Neuromuscular weakness in ICU

DM Seminar
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INTRODUCTION

- Neuromuscular weakness is commonly encountered problem in ICU
- Abnormalities can be found in majority of patients within 1 or more weeks
- Spectrum ranges from isolated nerve entrapment with focal weakness to severe myopathy or neuropathy

INTRODUCTION

- Less commonly recognized problem
- Electrophysiological abnormalities in more than 50% and overt clinical weakness in 25-30 % in patients mechanically ventilated for more than 7 days (*Leijten et al*)
- Large impact on morbidity and mortality

Innervation of Respiratory muscles

Muscle group	Level	Nerve
Upper airway		
Palate, Pharynx	IX, X, XI	Glossopharyngeal
Genioglossus	XII	Hypoglossal
Inspiratory muscles		
Diaphragm	C3-5	Phrenic
Scalenes	C4-8	
Parasternal intercostals	T1-7	Intercostals
Sternoceidomastoid	XI, C1, C2	Spinal accessory
Lat. Ext. intercostals	T1-12	Intercostals
Expiratory muscles		
Abdominal	T7-L1	Lumbar
Internal intercostals	T1-12	Intercostals

Neuromuscular assessment

Respiratory muscular dysfunction may manifest in variety of ways and can interfere with function of:

- CNS
- Spinal cord
- Peripheral nerves
- NMJ
- Muscles

Neuromuscular assessment

HISTORY AND PHYSICAL EXAM

- Index of suspicion Confirm weakness!
  - Difficult weaning
  - Presence of muscle atrophy
  - Neck weakness
  - Reversal with anticholinesterase
- Symptomatology (Cardinal and other)
  - Upper airway involvement
  - Impairment of cough
  - Sleep related abnormalities
- Drug history

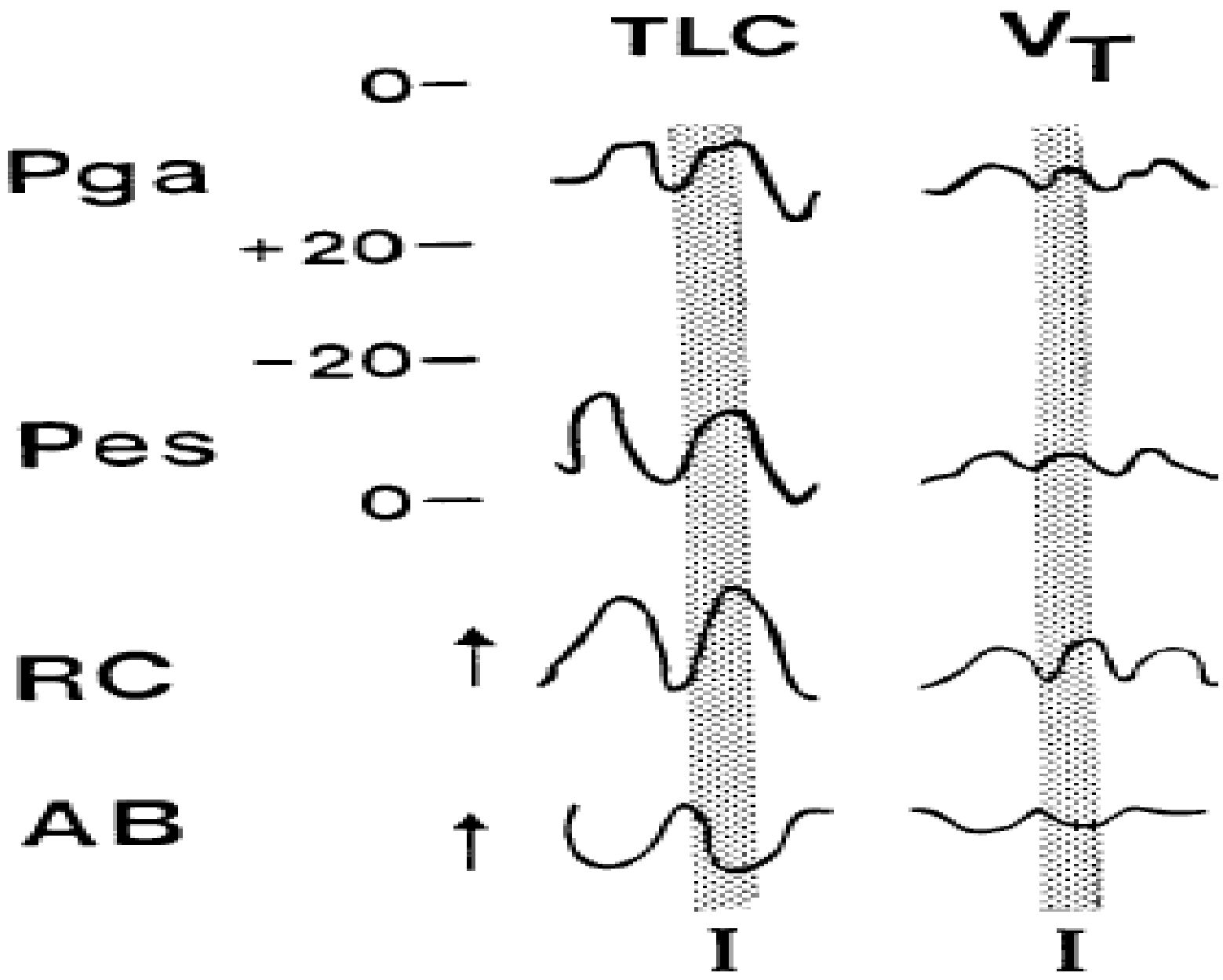
Neuromuscular assessment

- Vitals
- Respiratory rate
- Mental status - not affected in CIPN/CIM
- Pattern of weakness
  - symmetric, facial sparing
  - CN weakness - GBS, MG, BS stroke
- DTR - usually decreased
  - if increased, suggests central lesion

Neuromuscular assessment

- Recruitment of accessory muscles
- Ribcage and abdominal motions
  - Bedside
  - Magnetometry
  - Inductance plethysmography

Axial motion of chest wall can also be measured with magnetometry


TLC
V_T
0
Pga
+20
−20
Pes
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RC
AB
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I

Neuromuscular assessment

GLOBAL ASSESSMENT

Gas exchange and acid base status

- Ventilatory drive
- Partial pressures of O_2 and CO_2
- Alveolar arterial gradient
- Sleep monitoring
- Polysomnography

Neuromuscular assessment

Spirometry

- Restrictive pattern but RV is preserved till late
- More than 25% ↓ in VC from upright to supine highly suggestive of diaphragm weakness
- Usually FEV_1 is normal or decreased
- Maximum voluntary ventilation (weakness, poor coordination and reduced endurance)

Spirometry insensitive measures of respiratory muscle weakness

Neuromuscular assessment

Mouth pressures

- Simplest, most commonly used (*Black and Hyatt*)
- Maximal Inspiratory Pressures(Muller's maneuver)
- Maximal Expiratory Pressures(Valsalva maneuver)
- Varies according to lung volumes

Generalized weakness ↓ both MIP and MEP

Isolated diaphragm involvement may reduce only PI_{max}

Neuromuscular assessment

- PI_{max} and PE_{max} values are effected with
  - Age
  - Sex
  - Type of mouth piece
  - Lung volumes
  - Variable effort and learning

Simlified maneuver not requiring much patient effort required

Neuromuscular assessment

Maximal Sniff pressures

- Reduces variability seen in MIP and MEP
- Easy to perform, No mouthpiece required
- Initiated at FRC and either transdiaphragmatic (Pdi) esophageal (Pes) or nasal pressures (Pn) can be measured
- Pdi and Pn higher and less variability

Neuromuscular assessment

Studies suggest that sniff pressure,

- More reliable than Muller's maneuver
- Greater than Maximal static pressures

Fittilng JW et al 1999

Pn sniff measurements are test of global respiratory muscle function and give little information about diaphragm strength

Neuromuscular assessment

SPECIFIC ASSESSMENT OF DIAPHRAGM

Maximal transdiaphragmatic pressures

- Pdi = Pga – Pes

  Pdi – Trans diaphragmatic pressure

  Pga – Abdominal pressure

  Pes – Pleural pressure

- During quiet respiration change in Pdi = 10 cm of H_2O

Neuromuscular assessment

- With inhalation to TLC, Pdi is typically greater than 30 cm H2O and may increase to values greater than150 cm H2O during maximal inspiratory efforts (i.e. Muller maneuver)
- The coefficient of variation for Pdi during maximal Muller efforts is large, whereas the variability of Pdi during a sniff maneuver is less and the magnitude of Pdi greater
- Greater values obtained with more complex maneuvers (Combined maneuver)

Neuromuscular assessment

- Studies show that most reproducible results are seen with complex maneuvers

Disadvantages of Pdi measurement

- Invasive
- Proper placement of catheter difficult in patients with profound weakness
- Complex and difficult to perform

Neuromuscular assessment

Phrenic nerve stimulation

- Stimulated near the posterior triangle of neck with electric or magnetic stimulus
- Magnetic technique is non selective
- Demonstrates integrity of phrenic nerve
- Measuring Pdi following phrenic nerve stimulation assesses the mechanical output of the diaphragm

Neuromuscular assessment

- Conduction time of less than 9msec is normal
- Pdi following bilateral electric phrenic nerve stimulation is generally between 25 and 35 cm H_2O
- Requires no patient effort
- But depends on impedance of abdomen and rib cage

Neuromuscular assessment

Radiographic assessment

- Elevated hemi diaphragm
- Limited role in bilateral weakness
- Fluoroscopy
  - Quiet breathing
  - Sniff test

Ionizing radiation and poor specificity limit its role

Ultrasound can be used to avoid radiation but specificity is unaffected

Neuromuscular assessment

Imaging the diaphragm zone of apposition

- The zone of apposition is the area of the chest wall where the abdominal contents abut the lower rib cage

- With this approach, the contraction of the diaphragm muscle itself can be visualized

Neuromuscular assessment

- Diaphragm thickness (tdi) at end-expiration can be measured along with the change in tdi during inspiration

- Changes in tdi during inspiration are proportional to diaphragm shortening in adults and infants, whereas tdi measured at end-expiration is proportional to diaphragm strength

Neuromuscular assessment

In the ICU the techniques which are useful are:

- Clinical assessment
- MIP and MEP
- Transdiaphragmatic pressures
- Phrenic nerve stimulation
- Radiographic assessment

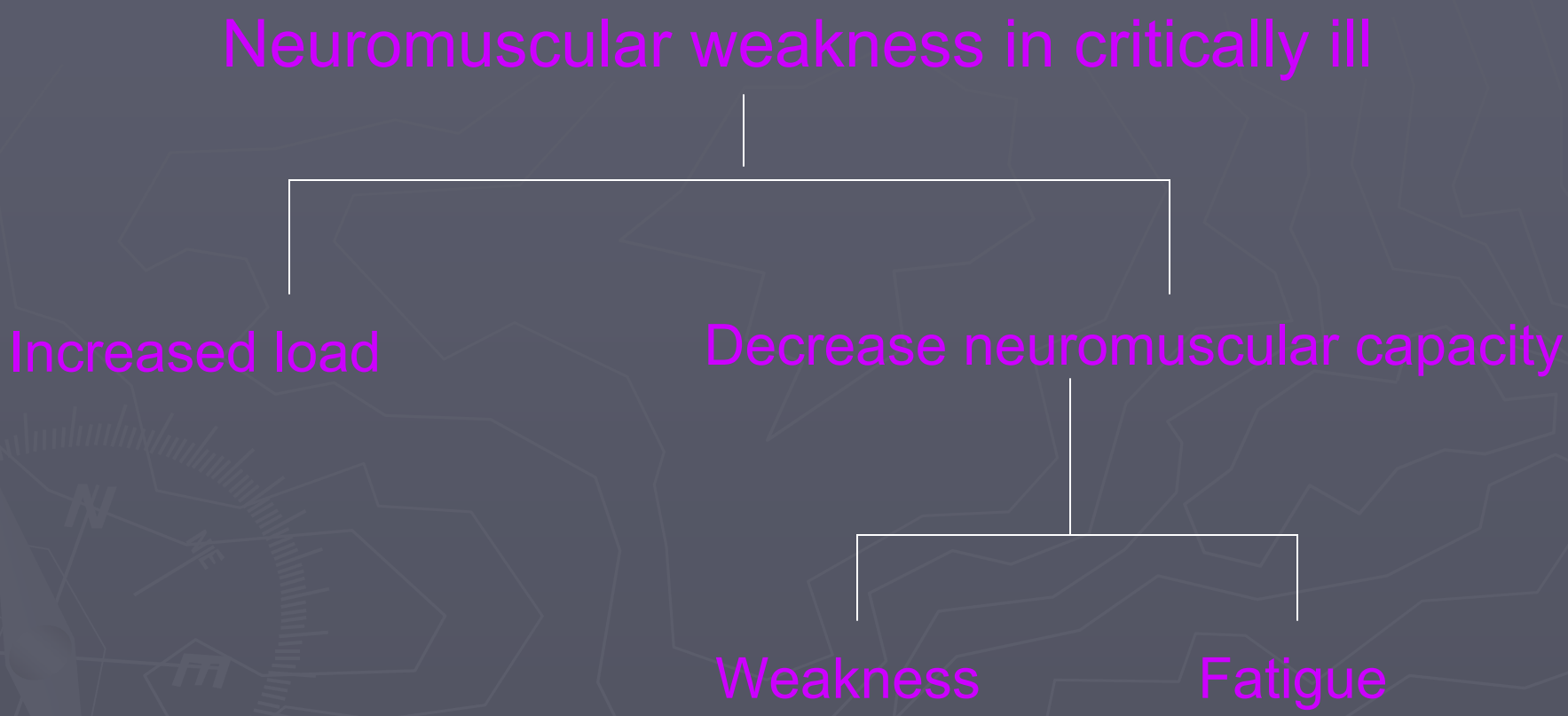
Neuromuscular assessment

- Ventilator measurements
  - P_{mus} 0.1 (preserved in neuromuscular weakness)
  - RSBI (>105)
  - Maximum inspiratory pressure (< 20 cm H_2O)
    - Integrated indices (e.g. CROP, SWI)
      - Demand vs. work of breathing
    - Negative inspiratory force

The 20 30 40 Rule

FVC < 20ml/kg
MIP < 30 cm of H_2O
MEP < 40 cm of H_2O

CLASSIFICATION



Considerable degree of overlap between subgroups

Increased load

Mechanisms

Increased respiratory resistance

Increased dynamic elastance

Increased intrinsic PEEP

Increased CO_2 production

Increased O_2 consumption

Increased dead space

Increased respiratory drive

Decrease NM capacity

Weakness

- Hyperinflation
- Critical illness polyneuropathy
- Critical illness myopathy
- Sepsis related myopathy
- Ventilator associated respiratory muscle damage
- Medications
- Malnutrition

Decrease NM capacity

Fatigue

- Contractile fatigue
  - Brief
  - Prolonged

Hyperinflation

- Tachypnea and the associated shortening of expiratory time can prevent complete lung emptying, leading to dynamic hyperinflation

- Dynamic hyperinflation is common in patients experiencing an exacerbation of COPD, and it also occurs in patients with pneumonia, acute respiratory distress syndrome, and chest trauma

Critical illness polyneuropathy (CIPN)

- Clinically significant muscle weakness in patients who achieve satisfactory awakening after at least 7 days of ventilation, has an incidence of 25%

- Electrophysiological incidence as high as 76% in patients with sepsis and 63-75% in patients with sepsis and MODS

De Jonghe B et al 2002Tepper M et al 2000, Garnacho-Montero J et al 2001

Clinical features

- Delayed weaning from ventilation
- Sensorimotor polyneuropathy
  - Generalized muscle atrophy
  - Flaccid paralysis
  - Decreased/absent DTRs
  - Sensory abnormalities (light touch/pain)
  - Cranial nerve sparing
- Physical exam often non diagnostic

- Electromyography and nerve biopsies reveal axonal degeneration, and muscle biopsies reveal denervation atrophy.
- Clinical improvement seen in about 60% to 90% of patients who survive intensive care.
- More than one-third of patients with severe involvement (quadriparesis and quadriplegia) display motor impairment after 2 years

Leijten et al 1995 ,De Jonghe B et al 2002

	Axonal Injury	Myelin Injury	Neuromuscular Conduction Defect	Myopathy
Compound muscle action potential, amplitude*	Reduced	Normal to slightly reduced	Normal†	Normal
Sensory nerve action potential, amplitude‡	Reduced	Normal to reduced	Normal	Normal
Conduction velocity	Normal to slightly reduced	Reduced	Normal	Normal
Spontaneous muscle depolarization§	Present	Absent	Absent	None to present
Amplitude of compound muscle action potential with stimulation at 3 Hz¶	Unchanged	Unchanged	Decreased	Unchanged
Motor unit activation	Decreased	Decreased	Normal	Increased

Examples of injuries and deficits: *axonal injury*, critical illness myopathy; *myelin injury*, Guillain-Barré; *neuromuscular conduction defect*, myasthenia, prolonged neuromuscular blockade; *myopathy*, critical illness myopathy.

* Elicited by motor nerve stimulation.

† Decreased in Lambert-Eaton syndrome.

‡ Elicited by sensory nerve stimulation.

§ Spontaneous muscle depolarization (caused by denervation) is detected by the presence of fibrillation potentials and positive sharp waves.

¶ Repetitive nerve stimulation is performed to exclude neuromuscular transmission defects such as prolonged neuromuscular paralysis.

- Results from release of cytokines in patients with sepsis and multiple organ failure
- However, has also been reported in mechanically ventilated patients without evidence of sepsis or multiple organ failure
- The importance of critical illness polyneuropathy in causing ventilatory failure is controversial
- In one study the duration of mechanical ventilation was longer in patients with critical illness polyneuropathy

Garnacho-Montero J et al 2001

- Other studies have demonstrated that severity of MODS was actually responsible for difficult weaning and increased ICU stay
- Risk of developing CIPN is more in patient with severe encephalopathy
- Hyperglycemia has been associated with an increased risk of CIPNM in multiple studies
- Tight glycemic control achieved decrease in CIPNM

Critical illness myopathy (CIM)

- Has been described with different names like acute quadriplegic myopathy, thick filament myopathy, acute necrotizing myopathy of intensive care
- Neuromuscular blocking agents and steroids play a dominant role
- CIM and CIPN both can coexist

- Has been most frequently reported with bronchial asthma but also occurs in patient with COPD, solid organ transplants, leukemia, lymphoma
- Muscle biopsies are usually required
- Biopsies reveal
  - general decrease in myofibrillar protein content
  - selective loss of thick filaments (myosin) within Type I and Type II fibers in up to 79% of patients who receive glucocorticoids for more than 2 weeks .
  - patchy necrosis and regeneration (78%), mild myopathy (14%), and atrophy of Type I and Type II fibers (7%)

Larsson L et al 2000 , Lacomis D et al 1996

- Indirect proteolysis of myosin filaments by activating calpain (a calcium-activated protease), cathepsins, lysosomal acid proteases, and the ubiquitin– proteasome pathway (a cytosolic ATP-dependent protease system)
- Decrease in myosin content might also result from reduced myosin transcription . But not in acute paralysis
- Impaired muscle membrane excitability is probably more important during the acute stage

Larsson L et al2000,Rich MM et al 1997, MMTiao G et al 1996

- Effect on duration of ICU stay variable in different studies
- Final outcomes also have reported as quite variable

Prolonged neuromuscular blockade

- Nondepolarizing neuromuscular blocking drugs (NMBDs), are either benzylisoquinolinium (atracurium, cisatracurium, and doxacurium) or aminosteroid (pancuronium, vecuronium, pipecuronium, and rocuronium) in structure

- Important risk factors for pronged weakness are
  - Renal failure
  - Hypermagnesemia
  - Metabolic acidosis
  - Female sex
  - Concomitant use of antibiotics (aminoglycosides, clindamycin) and steroids

- Usually improve with clearance of the agent from the body
- Duration of improvement is variable
- Most patients improve between 1 – 7 days after stopping the drug.

Sepsis related myopathy

- Mechanisms include the cytotoxic effect of nitric oxide and its metabolites, free radicals, and ubiquitin–proteasome proteolysis
- Immunohistochemical studies revealed the generation of peroxynitrite. Exposure of muscles to the amount of peroxynitrite found in patients caused an irreversible decrease in force generation
- These data suggest that sepsis decreases muscle force through the production of nitric oxide and its toxic by-products

Lanone S et al 2000

- This catabolism occurs primarily in Type II muscle fibers. The breakdown probably results from activation of the ubiquitin–proteasome proteolytic pathway secondary to release of tumor necrosis factor , interleukin-1, and interleukin-6
- Decreased diaphragmatic contractility can be improved by the administration of specific scavengers of superoxide ions, hydrogen peroxide, and hydroxyl radicals

Ventilator associated respiratory muscle damage

- 20% decrease in diaphragmatic strength and a 30% decrease in the amplitude of compound action potentials evoked by phrenic nerve stimulation after five days (animal studies)

- Likely mechanisms for the damage include activation of ubiquitin–proteasome proteolysis, calpain proteolysis (non-ubiquitin–proteasome system), and oxidative stress

Le Bourdelles G et al 1994, Yang L et al2002, Sassoon CS et al 2002

- Data on humans sparse
- In a retrospective study of 13 infants who received uninterrupted ventilator assistance for at least 12 days before death, most diaphragmatic fibers appeared atrophic
- The development of atrophy was suggested by a smaller diaphragmatic muscle mass in these infants than in 26 infants who died after receiving mechanical ventilation for 7 days or less

Cote HC et al 2002

Fatigue

Contractile fatigue

- Sufficiently large respiratory load is applied over a sufficiently long period
- Short-lasting fatigue results from
  - accumulation of inorganic phosphate,
  - failure of the membrane electrical potential to propagate beyond T-tubes,
  - intramuscular acidosis

- Long-lasting fatigue is consistent with the development of, and recovery from, muscle injury
- Load-induced injury occurs in two phases: an acute injury immediately after muscle contraction and a delayed or secondary injury
- Several mechanisms may contribute to the acute injury
  - eccentric contractions
  - activation of calpain (a calcium-dependent nonlysosomal protease),
  - increased muscle temperature,
  - excessive production of reactive oxygen species

Hypercapnia and antioxidant mechanisms plays a protective role

Animal models

- Delayed or secondary injury of the diaphragm is characterized by focal necrosis, flocculent degeneration of the sarcoplasm, influx of inflammatory cells, and sarcolemma disruption
- Delayed diaphragmatic injury is proportional to the load and peaks 3 days after applying the load
- Delayed injury decreases diaphragmatic force production at rest and it increases fatigability

- The sarcolemma disruption involves more Type I than Type II fibers and this mechanism may play a role in humans
- Sarcomere disruption has been reported in 18 patients with COPD
- Diaphragmatic damage has been reported in patients dying of asphyxia, sudden infant death syndrome, and status asthmaticus
- Whether or not critically ill patients develop either short lasting or long-lasting contractile fatigue of the respiratory muscles has not been clear

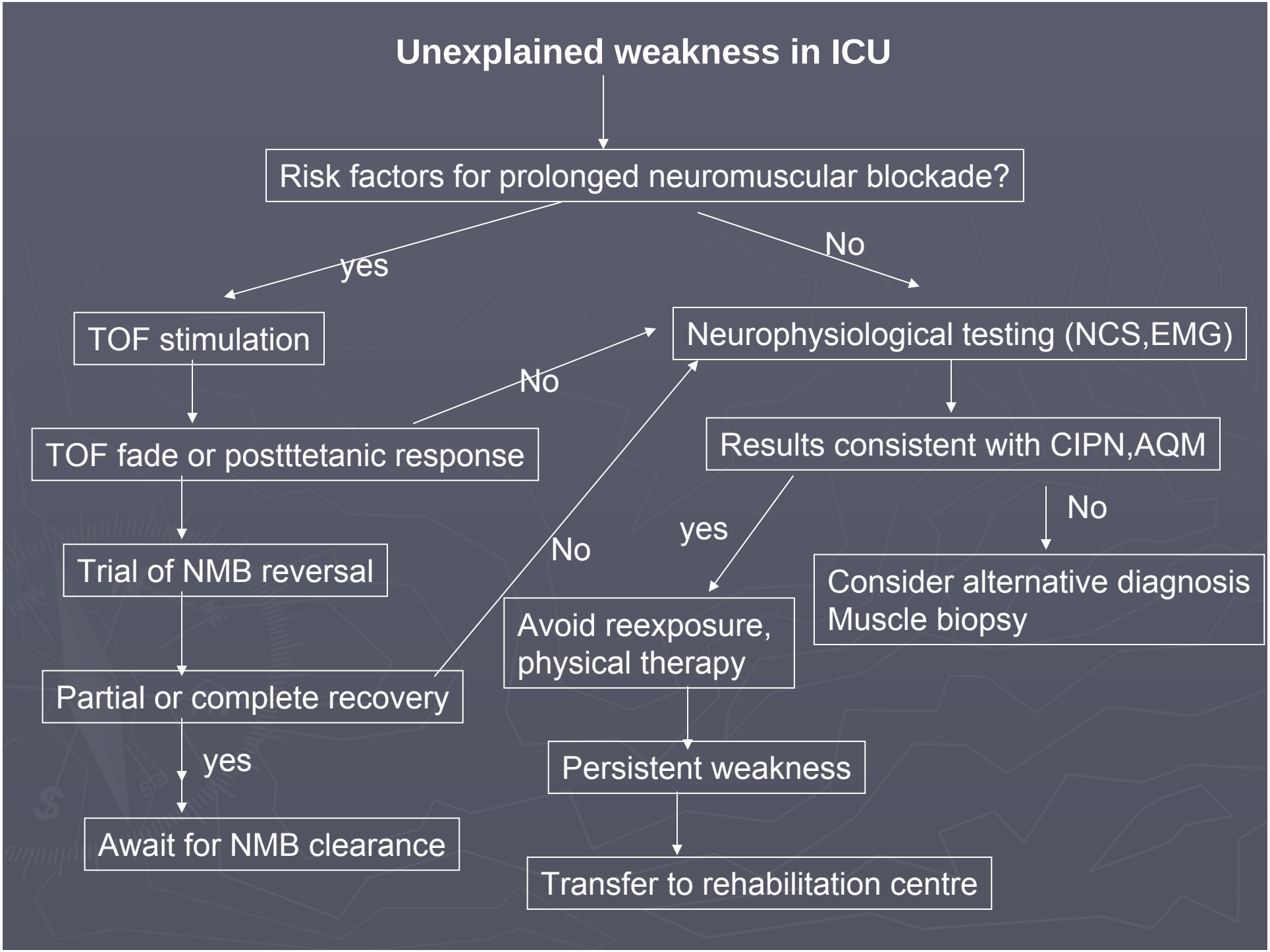
- In one controlled study the contractile response of the diaphragm to phrenic nerve stimulation was ↓ in nine patients who failed a weaning trial
- The weaning failure patients experienced a greater respiratory load and developed greater diaphragmatic effort than did the weaning success patients
- None developed a decrease in transdiaphragmatic twitch pressure elicited by phrenic nerve stimulation.
- Seven of the nine weaning failure patients had a tension–time index above 0.15

Laghi et al 2003

Role of muscle biopsy

When should it be done?

- Any patient with un explained neuromuscular weakness in ICU without EMG/NCS c/w pure CIPN/CIM
  - Normal sensory neurography
  - Low motor amplitudes
  - Little spontaneous EMG activity


Unexplained weakness in ICU
Risk factors for prolonged neuromuscular blockade?
yes
No
TOF stimulation
Neurophysiological testing (NCS,EMG)
No
TOF fade or postttetanic response
Results consistent with CIPN,AQM
No
yes
Trial of NMB reversal
No
Consider alternative diagnosis
Muscle biopsy
Avoid reexposure,
physical therapy
Partial or complete recovery
yes
Persistent weakness
Await for NMB clearance
Transfer to rehabilitation centre

Management

Prevention

- Avoiding and limiting the dose and duration of neuromuscular blockade
- Judicious use of corticosteroids
- Peripheral nerve stimulation with measurement of the response to four equal pulses over 2 seconds (train of four, or TOF) is the “gold standard” for monitoring neuromuscular blockade in the operating room
- Has not shown to decrease the incidence but hastens recovery

Management

- Pharmacologic reversal of neuromuscular blockade with a cholinesterase inhibitor may also be useful in establishing a diagnosis but recovery will likely be incomplete or short-lived in the presence of high concentrations of NMBDs or their metabolites

- Measures that reduce ICU length of stay may also decrease CIPNM

Management

- Intensive insulin therapy has been shown to reduce the risk of CIPNM, leading to a dramatic reduction in the risk of developing CIPNM compared with control subjects (odds ratio, 0.4; 95% confidence interval, 0.28–0.57; p 0.0001)

Van Den Berghe et al 2001

- Efforts to prevent and aggressively treat sepsis will likely reduce the incidence of CIPNM
- Nitric oxide synthase inhibitors and pretreatment with dexamethasone may prevent may decrease the incidence of CIM in patient with sepsis

Boczkowski et el 1996,Lin MC et al 1998

Management

- Pretreatment with glucocorticoid receptor (RU 38,486) antagonist has also shown to decrease the incidence of sepsis related myopathy

Tioa et al 1996

- Use of dantrolene to prevent increase intracellular calcium and antioxidants have also shown to decrease the occurrence of ventilator associated respiratory muscle damage

Treatment

- Treatment consists primarily of waiting for clearance of NMBD
- At this point in time, no treatments for established CIPNM have been proven to be effective
- Reexposure to corticosteroids and/or NMBDs should be avoided, as relapse of myopathy has been reported after recovery from an initial incident followed by reexposure to high-dose corticosteroids

Conclusions

- Acquired NM weakness more common than recognized and may result in substantial excess morbidity, mortality, and costs.
- Understanding of ICU-acquired paresis remains incomplete and recognition of its importance has implications for clinical practice and future research

Conclusions

- Avoiding neuromuscular blocking agents, limiting corticosteroids, treating hyperglycemia with intensive insulin therapy, limiting end-organ dysfunction, such as low tidal volume ventilation for patients with ARDS.
- Screening for weakness to help plan treatment, avoid potential toxin reexposure, and identify patients for rehabilitative treatments


Thank you