Intensive-Care Unit Acquired Weakness (ICUAW): Spectrum of Disability in Survivors of Prolonged Mechanical Ventilation at 7 days and 6 months post ICU discharge

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Translational Medicine collaboration with TOWARDS RECOVER
No Disclosures
Background

ICU-Acquired Weakness

CIPN  CIPNM  ICUAP  CRIMYNE  CINMA

Incidence 25% - 60%

surveillance, definition, diagnostic testing, bias, confounding, case-mix

Stevens et al. Int Care Med 2007; 33:1876-91
Hough et al. Int Care Med 2009; 35:63-68
Latronico Curr Opin Crit Care 2010; 16(2)
Background

Five-Year Outcomes in ARDS

ICUAW important legacy of episode critical illness

Persistent exercise limitation

Reduction in Physical QOL at 5-years after ICU discharge

Physical dysfunction is a source of morbidity

Significant economic consequences

Herridge et al. NEJM 2011
Background

**FIM Total Score**

- Total Functional Independence Measure scores at 7-days, 3, 6, and 12-months post ICU discharge

**6MWT (% of predicted)**

- Distance walked in 6 minutes (percent of predicted values) at 7-days, 3, 6, and 12-months post ICU discharge
Rationale

Advance our understanding of the molecular mechanisms that underlie ICUAW in order to:

- better identify those at risk for long term irreversible sequelae
- to inform effective interventions
Objectives

1) Quantify the degree of skeletal **muscle atrophy** and **functional impairment** in a prospective cohort of patients enrolled in Toward RECOVER at **7 days and 6 months** post ICU discharge.

2) Perform muscle biopsies (quadriceps femoris) for **molecular assessments at 7 days and 6 months** post ICU discharge.

3) Determine if these candidate cellular signalling/biologic processes identified in animal models that are critical to the development of ICU acquired muscle dysfunction are **activated in humans**.

4) Identify signalling networks/markers that are **associated with improvement or sustained functional disability**.
Methodology: Study design

❖ Inclusion Criteria:

❖ Pilot study - 20 individuals enrolled in Towards RECOVER

1. Acute presentation to ICU from the community or brief hospitalization (< 1 week) prior to ICU admission
2. Mechanical ventilation for at least 1 week
3. Functional independence prior to ICU admission with no pre-existing neurologic or muscle disease
4. Target 10 < 38 with no co-morbidity, 10 > 53 with co-morbidity
Methodology: Study design

Exclusion Criteria:

1. Immobile prior to ICU admission
2. Pre-existing primary neurologic or muscle disease
3. Other comorbid disease including Hepatitis B, C, HIV, post-transplant, active cancer, OR disease process requiring active anti-coagulation that cannot be held for biopsy OR decision to move to comfort care
Methodology

- **Functional Assessments:**
  - Skeletal muscle weakness & functional impairment, and atrophy assessed by
    - 6MW, SF-36, FIM
    - MRC bedside assessment of muscle power
    - Quiet postural standing, gait control, isokinetic and strength testing
    - CT mid-thigh quadriceps femoris cross-sectional area (CSA)
    - NCV & EMG to assess for peripheral neuropathy, (functional muscle denervation, dropout of myofibres)
Methodology: Molecular analysis

1) Molecular Assessment
   - i) Levels and activation of muscle specific signalling molecules
   - ii) Cellular localization/redistribution of key molecules
   - iii) Morphometric & ultrastructural analyses

2) Explorative Analysis
   - Microarray gene expression

Percutaneous biopsy of the vastus lateralis
Results

81 enrolled SMH Towards RECOVER
Sept 2010 – Sept 2012

- 36 excluded/died
  - 23 refused

- 22 consented
  - 12 - 7 day biopsy
    - 1 unsuccessful
  - 9 - 6 mo biopsy
    - 1 – withdrew
    - 1 - active cancer
    - 1 - died

58 Enrolled TGH Towards RECOVER
Sept 2011 – Sept 2012

- 32 excluded/died
  - 12 lost
  - 6 refused

- 8 consented
  - 4 - 7 day biopsy
  - 4 no biopsy
    - 3 died ICU
    - 2 transferred out
    - 1 Hep B positive
    - 2 refused biopsy
    - 1 heparinized
    - 1 leg unfit (vasculitis)

15 patients completed 7 day biopsy/assessment
11 completed 6 mo biopsy/assessment
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<th>EMG 6 Month</th>
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Results

Functional Independence Measure (FIM)
Six Minute Walk (6MW) percent predicted
Results

Quadriceps Strength Correlates with FIM Motor SubScore

Quadriceps Strength Does Not Correlate with 6MWD % Predicted

Functional Independence Measure (FIM)
Six Minute Walk (6MW) percent predicted
Discussion

• A total of 30 patients were consented
  – 16 patients ----- 7 day post-ICU d/c biopsy
  – 11 patients ----- 6 mo post-ICU d/c biopsy
• Not all patients who were “weak” had myopathy demonstrated by EMG
• Three patients who had myopathy at 7 days had normal EMGs at 6 mo
• FIM and 6MW remained significantly low in those patients with significant myopathy at 6 mo
• While FIM correlates with Quadriceps strength - 6MW does not
• Molecular analysis will inform regarding “mass” and/or “strength” determinants
48 yo F
myopathy

71 yo M
No myopathy
Linear Model of Microarray Analysis (LIMMA, N=1,321, adj p=0.05)

PCA Mapping (65.1%)

Day 7_ICUAW
6 Mo_ICUAW
Controls

PCA #1 (54.2%)
PCA #2 (6.72%)
Functional Enrichment for Gene Expression Modules

Down-Regulated Gene Modules

Module # 1
mitochondrion
mitochondrial part
mitochondrial inner membrane
organelle inner membrane
mitochondrial envelope
mitochondrial membrane
cellular respiration
respiratory electron transport chain
electron transport chain
oxidation-reduction process

Module # 2
contractile fiber
myofibril
sarcomere
structural constituent of muscle
I band
muscle system process
muscle contraction
phosphoric ester hydrolase activity
striated muscle contraction
cardiovascular system development
Special thanks to the **Research Coordinators** that have contributed to this work: at SMH: Yoon Lee, Julia Lee, Melissa Wang and Orla Smith and at TGH: Andrea Matte, Paulina Farias, and Leslie Chu.
Network state $S$ at time $t$ is the set of expression values $(x_1, x_2, x_3)$ of the 3 genes in the subnetwork (gene expression pattern).

Three states $(S_1, S_2, S_3)$ are shown in blue above in a 3D state space (one axis for each gene).

Most $S$ are not stable; $S$ are driven toward stable “attractor” states.

Perturbations move states in trajectories (red lines).