Respiratory muscle dysfunction and weaning

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Disclosure Summary

- Work was funded by a Veterans Affairs Merit Review Grant
- No commercial relationships to disclose
- No known institutional financial interests
- No tobacco relationships
- No “off-label” use of products/substances
Patient with community acquired pneumonia
After 2 weeks of antibiotics: the patient had clinically improved and satisfactory gas exchange.

Patient with community acquired pneumonia

Day 0

Day 14
Respiratory distress in weaning failure

- Inhalation

Flow
L/sec
Volume
Liters
$P_{es}$
cm H$_2$O
$P_{ga}$
cm H$_2$O

Time, sec

when disconnect from the ventilator the patient develops respiratory distress
Inhalation
Exhalation

Respiratory distress in weaning failure

Flow
L/sec

Volume
Liters

$P_{es}$
cm H$_2$O

$P_{ga}$
cm H$_2$O

Time, sec
What role does respiratory muscle play in respiratory distress in weaning failure?
What role does respiratory muscle dysfunction play in this picture?
Low maximal inspiratory pressure ($P_{I\text{max}}$)

Low $P_{I\text{max}}$ raises the possibility that respiratory muscle dysfunction contributes to weaning failure.
Why is $P_{\text{I}}\text{max}$ decreased?

Laghi and Tobin. AJRCCM 2003;168:10
Why is $P_{\text{max}}$ decreased?

![Graph showing airway pressure over time](image)

- Decreased recruitment
- Muscle fatigue
- Muscle weakness
- Spinal pathology
- Peripheral Neuropathy

**Laghi and Tobin. AJRCCM 2003;168:10**
Why is $P_{\text{max}}$ decreased?

- Decreased recruitment
- Muscle fatigue
- Muscle weakness
- Spinal pathology
- Decreased recruitment can be decreased by sleep deprivation and sleep fragmentation

Laghi and Tobin. AJRCCM 2003;168:10
In the study, none of the 20 patients had normal sleep.
Sleep Duration is Decreased in Patients Cared for in a Weaning Center (LTAC)

Ling, Jubran, Laghi. ARJCCM 2010:181:A6706
What are the mechanisms of sleep fragmentation in ventilated patients?

Ling, Jubran, Laghi. ARJCCM 2010:181:A6706
What are the mechanisms of sleep fragmentation in ventilated patients?

Ionita et al. ATS 2011 (abstract)

The sleep architecture of patients transferred to weaning units that specialize in weaning from prolonged mechanical ventilation usually is disrupted (AJRCCM 2010:181:A6706). We aimed to understand the mechanisms of such severe sleep disruption, we performed polysomnography in seven patients transferred to weaning units who were ventilated in the assist-controlled mode (ICM). We identified 119 awakenings according to standard criteria (Sleep Medicine 7(7) 2007). Sleep disruption associated with to a respiratory event (apnea or an awakening occurring within 15 seconds of an apnea) or an awakening occurring within 15 seconds of a ventilator event (ventilation or double triggering) (ICM) increased by 2.4-fold (p=0.05). Sleep disruption was identified according to the percentage of time that was classified as sleep stage 2, the number of awakenings identified by polysomnography, and the number of minutes of rapid eye movement (REM) sleep. The number of minutes of REM sleep was significantly lower in the group with sleep disruption compared to the group without sleep disruption (p=0.05). The number of awakenings identified by polysomnography was significantly higher in the group with sleep disruption compared to the group without sleep disruption (p=0.05). Sleep disruption was associated with a decrease in sleep efficiency (p=0.05). The number of minutes of sleep stage 2 was significantly lower in the group with sleep disruption compared to the group without sleep disruption (p=0.05). The number of minutes of rapid eye movement (REM) sleep was significantly lower in the group with sleep disruption compared to the group without sleep disruption (p=0.05). The number of minutes of stage 2 sleep was significantly lower in the group with sleep disruption compared to the group without sleep disruption (p=0.05).

Sleep architecture was recorded using a full-night PSG that specialized sleep technicians were disruption. Polysomnographic recordings were done during prolonged mechanical ventilation for an average of 5.7 days (range 3-11 days). Sleep arousals were observed during periods of mechanical ventilation. Sleep awakenings were identified according to sleep architecture (12). Sleep disruption associated with ventilator sighs or an awakening occurring within 15 seconds of an episode of noise from baseline values. Sleep disruption associated with ventilator sighs or an awakening occurring within 15 seconds of an episode of noise from baseline values.
SLEEP DISRUPTION IN PATIENTS BEING WEANED FROM PROLONGED MECHANICAL VENTILATION. Ionita R, Ekekwe I, Jubran A, Hettinger K, Tobin MJ, Laghi F. RMI Specialty Hospital-Hinsdale, Hines VA Hospital-

Ineffective triggering

![Ineffective triggering graph]

Identified according to "arousal or an awakening occurring within 15 seconds of an episode of an increase or decrease in inspiratory pressure, or an increase or decrease in inspiratory demand from baseline values. Sleep

Ionita et al. ATS 2011 (abstract)
Patients had ~30 arousals or awakenings per hour.
In no instance light caused sleep disruption.
Episodes of noise (> 10 db from baseline) were responsible for 11% of all arousals and awakenings.
SLEEP DISRUPTION IN PATIENTS BEING WEANED FROM MECHANICAL VENTILATION


Ventilator asynchronies were responsible for 17% of all arousals and awakenings.
Experimental data suggest that asynchronies could cause arousals through the activation of the pre-motor cortex.
Pre-motor cortex activation during inspiratory loading

Before inhalation the pre-motor cortex is silent

Pre-motor potentials are absent

Cz-A+ 10µV
Scal EMG 10mV
Press 2 cmH₂O
1 s

Before inhalation the pre-motor cortex is active

Pre-motor potentials are present

Cz-A+ 10µV
Scal EMG 10mV
Press 2 cmH₂O
1 s

Motor potentials during muscle contraction

Whether this cortical activation contributes to sleep disruption in vented pts remains to be determined

Raux-Similowski et al.
J Physiol 2007;578:569
Could sleep deprivation and sleep fragmentation participate in respiratory muscle dysfunction and poor weaning outcome?
Effect of impaired sleep on respiratory muscles

**Acute effects**

*Decreased hypercapnic response*

![Graph showing decreased hypercapnic response](image)

**Normal**

**Sleep deprived**

White *ARRD* 1983;128:984

*Decreased endurance*

![Bar graph showing decreased endurance](image)

Normal vs Sleep deprived


*Decreased strength*

![Bar graph showing decreased strength](image)

Normal vs Sleep deprived

*Chen. ARRD 1989;140:907*
Effect of impaired sleep on respiratory muscles

**Acute effects**

**Decreased hypercapnic response**

The duration of these experiments is too short to think that decreases in muscle performance are caused by structural insults to the muscle.
Effect of impaired sleep on respiratory muscles

Acute effects

Decreased hypercapnic response

It is more likely that the decrease in muscle performance is caused by impaired respiratory muscle recruitment originating in the CNS.

Decreased strength

Decreased endurance


Chen. ARRD 1989;140:907
Reduced $P_{1\text{max}}$ does not distinguish between decreased recruitment and intrinsic muscle dysfunction.
Phrenic Nerve Stimulation: Technique

Pes
Pga
Pdi
R - EMG
L - EMG

40 cm H₂O
100 msec
Diaphragmatic dysfunction in ventilated patients

Transdiaphragmatic Twitch Pressure (cm H₂O)

Cattapan et al. Thorax 58:58
Watson et al Crit Care Med 29:1325
That respiratory muscle dysfunction is an important determinant of weaning failure.
That respiratory muscle dysfunction is an important determinant of weaning failure and need of mechanical ventilation is supported by Tulaimat et al, AJRCCM 2002;165:A166.
Weaning Outcome and Respiratory Muscle Dysfunction

Only patients who maintained spontaneous respiration for 3 days demonstrated an improvement in respiratory muscle function.
In patients developing signs of respiratory failure every time they tried to sustain spontaneous breathing, respiratory muscle dysfunction did not improve.

Tulaimat et al, AJRCCM 2002;165:A166
If weaning success is more common in patients who show improvement in respiratory muscle strength.
If weaning success is more common in patients who show improvement in respiratory muscle strength, might conditioning of the respiratory muscles using specific rehabilitation strategies be helpful?
Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial

A Daniel Martin¹,4*, Barbara K Smith¹, Paul D Davenport², Eloise Harman³, Ricardo J Gonzalez-Rothi³, Maher Baz³, A Joseph Layon³,4,5, Michael J Banner⁴, Lawrence J Caruso⁴, Harsha Deoghare¹, Tseng-Tien Huang¹, Andrea Gabrielli⁴,5

Abstract

Introduction: Most patients are readily liberated from mechanical ventilation (MV) support, however, 10% - 15% of patients experience failure to wean (FTW). FTW patients account for approximately 40% of all MV days and have significantly worse clinical outcomes. MV induced inspiratory muscle weakness has been implicated as a contributor to FTW and recent work has documented inspiratory muscle weakness in humans supported with MV.

Methods: We conducted a single center, single-blind, randomized controlled trial to test whether inspiratory muscle strength training (IMST) would improve weaning outcome in FTW patients. Of 129 patients evaluated for participation, 69 were enrolled and studied. 35 subjects were randomly assigned to the IMST condition and 34 to the SHAM treatment. IMST was performed with a threshold inspiratory device, set at the highest pressure tolerated and progressed daily. SHAM training provided a constant, low inspiratory pressure of 6-10 training breaths, 5 days per week. Subjects also performed progr...
Inspiratory muscle strength training improves weaning outcome in failure to wean patients: a randomized trial

Abstract

Introduction: Failure to wean patients from mechanical ventilation is a significant contributor to mortality. Inspiratory muscle training (IMT) is a non-invasive approach to improving weaning outcome. The aim of this study was to compare the effects of inspiratory muscle strength training (IMST) and sham training on weaning outcome.

Methods: Intermittent positive pressure ventilation (IPPV) was provided to 69 patients meeting weaning criteria. Subjects were randomized to receive IMST or sham training ( Sham group ) for 10 sessions. Pmax, cm H2O, was assessed in a blinded fashion before training (BL) and 3 days after 10 IMST sessions. The intervention group received a threshold load group during the training sessions and progressed daily. SHAM training provided a constant, low inspiratory load of 6–10 training breaths, 5 days per week. Both groups also performed progressive physical therapy.

Results: Pmax increased significantly in the threshold load group ( p < .0001) and was not different in the sham group ( p = .39). Weaning success was significantly higher in the threshold load group compared to the sham group ( p = .039). 71% of the threshold load group achieved weaning compared to 47% in the sham group.

Conclusion: IMST leads to a significant improvement in Pmax and weaning success compared to sham training. This study provides evidence supporting the use of IMST in weaning patients from mechanical ventilation.

Martin et al. Crit Care 2011;15:R84
Respiratory muscle dysfunction

- Ventilator-induced muscle dysfunction
- Hyperinflation
- Sepsis
- Medications
- Decreased cardiac output
- Electrolyte Δ Malnutrition
- ICU-AP
EFFECT OF PROLONGED MECHANICAL VENTILATION ON DIAPHRAGMATIC FUNCTION: A PRELIMINARY STUDY OF A BABOON MODEL. A Anzueto, MJ Tobin, G Moore, JJ Peters, JJ Seidenfeld, JJ Coalson. University of Texas Health Science Center at San Antonio and Houston, Tx.

Mechanical ventilation (MV) may have both beneficial and detrimental effects on respiratory muscle (RM) function. It may improve RM function since rest is the only satisfactory method of treating RM fatigue. On the other hand, it may cause RM atrophy. Scientific information on the effect of MV on RM is limited because of the difficulty in obtaining measurements of RM function in the clinical setting. An experimental model of prolonged MV does not exist. To obtain preliminary information, we studied baboons that received controlled MV over 11 days. Hemoglobin, exchange, FRC, O2 consumption, and electrolyte levels all remained stable during the period of MV. Measurements at baseline and days of MV included (1) RM strength as reflected by transdiaphragmatic pressure (Pdi\text{max}) during phrenic nerve stimulation at 100 Hz, (2) endurance time while breathing against a variable inspiratory resistor sufficient to require the generation of 60% of Pdi\text{max}, and (3) fatigability as measured by performing force-frequency stimulation before and after the experimental period.

Since the late 1980s several groups have studied the effect of mechanical ventilation on the respiratory muscles of laboratory animals.
Accumulating experimental data

Redox regulation of diaphragm proteolysis during mechanical ventilation


Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, Florida

Submitted 22 January 2008; accepted in final form 27 February 2008

McClung JM, Whidden MA, Kavazis AN, Falk DJ, DeRuisseau KC, Powers SK. Redox regulation of diaphragm proteolysis during mechanical ventilation. Am J Physiol Regul Integr Comp Physiol 294: R1609–R1617, 2008. First published March 5, 2008; doi:10.1152/ajpregu.00544.2008.—Prevention of oxidative stress via antioxidant treatment delays myofiber atrophy associated with mechanical ventilation (MV). However, the specific redox-sensitive mechanisms responsible for this remain unknown. We tested the hypothesis that regulation of skeletal muscle proteolytic activity is a critical site of redox action during MV. Sprague-Dawley rats were assigned to five experimental groups: 1) control, 2) 6 h of MV, 3) 6 h of MV with infusion of the antioxidant Trolox, 4) 18 h of MV, and 5) 18 h of MV with Trolox. Trolox did not attenuate MV-induced increases in diaphragmatic levels of ubiquitin-protein conjugation, polyubiquitin mRNA, and gene expression of proteasomal subunits (20S proteasome α-subunits 7, 14, and E2, and proteasome-activating complex PA28). However, Trolox reduced both muscle atrophy and peptide hydrolysis (PCO4-like) MV proteasome activities in the diaphragm after 18 h of MV. In addition, Trolox rescued diaphragm myofiber protein concentration (gaging muscles) and the necrosis of easily releasable myofiber protein proteasome regulatory complexes (i.e., PA700 and PA28; Ref. 20). In general, oxidative stress is known to stimulate activation of the ubiquitin-proteasome system in skeletal muscle (17, 18, 30). MV-induced oxidative stress activates the UPP in the diaphragm (8), and antioxidant administration during MV significantly retards protein breakdown and chymotrypsin-like activity of the 20S proteasome (5). These facts suggest that regulation of proteasome function may be a critical mechanism linking oxidative stress to MV-induced diaphragmatic atrophy. Nonetheless, it is unknown whether the protective effects of antioxidant administration on diaphragmatic atrophy and contractile function during MV are directly linked to the regulation of specific components governing proteasome activity.

To address these gaps in our knowledge, we hypothesized that the regulation of skeletal muscle proteolytic activity is a critical site of redox action altering protein balance during MV disease. To test this postulate, we prevented MV-induced diaphragmatic oxidative stress via infusion of the antioxidant Trolox and examined key regulatory elements of proteasomal function.
Accumulating experimental data suggests that mechanical ventilation
Assist–Control Mechanical Ventilator-induced Diaphragm Dysfunctional

Accumulating experimental data suggests that mechanical ventilation may contribute to respiratory muscle dysfunction in laboratory animals.

Human data, however, have been scant and indirect until 2008 when...
Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans


ABSTRACT

BACKGROUND
The combination of complete diaphragm inactivity and mechanical ventilation (for more than 18 hours) elicits disuse atrophy of myofibers in animals. We hypothesized that the same may also occur in the human diaphragm.

METHODS

From the Department of Surgery (S.L., T.N., N.T., M.E.F., M.T.B., P.R., J.Z., S.S., L.R.K., J.B.S.), the Department of Cell and Developmental Biology (N.A.R.), and the Pennsylvania Muscle Institute (S.L., M.T.B., N.A.R., J.B.S.), University of Pennsylvania the City of Hope Cancer Program (E.D.).
Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans

Sanford Levine, M.D., Taitan Nguyen, B.S., Murat T. Budak, M.D., Ph.D., Pamela Rotondo, M.D., Seema Sonnad, Ph.D., Larry R. Kaiser, M.D., and Josephine Amador, M.D.

BACKGROUND
The combination of complete diaphragm inactivity for more than 18 hours (e.g., under controlled mechanical ventilation) elicits disuse atrophy of muscles. The goals of this study were to determine whether this same phenomenon may occur in the human diaphragm and to describe the pathophysiologic characteristics of this atrophy.

METHODS

Controlled Mechanical Ventilation (Complete Muscle Rest)
Ventilator-induced respiratory muscle atrophy

Brief CMV (2-3 hrs)

2-3 hours vs. 18-69 hrs of Controlled Mech Ventilation

Flow

Paw

Pes

Pga
Prolonged CMV (18-69 hrs)

Ventilator-induced respiratory muscle atrophy

2-3 hours vs. 18-69 hrs of Controlled Mech Ventilation

Brief CMV (2-3 hrs)
Ventilator-induced respiratory muscle atrophy

2-3 hours vs. 18-69 hrs of Controlled Mech Ventilation

- Atrophy fast twitch fibers

Brief CMV (2-3 hrs)

Prolonged CMV (18-69 hrs)

Flow
Paw
Pes
Pga

50 μm

50 μm
Ventilator-induced respiratory muscle atrophy

2-3 hours vs. 18-69 hrs of Controlled Mech Ventilation
- Atrophy fast twitch fibers
- Atrophy slow twitch fibers

Brief CMV (2-3 hrs)

Prolonged CMV (18-69 hrs)
Ventilator-induced respiratory muscle atrophy

2-3 hours vs. 18-69 hrs of Controlled Mech Ventilation

- Atrophy fast twitch fibers
- Atrophy slow twitch fibers
- Enhance oxidation ($\downarrow$ glutathione) and proteolysis ($\uparrow$ caspase & ubiquitin ligases)

Caspase 3
How long does it take for ventilator-induced
How long does it take for ventilator-induced respiratory muscle dysfunction to occur?
the most accurate strategy to identify respiratory muscle dysfunction over time would be to record serial PdiTw

this requires repeated placement of esophageal & gastric balloons which is inconvenient

Can diaphragmatic contractility be assessed by airway twitch pressure in mechanically ventilated patients?

Conclusions: Despite a good correlation between Paw tw and Poes tw, Paw tw did not reliably predict Poes tw or Pdi tw in mechanically ventilated patients. Nevertheless, the excellent reproducibility of Paw tw suggests that it may be a useful means of monitoring inspiratory muscle contractility in the routine care of mechanically ventilated patients.
Can diaphragmatic contractility twitch pressure in mechanically

In critically ill patients the assessment of inspiratory muscle

PawTw reliably predicts Pdi tw and Poes tw in critically ill.

Cattapan et al. Thorax 2003;58:58
Can diaphragmatic contractility twitch pressure in mechanically

S E Cat

These three characteristics make Paw tw a potentially powerful tool in the evaluation of respiratory muscle contractility in critically ill patients. In particular, repeated Paw tw measurements should make it possible to track changing inspiratory muscle function over days or weeks, such as in patients with Guillain-Barré syndrome, and better guide management of patients who repeatedly fail trials of weaning from mechanical ventilation.

In critically ill patients the assessment of inspiratory muscle function is crucial. Pdi tw and Poes tw are widely used as measures of inspiratory muscle function, but they are limited in their ability to assess the contractility of the diaphragm. Paw tw reliably predicts Pdi tw and Poes tw in critically ill patients. This finding suggests that Paw tw may provide a valuable tool for monitoring changes in diaphragm contractility over time. Further research is needed to validate the use of Paw tw in clinical practice.
Rapidly Progressive Diaphragmatic Weakness and Injury during Mechanical Ventilation in Humans

Samir Jaber¹,²,⁶, Basil J. Petrof³, Boris Jung¹,², Gérald Chanques¹,², Jean-Philippe Berthet⁴, Christophe Rabuel⁵, Hassan Bouyabrine⁶, Patricia Courouble¹,², Christelle Koehlman-Ramonatxo⁷, Mustapha Sebbane¹,², Thomas Similowski⁸, Valérie Scheuermann⁹, Alexandre Mebazaa⁵, Xavier Capdevila¹,², Dominique Mornet², Jacques Mercier²,¹⁰, Alain Lacampagne⁹, Alexandre Philips², and Stefan Matecki²,¹⁰

Rationale: Diaphragmatic function is a major determinant of the ability to successfully wean patients from mechanical ventilation (MV). Paradoxically, MV itself results in a rapid loss of diaphragmatic strength in animals. However, very little is known about the time course or mechanistic basis for such a phenomenon in humans.

Objectives: To determine in a prospective fashion the time course for development of diaphragmatic weakness during MV; and the relationship between MV duration and diaphragm function, and the status of candidate cellular mediators involved in these phenomena.

Methods: Airway occlusion pressure (Pawtw) increased during phrenic nerve stimulation with 0.06 mmol/L acetylcholine for 0.5 h (n = 6) and long-term (>5 d; n = 6) MV was performed in both animal and human subjects. Biopsies obtained during thoracic surgery (n = 24–25) were assessed for ultrastructural injury, atrophy, and expression of ubiquitinated proteins (ubiquitin, nuclear factor-κB, and others). Measurements and Main Results: Pawtw decreased progressively during MV, with a mean reduction of 32 ± 6% after 24 h. MV was associated with significant gross ultrastructural injury (26.2 ± 4.8 vs. 4.7 ± 0.6% area), decreases in muscle fibers (1,904 ± 220 vs. 3,100 ± 529 μm²), an increase in ubiquitinated proteins (+19%), higher expression of p65 nuclear factor-κB (5.9±3.9), and decreased levels of health care resources (1). Diaphragmatic function is preserved throughout the hospital course of these patients with Guillain-Barré syndrome, and better guide management of patients who repeatedly fail trials of weaning from mechanical ventilation.
...diaphragmatic weakness, injury, and atrophy occur rapidly in critically ill patients during mechanical ventilation, and are correlated with duration of ventilator support...

(Jaber et al. AJRRM 2011;183:364)
...diaphragmatic weakness, injury, and atrophy occur rapidly in critically ill patients during mechanical ventilation, and are correlated with duration of ventilator support...

(Jaber et al. AJRRM 2011;183:364)
...diaphragmatic weakness, injury, and atrophy occur rapidly in critically ill patients during mechanical ventilation, and are correlated with duration of ventilator support...

(Jaber et al. AJRRM 2011;183:364)
Preservation Of Diaphragm Muscle Fiber Contractility In Mechanically Ventilated Humans

P. E. Hooijman\(^1\), H. W. van Hees\(^2\), M. A. Paul\(^3\), G. J. Stienen\(^4\), A. Farooqui\(^5\), A. Abedi \(^1\)

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Rationale: The combination of prolonged mechanical ventilation (MV) and diaphragm fatigue is a well-established phenomenon in models of experimental ventilator-induced diaphragm dysfunction (VIDD) and in clinical models of ventilator associated diaphragm dysfunction (VAD). The mechanism of how diaphragm dysfunction arises is poorly understood. Isolated diaphragm fibers from brain death donors were isolated and short-term cultured. For control fibers (n=9), the fibers were cultured and permeabilized membranes were exposed to 20nM caffeine (i.e. pCa\(_{50}\)).

No difference was noted between case (long-lasting CMV; n=9) and control fibers (short-lasting CMV; n=9) with respect to:

- Maximum force per unit area
- Calcium sensitivity of contractile force
- Rate constant of redevelopment of force
- Passive tension per unit fiber stretch

Results: The table below compares slow- and fast-twitch diaphragm fibers with respect to these measurements as mean ± SD.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Case Slow</th>
<th>Control Slow</th>
<th>Case Fast</th>
<th>Control Fast</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal force (kPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate constant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive tension</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
No difference was noted between case (long-lasting CMV; n=9) and control fibers (short-lasting CMV; n=9) with respect to:

• Maximum force per unit area
• Calcium sensitivity of contractile force
• Rate constant of redevelopment of force
• Passive tension per unit fiber stretch

How do extra-diaphragmatic muscles respond to
How do extra-diaphragmatic muscles respond to diaphragmatic dysfunction in weaning failure?
There is a hierarchy of respiratory muscle activation in weaning failure.

*J Appl Physiol, 2007:103:140*
The sequence begins with greater activity of inspiratory rib-cage muscles in WF than in WS.
Recruitment of sternomastoids and rib-cage muscles is near maximum within four minutes of trial commencement.
The expiratory muscles are not recruited until quite late in the trial (at 17-20 minutes).
Extradiaphragmatic muscle recruitment may be a mechanism for offsetting the effects of increased load on a weak diaphragm.
Extradiaphragmatic muscle recruitment may be a mechanism for offsetting the effects of increased load on a weak diaphragm.

Switching from strength to fatigue…

Extradiaphragmatic muscle recruitment may be a mechanism for offsetting the effects of increased load on a weak diaphragm.
Switching from strength to fatigue…

Abnormal lung mechanics in failed weaning trials

Laghi. CCM 2011 (in press)

Diaphragm weakness in MV patients

Jubran & Tobin. AJRCCM 1997;155:900
Does diaphragmatic fatigue contribute to weaning failure?
Fatigue-induced structural injury

Normal Load-induced disruption of sarcomeric structure

loss of distinct A-bands
I-bands

Z-band streaming

loss of cytoskeletal protein elements e.g., desmin

Fatigue

hamster

Walker & Reid. AJRCCM 2003;168:10
Time for recovery from diaphragmatic fatigue

Laghi et al. JAP 1995;79:539
Twitch Pressure Does Not Fall After a Failed Weaning Trial

<table>
<thead>
<tr>
<th>Pdi (cm H&lt;sub&gt;2&lt;/sub&gt;O)</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-EMG (a.u.)</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>L-EMG (a.u.)</td>
<td>Before</td>
<td>After</td>
</tr>
</tbody>
</table>
Twitch Pressure Does Not Fall After a Failed Weaning Trial

Laghi et al, AJRCCM 2003;167:120
Tension-Time Index Predicts Time to Task Failure

Time to Task Failure = 0.1 (TTdi) \(-3.6\)

Bellemare & Grassino  JAP 1982; 53: 1190
Tension-Time Index Predicts Time to Task Failure

TTI is related to the time a load can be sustained until task-failure according to an inverse-power function

\[ \text{Time to Task Failure} = 0.1 \ (\text{TTdi})^{-3.6} \]

Bellemare & Grassino  JAP 1982; 53: 1190
Based on repeated measurements of TTI over the course of a weaning trial, one can estimate how long a patient should be able to sustain that load.

**Tension-Time Index Predicts Time to Task Failure**

Time to Task Failure = 0.1 (TTdi) **-3.6**
Plot of interrelationship between trial duration, TTI, and predicted time to task failure in 9 WF patients.
The 9 patients tolerated trials for 44 minutes.
At start, tension-time index was 0.17: Inverse-power function predicts pts can sustain spontaneous breathing for another 59 minutes before developing task failure
Duration of Spontaneous Breathing Trial

Predicted Time to Task Failure

Tension-Time Index

Duration of Spontaneous Breathing Trial

minutes

minutes
As trial progressed, tension-time index progressively increased, marching backwards on the floor of the plot.
And predicted time to task failure decreased, as shown by the progressive decrease in the height of the orange pillars.
Patients tolerated trials for 44 minutes. At the end of the trial, the TTI was 0.26: the last orange pillar predicts the time to task failure not to be zero – trial should have gone for another 13 min.
Patients were predicted to sustain spontaneous breathing for another 13 minutes before developing task failure.
Patients were predicted to sustain spontaneous breathing for another 13 minutes before developing task failure.

This clarifies why patients did not develop a decrease in twitch Pdi.
Tension-Time Index 0.26: predicts trial to go another 13 minutes

Physicians interrupted the trial based on clinical manifestations of respiratory distress before patients had sufficient time to develop contractile fatigue.
Patients tolerated trials for 44 minutes. Tension-Time Index 0.26: predicts trial to go another 13 minutes. Had the trial been continued for another 13 minutes, there is every reason to suspect that these patients would have developed contractile fatigue.
Patients tolerated trials for 44 minutes. Tension-Time Index 0.26 predicts trial to go another 13 minutes. Had the trial been continued for another 13 minutes, there is every reason to suspect that these patients would have developed contractile fatigue.

Can a stable twitch pressure recorded 30 minutes after weaning failure exclude any form of fatigue?
Very forceful contractions cause muscle damage and long-lasting fatigue. Can a stable twitch pressure recorded 30 minutes after weaning failure exclude any form of fatigue? Very forceful contractions can be sustained only briefly and cause short-lasting fatigue.
Very forceful contractions can be maintained only briefly and cause short-lasting fatigue.

Modified from Skurvydas A. Medicina (Kaunas). 2007;43:226

What causes short-lasting fatigue?
Very forceful contractions can be maintained only briefly and cause short-lasting fatigue.

What causes short-lasting fatigue?

Does it occur in weaning failure?

Modified from Skurlydas A. Medicina (Kaunas). 2007;43:226
Very forceful contractions can be maintained only briefly and cause short-lasting fatigue.

What causes short-lasting fatigue?

Does it occur in weaning failure?

What are the clinical implications?

(Modified from Skurlydas A. Medicina (Kaunas). 2007;43:226)
Very forceful contractions can be maintained only briefly and cause short-lasting fatigue.

What causes short-lasting fatigue?

Does it occur in weaning failure?

What are the clinical implications?

Modified from Skurlydas A. Medicina (Kaunas). 2007;43:226
Respiratory muscle contraction is an energy-consuming process.
Forceful muscle contractions can deplete the myocytes’ energy-rich phosphates.
Less energy-rich phosphates cause a reduction in release of Ca\(^{++}\) in response to action potentials,
Less energy-rich phosphates cause a reduction in release of Ca\(^{++}\) in response to action potentials, and impair function of cross-bridges ("metabolic" short-lasting fatigue)
Less energy-rich phosphates cause a reduction in release of Ca\(^{++}\) in response to action potentials, and impair function of cross-bridges (short-lasting "metabolic" fatigue).

Short-lasting fatigue is associated with decreased amplitude of the compound motor action potentials.

Less energy-rich phosphates cause a reduction in release of $Ca^{++}$ in response to action potentials, and impair function of cross-bridges (short-lasting “metabolic” fatigue).


Short-lasting fatigue is associated with decreased amplitude of the compound motor action potentials. This indicates reduced muscle excitability.
Less energy-rich phosphates cause a reduction in release of Ca\(^{++}\) in response to action potentials, and impair function of cross-bridges (short-lasting "metabolic" fatigue). The decrease in the amplitude of the compound motor action potential is proportional to the decrease in force.

Recording high-quality diaphragmatic action potentials to identify short-lasting fatigue in patients.
Recording high-quality diaphragmatic action potentials to identify short-lasting fatigue in patients requires needle electrodes,
Recording high-quality diaphragmatic action potentials to identify short-lasting fatigue in patients requires needle electrodes, a procedure that can be dangerous even when using ultrasound guidance.
To overcome this obstacle we tested a multiple electrode array esophageal catheter to record the diaphragmatic EMG.
Hypothesis: diaphragmatic electrical activity to transdiaphragmatic pressure (Edi/Pdi) ratio identifies short-lasting fatigue

If fatigue occurs, a given transdiaphragmatic pressure (Pdi) will be achieved only by greater muscle fiber recruitment – that is the ratio of total electrical activity generated by the diaphragm (Edi) to Pdi increases with fatigue.
Twitch pressure identifies long-lasting fatigue

FATIGUE RUN

Twitch Pdi, % of baseline

Recovery (Minutes)

60
80
100

BL 1 10 30

Long-lasting fatigue
Twitch pressure identifies long-lasting fatigue

Fatigue run

Twitch Pdi, % of baseline

Recovery (Minutes)

Long-lasting fatigue

multiple electrode array esoph catheter to calculate Edi/Pdi

Twitch pressure identifies long-lasting fatigue

Fatigue run

Twitch Pdi, % of baseline

Recovery (Minutes)

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multiple electrode array esoph catheter to calculate Edi/Pdi
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Fatigue run

Twitch Pdi, % of baseline

Recovery (Minutes)

Long-lasting fatigue

Edi/Pdi ratio may identify short-lasting fatigue

* p < 0.05
** p < 0.01
vs Quintile 5 of Loading

Edi/Pdi ratio may identify short-lasting fatigue (?)
The efficiency to convert neuromuscular activity into inspiratory pressure was greater in WS than WF and in neither group it decreased at end of CPAP weaning.
Conclusion

- Respiratory muscles of patients requiring mechanical ventilation are weak
Conclusion

- Respiratory muscles of patients requiring mechanical ventilation

- **Weakness may be due to many coexisting processes:**
  - Ventilator-induced respiratory muscle dysfunction
  - Sepsis
  - ICU-Acquired Paresis
  - ICU therapy: steroids, NMBA...
  - Pre-existing conditions: hyperinflation...
  - Malnutrition/Electrolyte abnormalities
Conclusion

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• Does fatigue cause weaning failure?
  (a) Long lasting fatigue: no
  (b) Short lasting fatigue: may be not
Conclusion

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One of the major determinants of weaning failure is respiratory muscle dysfunction
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Improvement of respiratory muscle function is associated with successful weaning
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● Does fatigue cause weaning failure?
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  (b) Short lasting fatigue: possibly

Development of strategies to train the respiratory muscles of patients who consistently fail weaning is probably beneficial
What are possible strategies to prevent respiratory muscle dysfunction during mechanical ventilation?

- **Antioxidants**
  - McClung J Physiol. 2007;585:203 (Trolox+)
  - Spapen et al. Chest 2005;127:1413 (NAC-)
  - Agten et al. CCMed. 2011;39:777 (NAC+)

- **Calpain inhibition**
  - Sassoon et al. AJRCCM 2004;170:626 (ACV)
  - Yang et al. AJRCCM 2002;166:1135 (PEEP)
  - Jung et al. Anesthesiology 2012;1495 (ASV)
  - Futier et al. Critical Care 2008, 12:RT16 (PSV)
  - Spapen et al. Chest 2005;127:1413 (NAC-)
  - Agten et al. CCMed. 2011;39:777 (NAC+)

- **Proteasome inhibition**
  - Sassoon et al. AJRCCM 2004;170:626 (ACV)
  - Yang et al. AJRCCM 2002;166:1135 (PEEP)
  - Jung et al. Anesthesiology 2012;1495 (ASV)
  - Futier et al. Critical Care 2008, 12:RT16 (PSV)
  - Spapen et al. Chest 2005;127:1413 (NAC-)
  - Agten et al. CCMed. 2011;39:777 (NAC+)

- **Lysosomal protease inhibition**
  - Sassoon et al. AJRCCM 2004;170:626 (ACV)
  - Yang et al. AJRCCM 2002;166:1135 (PEEP)
  - Jung et al. Anesthesiology 2012;1495 (ASV)
  - Futier et al. Critical Care 2008, 12:RT16 (PSV)
  - Spapen et al. Chest 2005;127:1413 (NAC-)
  - Agten et al. CCMed. 2011;39:777 (NAC+)

- **Anabolic agents**
  - Pichard. CCM 1996;24:403 (GH)(no effect)
  - Takala. NEJM 1999;341:785 (GH) (-)
  - Hussain & Vassilakopoulos. AJRCCM 2002;166:1307 (Dantrolene)(?)
  - Maes et al. AJRCCM 2007;175;1134 (leupeptin)(+)
  - Shanely et al. AJRCCM 2002;166:1369 (Lactacystin) (+)
  - Agten et al. CCM 2012;40:2449 (bortezomib) (+/-)
  - Maes et al. AJRCCM 2007;175;1134 (leupeptin)(+)
Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study

Greet Hermans*1, Anouk Agten2, Dries Testelmans2, Marc Decramer2 and Ghislaine Gayan-Ramirez2

Weakness is an important risk factor for delayed weaning. Animal data show that atrophy and weakness of the diaphragm, called ventilator-induced diaphragmatic weakness (VWD), is a significant risk factor for delayed spontaneous breathing. Measurement of TwPdi BAMPS allows evaluation of the diaphragmatic strength over time. The aim of this study was to evaluate the repeatability of the measurement of TwPdi BAMPS in critically ill, mechanically ventilated patients and the correlation between TwPdi and the duration of mechanical ventilation.

A prospective observational study was performed in critically ill and mechanically ventilated patients admitted to a university hospital. Nineteen measurements were made in a total of 10 patients at different times during mechanical ventilation. In seven patients, measurements were made on two or more occasions.

Results: The TwPdi was 11.5 ± 3.9 cm H2O (mean ± SD), indicating a poor diaphragmatic function.
MECHANICAL VENTILATION

↑ ROS → ↑ NFκB

↓ AKT-P

↑ CASPASE + CALPAINS
- ↑ Caspase-3 protein
- ↑ Calpain 1,2,3 protein

↑ UBIQUITIN-PROTEASOME
- ↑ Atrogin-1 and MuRF1 mRNA transcripts
- ↑ Ubiquitinated proteins

↑ LYSOSOME-AUTOPHAGY
- ↑ Autophagy-related gene transcripts and protein levels
- Presence of autophagosome vacuoles

↓ PROTEOLYSIS

Myofiber Atrophy and Injury

VENTILATOR INDUCED DIAPHRAGMATIC DYSFUNCTION
Diaphragm Muscle Thinning in Mechanically Ventilated Patients.

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Abstract

Diaphragm muscle thinning is a rare but severe complication of long-term mechanical ventilation. Although the reported incidence is less than 10%, the clinical significance is significant. A significant number of studies suggest that diaphragm muscle thinning contributes to ventilator-associated lung injury (VALI) and ventilator-induced diaphragmatic dyspnea (VIDD). The importance of early detection and diagnosis has been emphasized. The aim of this study was to evaluate diaphragm muscle thickness in mechanically ventilated patients and its correlation with patient outcome.

METHOD

Patients who were intubated and mechanically ventilated for more than 2 days were included. Diaphragm muscle thickness was measured in the day of intubation until the patient underwent extubation or tracheostomy or died. We analyzed the correlation between diaphragm muscle thickness and patient outcome.

The graph shows the diaphragmatic thickness over time for each patient.