

Enteral
Clinical Context

Feeding During Early Critical Illness: Using Translational Skeletal Muscle Science to Design Future Clinical Trials

D Bear, Z Puthucheary & N Hart Lancet Respiratory 2014
• Early feeding of critically ill patients is common with strong international clinical recommendation
• Assumed major goal of feeding is to attenuate skeletal muscle wasting and enhance long-term functional outcome
• There are limited data informing the type, quantity and timing of feeding with skeletal muscle wasting
• EPaNIC trial showed that late parenteral nutrition had fewer infections and shorter length of stay
• EDEN trial showed there was no difference in clinical outcome between trophic and full enteral feeding in ALI

Rice et al. JAMA 2013; 307(8): 795-803
Conclusion

- Clinicians need to consider the structure to function paradigm to develop novel approaches to assessment and treatment of skeletal muscle wasting during critical illness.
- Critical illness induced muscle wasting is most pronounced in multi-organ failure.
- Early critical illness is characterised by muscle protein synthesis at a similar level to healthy fasted ‘starved’ controls.
- By the end of the first week muscle protein synthesis is at a level similar to healthy ‘fed’ controls.
- Muscle protein breakdown is elevated early in critical illness and remained elevated at the end of the first week.
- Critical illness muscle wasting correlates directly with hypoxaemia and indirectly protein loading.
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Bronwen Connolly  Zudin Puthucheary  Stephen Harridge  Hugh Montgomery