ASSESSMENT OF ICU ACQUIRED MUSCLE WEAKNESS INCLUDING THE ROLE OF ULTRASOUND

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POINTS OF DISCUSSION

- Incidence
- Phenotypes
- Criteria
- Significance of ICUAW
- Methods of assessment of ICUAW
  - ✓ Volitional
  - ✓ Non – volitional
- Role of USG and CT in peripheral muscle weakness
- VIDD
- Methods of assessment of diaphragmatic dysfunction
- Role of USG
- Approach to a suspected case of ICUAW
- Take home message

INCIDENCE

- The incidence of ICU-AW varies across different settings but is reported to be around **25 to 50%** in the general ICU setting across several studies
- In those who have **severe sepsis and SIRS** ICUAW occurrence has been documented upto **100 percent.**
- **30% patient** who develops CINMA may **be left with residual weakness** at the end of one year.

Tennila AI et al Intensive Care Med 2000; 26:136
Jonghe etal, JAMA2002; 288: 2859–2867, 0–1363
Fletcher S etaliCrit Care Med 2003; 31: 1012–1016

	Incidence	Clinical features	Electrophysiological findings	Serum creatine kinase	Muscle biopsy	Prognosis
Polyneuropathy						
Critical illness polyneuropathy	Common	Flaccid limbs, respiratory weakness	Axonal degeneration of motor and sensory fibres	Nearly normal	Denervation atrophy	Variable
Neuromuscular transmission defect						
Transient neuromuscular blockade	Common with neuromuscular blocking agents	Flaccid limbs, respiratory weakness	Abnormal repetitive nerve stimulation studies	Normal	Normal	Good
Critical illness myopathy						
Thick-filament myopathy	Common with steroids, neuromuscular blocking agents, and sepsis	Flaccid limbs, respiratory weakness	Abnormal spontaneous activity	Mildly elevated	Loss of thick (myosin) filaments	Good
Acute myopathy with scattered necrosis	Common	Flaccid limbs, respiratory weakness	Myopathy	Mildly or moderately raised	Scattered necrosis	Variable
Acute myopathy with diffuse necrosis (necrotising myopathy of intensive care)	Rare	Flaccid weakness, myoglobinuria	Severe myopathy	Greatly raised, myoglobinuria	Marked necrosis	Poor
Disuse (cachectic) myopathy	Common	Muscle wasting	Normal	Normal	Normal or type II fibre atrophy	Variable
Rhabdomyolysis	Rare	Flaccid limbs	Near normal	Markedly elevated (myoglobinuria)	Normal or mild necrosis	Good
Combined polyneuropathy and myopathy	Common	Flaccid limbs, respiratory weakness	Indicative of combined polyneuropathy and myopathy	Variable	Denervation atrophy and myopathy	Variable

Modified from Bolton,[17] by permission of Springer.

Table: **Generalised neuromuscular disorders associated with critical illness**

Lancet Neurol 2011; 10: 931–41

CRITICAL ILLNESS POLYNEUROPATHY CRITERIA

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. Electrophysiological evidence of axonal motor and sensory polyneuropathy
4. Absence of a decremental response on repetitive nerve stimulation

Definite diagnosis of critical illness polyneuropathy is established if all four criteria are fulfilled. Probable diagnosis of critical illness polyneuropathy is established if criteria 1, 3, and 4 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. Modified from Bolton,[11] by permission of John Wiley & Sons.

Lancet Neurol 2011; 10: 931–41

CIM

1. The patient is critically ill (multiorgan dysfunction and failures)
2. Limb weakness or difficulty weaning patient from ventilator after non-neuromuscular causes such as heart and lung disease have been excluded
3. CMAP amplitudes less than 80% of the lower limit of normal in two or more nerves without conduction block
4. Sensory nerve action potential amplitudes more than 80% of the lower limit of normal
5. Needle electromyography with short duration, low-amplitude motor unit potentials with early or normal full recruitment, with or without fibrillation potentials in conscious and collaborative patients; or increased CMAP duration or reduced muscle membrane excitability on direct muscle stimulation in non-collaborative patients
6. Absence of a decremental response on repetitive nerve stimulation
7. Muscle histopathological findings of primary myopathy (eg, myosin loss or muscle necrosis)

Definite diagnosis of critical illness myopathy is established if all seven criteria are fulfilled. Probable diagnosis of critical illness myopathy is established if criteria 1 and 3–6 are fulfilled. Diagnosis of intensive care unit-acquired weakness is established if only criteria 1 and 2 are fulfilled. CMAP=compound muscle action potential. Modified from Lacomis and colleagues,[4] by permission of John Wiley & Sons.

Lancet Neurol 2011; 10: 931–41

RULE OUT MIMICS

Condition and Pathogenesis	Clinical Manifestations
Guillain–Barré syndrome	
Autoimmune mechanism	Diarrheal prodrome (e.g., *Campylobacter jejuni* infection)
Myelin loss	Autonomic instability, ascending paralysis, ventilatory failure
Myasthenia gravis	
Autoimmune mechanism	Bulbar palsy
Antibodies against neuromuscular junction	Ventilatory failure
Porphyria	
Porphyrin accumulation with resulting nerve toxicity	Motor axonal neuropathy, autonomic instability, abdominal pain, psychiatric manifestations
Eaton–Lambert syndrome	
Paraneoplastic syndrome	Proximal weakness
Presynaptic calcium-channel antibodies	Autonomic instability
Amyotrophic lateral sclerosis	
Upper and lower motor-neuron degeneration	Bulbar involvement, fasciculations, muscle atrophy
Vasculitic neuropathy	
Occlusion of vasa nervorum vessels	Paresthesia, numbness, pain, weakness
Cell and immune-complex mediated	Distal polyneuropathy
Cervical myelopathy	
Mechanical injury to cervical spinal cord	Paresthesia, numbness, pain, weakness
Botulism	
Botulinum toxin	Bowel dysfunction, bladder dysfunction, or both, inhibition of acetylcholine release from presynaptic membrane, bulbar palsy, descending paralysis, autonomic dysfunction

N Engl J Med 2014;370:1626-35

SIGNIFICANCE OF ICUAW

- ICUAW is a **clinically relevant complication** during the acute stage of a disease and after discharge from the acute-care hospital.
- Also it is independently associated with **prolonged mechanical ventilation, ICU stay, hospital stay and increased mortality**.
- Patients developing weakness during the ICU stay **have reduced quality of life and increased mortality 1 year after ICU discharge**.

Latronico N, Bolton CF. Lancet. Neurol.2011;10(10):931-41.
Hermans G, Van Mechelen H, Clerckx Am J Respir Crit Care Med. 2014;190(4):410-20.

METHODS OF ASSESSMENT OF ICUAW

- **Clinical assessment**
- **Volitional tests**
  - MRC sum score
  - Handgrip dynamometry
  - Handheld dynamometry
- **Non-volitional tests**
  - Electrophysiological studies
  - Imaging
- **Biopsy**

CLINICAL ASSESSMENT

Feature	CIP	CIM
Weakness	Flaccid Worse distally more than proximally	Flaccid Worse proximally more than distally
Muscle atrophy	(±)	(±)
Ventilatory failure	(±)	(±)
Muscle stretch reflexes	Hyporeflexia or areflexia	Normal or hyporeflexia
Sensory loss	May experience distal sensory loss[18,19]	Normal
Extraocular muscles	(-)	Rare, although facial weakness may occur

Richard et al. CHEST 2016; 150(4):966-971

VOLITIONAL TESTING	NON-VOLITIONAL TESTING
Non-time consuming	Time-consuming
Easy to perform	Technically challenging
Non- expensive	Expensive
Easily availability	Not easily available
Requires the patient to be alert, cooperative	Can be done even in sedated and comatose patients

Griffiths RD, Hall JB. Intensive care unit-acquired weakness. Crit Care Med 2010;38:779–787.

VOLITIONAL/ MANUAL MUSCLE TESTING

ASSESSMENT OF LEVEL OF COOPERATION

Open and close your eyes
Look at me
Open your mouth and put out your tongue
Nod your head
Raise your eyebrows after I have counted to five

A SCORE OF 5/5 IS CONSIDERED AS FIT FOR VOLITIONAL MUSCLE STRENGTH TESTING

Jonghe et al. JAMA 2002; 288: 2859-2867

CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT (CAM-ICU)

1) Acute onset of changes or fluctuations in the course of mental status,
2) Inattention,
3) Disorganized thinking and
4) Altered level of consciousness

Delirious according to the CAM-ICU if he/she manifests both features 1 and 2, plus either feature 3 or 4

EW et al. JAMA 2001; 286: 2703-2710

MANUAL MUSCLE STRENGTH TESTING

MRC sum score

HHD (Hand Held Dynamometry)

HGD (Hand Grip Dynamometry)

MRC SUM SCORE

- **Kleyweg et al developed the MRC-sum score** to identify general peripheral muscle weakness in GBS patients.

- This sum score **comprehends the individual score for (bilateral) muscle groups** of the upper limbs and the lower limbs.

- **The MRC and MRC-sum score have been implemented in the examination of muscle strength in critically ill patients to assess ICU-acquired weakness** (ICUAW)

Kleyweg et al. Muscle Nerve 1991; 14: 1101-1109

MRC ASSESSMENT OF MUSCLE STRENGTH

Grade 0	No contraction visible or palpable
Grade 1	Flicker of contraction visible or palpable, although no limb movement
Grade 2	Movement with gravity eliminated over almost full range of motion
Grade 3	Movement against gravity over almost full range of motion
Grade 4	Movement against moderate resistance over full range of motion
Grade 5	Normal power

Hermans et al; Muscle Nerve 2012;45: 18-25

STANDARDISED TESTING POSITIONS

- To perform movements against gravity (MRC ≥ 3**), the head end of the bed is placed in 45**°. For movements with elimination of gravity (MRC < 3), **the head end of the bed is placed in 10°**
- The head of the patient is supported by a pillow, to enable the patient to see the limb to be tested.
- **Fixation and positioning materials must be removed. Side rails are removed**. Make sure that catheters do not interfere with the movements that have to be performed.
- If necessary, bronchial toilet is performed prior to testing, followed by a short recuperation period for the patient.
- **First test muscle strength for an MRC-score of 3**. Then continue the test for an MRC-score 4 or 2 depending on the result.

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

PROCEDURE

- First, **perform the movement passively** so the patient knows which movement he/she is expected to do. Next, ask the patient to perform the movement actively.
- Begin the test at the **right hand side**. **Finish muscle strength examination for 1 muscle group bilateral** before continuing to the next muscle group. The muscle test must always be carried out in the same order
- **Three attempts for each muscle group may be performed. When the first attempt is correctly performed, continue to the next muscle group.**
- **Resting periods in between measurements may be short (less 30 seconds**) unless the patient needs more time to recover
- Since contraction time is delayed in critically ill patient, encourage the patients to maintain the effort for at least 5-6 seconds

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09
Baldwin ET AL. J Crit Care 2013; 28: 77-86

Muscle test 1: shoulder abduction	
Commands: - move your elbow upwards	
	
Grade 1	Grade 2
	
Grade 3	Grade 4/5

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

Muscle test 2: Elbow flexion

Commands: - Move your hand towards your shoulder

Grade 1

Grade 2

Grade 3

Grade 4/5

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

Muscle test 3: Wrist extension

Commands: - Move your hand to the side (grade 2)

- lift your hand of the matras (grade 3)

Grade 1

Grade 2

Grade 3

Grade 4/5 (fingers in extension)

Grade 4/5 (fingers in flexion)

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

Muscle test 4: Hip flexion

Commands: - Move your knee towards your chest

Grade 1

Grade 2

Grade 3

Grade 4/5

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

Muscle test 5: Knee extension

Commands: - Lift your foot of the matras

Grade 1

Grade 2

Grade 3

Grade 4/5

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

Muscle test 6: Ankle dorsiflexion	
Commands: - Pull up your toes	
	
Grade 1	Grade 2
	
Grade 3	Grade 4/5

Kleyweg R.P., et al. Muscle Nerve 1991; 14(II): 1003-09

MRC SUM SCORE

- 6 joint movements are examined
  - Shoulder abduction
  - Elbow flexion
  - Wrist extension
  - Hip flexion
  - Knee extension
  - Ankle dorsiflexion
- For global muscle strength, calculate the MRC-sum score by summing all the obtained strength values of upper limbs and lower limbs

Hermans et al. Muscle Nerve 2012; 45: 18-25

SPECIAL SITUATIONS

- When muscle strength cannot be evaluated due to orthopedic, neurologic or other reasons**, results of the contralateral muscle group will be substituted to calculate the MRC-sum score**. The only exception is paraplegia. The values of the arm are then extrapolated to the leg (ipsilateral limb here). When there are more than two extrapolations the MRC sum score cannot be used

Hermans et al. Muscle Nerve 2012; 45: 18-25

MRC SUM SCORE INTERPRETATION

A summed score **below 48/60 designates ICUAW** or significant weakness, and an **MRC score below 36/48 Indicates severe weakness**

A score of less than 48 is associated with prolongation of mechanical ventilation and length of stay in ICU, increased mortality, and reduced quality of life in survivors of critical illness.

A simplified version of the scale with only four categories was proposed

Hermans et al. Muscle Nerve 2012; 45: 18-25

Bolton et al.Lancet Neurol 2011; 10: 931-41

STUDY	De Jonghe etal (France /2002)	Nanas etal (Greece/2008)	Naeem etal (USA /2008)
Method	95 Pts on MV assessed with MRC score (**MRC<48 as ICUAP) on D7 after awakening.**	185 patients assessed **after 48-72 hrs after awakening with MRC (MRC<48 as ICUAP**)	136 pt on MV for ≥5 days were assessed on day of awakening with **MRC and hand grip strength**
Objective	ICUAP –incidence, risk factors and outcome	ICUAP –risk factors	ICUAP -outcome
Result	Pt with MRC<48 had **longer duration of MV(P=0.03)**	Pt with MRC<48 had a **higher ICU mortality (P<0.05)**	**Both average MRC <4 and hand grip** strength were associated with increased hospital mortality

Study design	Cross sectional observational study
Subjects	**ICU patients who had stayed in ICU for ≥7 days**.
Objective	Interobserver aggrement and cut off values for MRC sum score and handgrip
Method	2 observers independently measured Medical Research Council (MRC) sum-score (n = 75) and handgrip strength (n = 46)
Results	•The agreement on identifying patients with **an MRC sum-score <48 was good (kappa = 0.68 +/- 0.09)**. • For identifying ‘‘severe weakness,’’ as revealed by **an MRC-sum score <36, agreement was excellent (kappa = 0.93 +/- 0.7).** • Agreement was also good for handgrip strength

Hermans etal. Muscle Nerve , 2012; 45: 18–25

SIMPLIFIED MRC SCALE

0	PARALYSIS
1	SEVERE WEAKNESS DEFINED AS > 50 % LOSS OF STRENGTH
2	SLIGHT WEAKNESS DEFINED AS < 50 % LOSS OF STRENGTH
3	NORMAL STRENGTH

A score of less than 24 out of 36 is suggestive of weakness.

Parry et al. Crit Care . 2015;19:52.

STUDY TYPE	SINGLE CENTRE OBSERVATIONAL
Subjects	**Part 1** : Muscle strength test on 29 patients on MV > 48 hours **Part 2**: Handgrip test on 60 patients on MV > 48 hours
Objective	The inter-rater reliability and agreement of manual muscle strength testing using both **isometric and through-range techniques** using the MRC sum score and a new four-point scale, and to examine the **validity of HGD** and **determine a cutoff score for the diagnosis of ICU-AW for the new four-point scale**
Results **Parry et al. Crit Care . 2015;19:52.**	The highest reliability and agreement was observed for **the isometric technique using the four-point scale.(kappa value 0.85)** **HGD had a sensitivity of 0.88 and specificity of 0.80 for diagnosing ICU-AW.** A cutoff score of **24 out of 36 points** was identified for the four-point scale
Inference	**SIMPLIFIED MRC SCALE CAN BE USED**

MANUAL MUSCLE TESTING PREDICTIVE VALUE

Study design		Observational cohort study
Method		Inter-observer agreement for ICU-AW between two clinicians in critically ill patients within ICU on MV (n = 20) was compared with simulated presentations (n = 20). And also the clinical predictability of LOS and mortality was assessed
Results	ICU LOS (upto 2 weeks)	Hospital LOS (more than 4 weeks)
Sensitivity	**92.9 %** (76.5-99.1)	**84.2 %** (68.7-94)
Specificity	40.5 % (24.8-57.9)	40.7 % (22.4-61.2)
PPV	54.2 %(39.2-68.6)	66.7% (51.6-79.6)
NPV	**88.2% (**63.6-98.5)	**64.7 %** (38.3-85.8)

Connolly et al. Critical Care 2013, 17:R229

MRC SCALE- ANY DISADVANTAGE?

- Several studies indicate **difficulties in differentiation between grades 4 and 5,** inaccuracy in identifying muscle weakness in patients compared with healthy subjects
- Also there is **lack of sensitivity to detect progress in muscle strength when applied to stronger muscles.**

Bohannon et al. Am J Phys Med Rehabil 2001;80: 13-18

Bohannon et al. Clin Rehabil 2005; 19:662-667

HHD and HGD

Handheld dynamometry (HHD) and handgrip dynamometry (HGD) have been designed to measure volitional isometric muscle strength more objectively in patients who are **cooperative and have a score of 3 or more on the MRC**

Bohannon et al. Arch Phys Med Rehabil 1997; 78:26-32

Andrews et al. Phys Ther 1996; 76:248-259

DYNAMOMETER

HGD

HHD

OBSERVER	Hough et al	Hermans et al	Fan et al	Ali et al	Vanpee et al	Baldwin et al
Population	10 critically ill patients and 20 survivors of ICU stay	75 critically ill patients	9 patients recovering from critical illness and 10 simulated patients	10 critically ill patients	39 critrically ill patients	17 critically ill patients
Eligibility	Mechanical ventilation ≥ 3 days	Admitted to ICU ≥ 7 days	ND	Mechanical ventilation ≥ 5 days	Admitted to ICU 7 days	Admitted to ICU ≥ 7 days
Mean age (years)	49	59	ND	57	64	78
Measuring method	MRC scale	MRC scale MRC sum scale Hand grip strength	MRC sum score	MRC sum score Hand grip	Hand held dynamometry	Handgrip and Handheld dynamometry
Reliability	ICC= 0.83	MRC-ICC > 0.83 MRC sum-	ICC= 0.99	ICC = 0.93	ICC > O.91	Elbow flexion and knee

HANDGRIP CAN BE USED AS AN ALTERNATIVE TO MRC score

HANDGRIP DYNAMOMETRY

- Measures isometric muscle strength and can be used as a quick diagnostic test.

- Cut-off scores of **less than 11kg in males** and **less than 7kg in females** are considered to be indicative of ICUAW

Ali et al. Am J Respir Crit Care Med Vol 178. pp 261–268, 2008

HANDGRIP PREDICTABILITY

STUDY	PROSPECTIVE MULTICENTRE COHORT STUDY
Subjects	Adults with ≥ 5 days of mechanical ventilation
Objective	Test the hypothesis that ICUAP increases mortality Handgrip weakness for prediction of ICUAP and mortality
Results	ICUAW **(p < 0.001)** and handgrip **(P = 0.007)** weakness a/w **increased mortality** Force value cut off < 11 Kg in males, < 7 kg in females adequate for diagnosing weakness
Inference	Overall **sensitivity 80.6%, specificity 83.2%, negative predictive value 92.3%, positive predictive value, 63.0%)** when compared with an ICUAP diagnosis by MRC exam

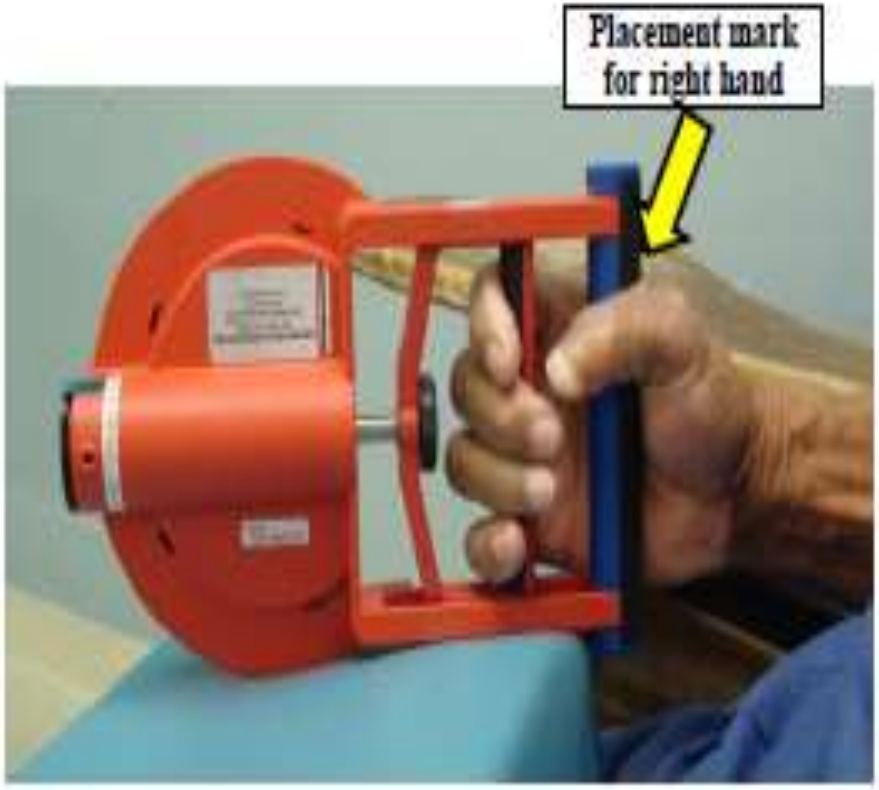
Ali et al. Am J Respir Crit Care Med Vol 178. pp 261–268, 2008

HGD- PROCEDURE

- Age ≥ 6 years
- Calibration checks are performed at the start of each stand to confirm that the dynamometer is working properly
- Pretest questionnaire
  - Limitations/ deformities
  - Recent (< 3 months surgery)
  - Pain / arthritis/tendinitis/ CTS
  - Dominant hand

Adopted from Muscle strength procedures manual /NHANES/ CDC/April 2011

HGD PROCEDURE



HGD PROCEDURE

- The dominant hand is tested thrice
- A gap of 60 seconds given between each exam
- Best score of the three used
- A score of < 11 kg in males and < 7 kgs in females has the best sensitivity and specificity to diagnose weakness

Ali et al. Am J Respir Crit Care Med Vol 178. pp 261–268, 2008

HANDHELD DYNAMOMETRY

- Here the manual strength of muscles is assessed by using a hand held dynamometer and **evaluating the action of 6 upper limb and 4 lower limb joints**
- The values are read in Newtons and the reference values obtained from the observational study conducted by Bohannan are used to define weakness

Bohannon et al. Arch Phys Med Rehabil 1997;78:26-32.

HANDHELD DYNAMOMETRY

STUDY DESIGN	DESCRIPTIVE STUDY
Subjects	106 men and 125 women volunteers (aged 20-79 years) was tested twice with an Ametek digital hand-held dynamometer
Objective	**Provide reference values for the strength of 10 extremity muscle actions**
Method	The isometric strengths of six upper extremity and four lower extremity muscle actions of distal, middle, and proximal joints were measured twice bilaterally by a single tester with more than 10 years of experience with hand-held dynamometry. At least 1 minute of rest was allowed between repeated tests of the same action.
Actions checked **Bohannon et al. Arch Phys Med Rehabil1997;78:26-32**.	**Wrist extension, elbow flexion, elbow extension, shoulder lateral rotation, shoulder abduction, shoulder extension, Ankle dorsiflexion, Knee extension, Hip flexion, Hip abduction**

HHD methods

Two methods of isometric testing with HHD have been described.

- **The make technique** requires the patient to exert a maximal isometric contraction while the examiner holds the dynamometer in a fixed position.
- **The break technique**, in contrast, requires the examiner to overpower a maximal effort by the patient, thereby producing a measurement of eccentric muscle strength

Vanpee et al. Crit care med. March 2014; 42(3)

NON-VOLITIONAL TESTS

ELECTROPHYSIOLOGICAL STUDIES

- It has been demonstrated that patients with ICUAW present muscle atrophy and neuromuscular electrophysiological disorders (NED)
- Muscle atrophy can occur without the presence of ICUAW
- **Electrophysiological changes can be detected as early as 24 to 48 h following the onset of ICUAW**, and often precedes clinical onset of weakness

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NEED FOR EPS

- These tests are considered to be standard methods for diagnosing neuromuscular disease, allowing quantitative grading**, type and localization of the neurogenic lesions**
- **Early identification of neuromuscular alterations by means of electrophysiologic tests may be of value for targeted treatments** and to anticipate the risk of short-term disability

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TEST		CIP	CIM
NCS	CMAP Amplitude	Reduced	Reduced
	SNAP Amplitude	Normal or reduced	Normal
	CMAP duration	Not prolonged	Prolonged
	Direct muscle CMAP	Not Reduced	Reduced
	Nerve evoked CMAP to dmCMAP ratio	< 0.5	> 0.5

Bolton et al. Lancet Neurol 2011; 10: 931–41

Richard et al. CHEST 2016; 150(4):966-971

FEASIBILITY AND DIAGNOSTIC ACCURACY OF EARLY EPS FOR ICUAW

Study design	Prospective observational cohort study
Subjects	Newly admitted patients, mechanically ventilated > 2 days and un-reactive to verbal stimuli
Objective	**Feasibility and accuracy of electrophysiological recordings** to diagnose ICU-AW early in non-awake critically ill patients.
Results	When using cut-off values from critically ill patients with and without ICU-AW, EDB peroneal CMAP amplitude and ulnar SNAP amplitude had good diagnostic accuracy With electrophysiological parameters, a diagnosis **of ICU-AW can be established six days earlier than that for conventional muscle strength assessment.**

Wieske et al. Neurocritical care. 22. 10.1007/s12028-014-0066-9.

	ICU-based cut-off value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Ulnar SNAP amplitude	<17.6 μV	100 % (68–100)	79 % (49–95)	82 % (57–96)	100 % (62–100)
EDB peroneal CMAP amplitude	<0.43 mV	80 % (52–96)	75 % (48–93)	75 % (48–93)	80 % (52–96)
Ulnar SNAP and EDB peroneal CMAP amplitude abnormal	n.a.	77 % (46–95)	100 % (70–100)	100 % (59–100)	83 % (59–96)

Wieske et al. Neurocritical care. 22. 10.1007/s12028-014-0066-9.

EPS

Study Design	Prospective study
Subjects	Subanalysis of EPaNIC study **with patients requiring ICU admission for > 8 days**
Objectives	Sensitivity, Specificity, PPV, NPV and 1 year mortality of abnormal EPS, done at day 8 and day 15 of Intensive care admission

Hermans et al. Intens Care Med. 2015;41(12):2138-2148.

Table 2 Incidence of electrophysiological abnormalities on the first and second evaluation and their predictive value for intensive care unit-acquired weakness (ICUAW)

	Incidence in total population	Incidence in patients with MRC sum-score	Sensitivity (95 % CI)	Specificity (95 % CI)	Positive predictive value (95 % CI)	Negative predictive value (95 % CI)
First electrophysiological screening	$N = 730$	$N = 432$				
CMAP reduced or absent	527/698 (75.5 %)	302/415 (72.8 %)	88.6 % (83.0–92.6)	41.0 % (34.5–47.8)	56.6 % (50.8–62.3)	80.5 % (71.8–87.1)
SNAP reduced orabsent	71/638 (11.1 %)	37/384 (9.6 %)	13.6 % (9.0–19.9)	93.5 % (89.1–96.3)	62.2 % (44.8–77.1)	37.9 % (32.5–63.1)
Abnormal SEA	146/716 (20.4 %)	65/423 (15.4 %)	20.7 % (15.4–27.2)	89.3 % (84.4–92.9)	63.1 % (50.2–74.4)	56.1 % (50.8–61.3)
Second electrophysiological screening	$N = 327$	$N = 195$				
CMAP reduced or absent	284/320 (88.8 %)	167/189 (88.4 %)	92.3 % (85.9–96.0)	20.3 % (11.4–33.2)	71.9 % (64.3–78.4)	54.5 % (32.6–74.9)
SNAP reduced orabsent	45/290 (15.5 %)	24/172 (14.0 %)	18.5 % (12.2–26.9)	96.2 % (85.9–99.3)	91.7 % (71.5–98.5)	34.5 % (27.0–42.8)
Abnormal SEA	129/324 (39.8 %)	55/193 (28.5 %)	33.1 % (25.3–41.8)	81.7 % (69.1–90.1)	80.0 % (66.6–89.1)	35.5 % (27.7–44.2)

Different denominators are due to technical issues precluding evaluation of certain electrophysiological tests in some patients
MRC Medical Research Council, *CMAP* compound muscle action potential, *SNAP* sensory nerve action potential, *SEA* spontaneous electrical activity

Hermans et al. Intens Care Med. 2015;41(12):2138-2148.

Table 3 Multivariate logistic regression analysis for the risk of death 1 year after ICU admission

	OR	*p* value
Uncorrected		
Abnormal CMAP	3.076 (1.954–4.844)	**<0.001**
Corrected for weakness		
Abnormal CMAP	3.115 (1.466–6.616)	**0.003**
MRC sum-score <48	2.128 (1.274–3.556)	**0.004**
Corrected for weakness, baseline risk factors[a], ICU risk factors prior to electrophysiological testing[b], and site of testing		
Abnormal CMAP	2.463 (1.113–5.452)	**0.026**
MRC sum-score <48	1.955 (1.116–3.425)	**0.019**
Age	1.045 (1.022–1.069)	**<0.001**
BMI <25 or >40	1.800 (1.045–3.099)	**0.034**
Malignancy	2.892 (1.669–5.011)	**<0.001**
Sepsis on admission	1.849 (1.056–3.237)	**0.032**
NRS ≥5	1.508 (0.870–2.614)	0.143

Hermans et al. Intens Care Med. 2015;41(12):2138-2148.

WHAT IS *SET?*

- Stimulus Electrogenesis Test
- Surrogate method to detect NED
- Evaluates neuromuscular excitability evoked by **transcutaneous electrical stimulus**
- **Non-invasive and low cost test conducted with universal pulse generators**.
- Based on the analysis of different neuromuscular responses evoked by pre-established electrical stimuli
- **Non-specific** but can be used as an initial screening exam and its results can provide a rational course of action for subsequent NCS and DMS in ICU settings

P.E. Silva et al. Journal of Critical Care 44 (2018) 87–94

HOW IS *SET* USEFUL?

- The SET has been **validated for detecting NED in patients with peripheral nerve disease** when measuring chronaxie
- NED is diagnosed when **chronaxie is ≥1000 µs** (Normal value- 60 to 200)
- Sensitivity to detect NED ranges from **88 to 100%** when compared with needle electromyography

P.E. Silva et al. Journal of Critical Care 44 (2018) 87–94

STUDY DESIGN	PROSPECTIVE OBSERVATIONAL STUDY
Subjects	49 TBI patients on MV
Objective	Incidence of NED(using SET) and Muscle atrophy
Muscles tested	Tibialis anterior, Rectus Femoris, Biceps Brachialis
Results	**An increase of 48% in NED from day 1 to day 14 was detected in TA** ($p = 0.004$). All muscles presented a **significant decrease in thickness (~18%, $p < 0.05$),** but **echogenicity increased only in TA (19%), $p = 0.01$ and RF (23%), $p = 0.01$.**

P.E. Silva et al. Journal of Critical Care 44 (2018) 87–94

WHY TIBIALIS ANTERIOR?

- Higher incidences of axonopathy in the peroneal nerve
- One hypothesis is related to the **nerve length**.
- The longest nerve in the body and it might become **more vulnerable to the energy deficit caused by tissue ischemia or hypoxia**
- **E-selectin expression in the peripheral-nerve vascular endothelium** which can suggest the presence of endothelial-cell activation and microvascular leaking
- Defective nutrient transport
- Changes in capillary pressure

P.E. Silva et al. Journal of Critical Care 44 (2018) 87–94

EPS

TEST	CIP	CIM
EMG	Fibrillation potentials and positive sharp waves are recorded Motor unit potentials can be normal or mildly myopathic Recruitment- decreased	Fibrillation potentials and positive sharp waves are recorded **Myopathic** motor unit potentials with low amplitude, short duration and **early rapid recruitment**

Bolton et al. Lancet Neurol 2011; 10: 931–41

Richard et al. CHEST 2016; 150(4):966-971

EPS VS CLINICAL TESTING

FOR EARLY EPS	AGAINST EARLY EPS
CIM/CIP may masquerade as coma which is considered a deadly sign in clinical medicine. A confirmed diagnosis may obviate need for pessimistic prognostication	Limitation of EP study due to **technical Difficulties**
EPS **can overcome the disadvantage of clinical examination in that they can be performed even on sedated** and comatose patients	EP testing **cannot predict reversibility** of ICUAW
Early diagnosis	EP also **cannot predict clinically meaningful outcome** e.g. length of mechanical ventilation/ ICU stay etc
Sensitivity higher	As **no specific curative treatment** is available, making a highly specific diagnosis doesn't translate into any benefit in decision making

Schweickert et al chest 2007; 131:1541–1549

SIMPLIFIED EPS

- Measurement of the **nerve action potential amplitude of the peroneal nerve** is a simplified electrophysiologic investigation in critically ill patients
- Reduction of the amplitude **2 standard deviations of the normal value identifies patients with ICU-acquired neuromuscular alterations with 100% sensitivity and 67% specificity**
- **Takes less than 5 mins** as compared to 45 mins to 1 hour for a complete EPS

Latronico et al. Critical Care 2007, 11:R11

SIMPLIFIED EPS AS A SCREENING TOOL

OBSERVER	Latronico et al
Study design	Prospective multicentre study
Subjects	**92 ICU admitted patients more than 15 years age**
Objective	Simplified EPS **of sural and peroneal nerve as good as complete EPS**
Result	A unilateral peroneal CMAP reduction of more than two standard deviations of normal value showed the best combination of sensitivity **(100%) and specificity (67%)** **Median time from ICU admission to CRIMYNE was six days** (95% CI five to nine days).

The test can therefore be proposed as a screening test before a patient's discharge from the ICU or the acute hospital: patients with bilaterally normal peroneal CMAP need no further evaluation

Latronico et al. Critical Care 2007, 11:R11

OBSERVER	Latronico et al
Study design	Multicentre observational study
Subjects	121 adult neurologic and non-neurologic patients with ICU stay ≥ 3 days
Objective	Predictability of abnormal peroneal CMAP for CIP/CIM as compared to conventional eps
Result	**Sensitivity and specificity** of PENT were **100%** (95% CI 96.1-100.0) and **85.2%** (95% CI 66.3-95.8).

Latronico et al. F1000Research 2014, 3:127

DIRECT MUSCLE STIMULATION

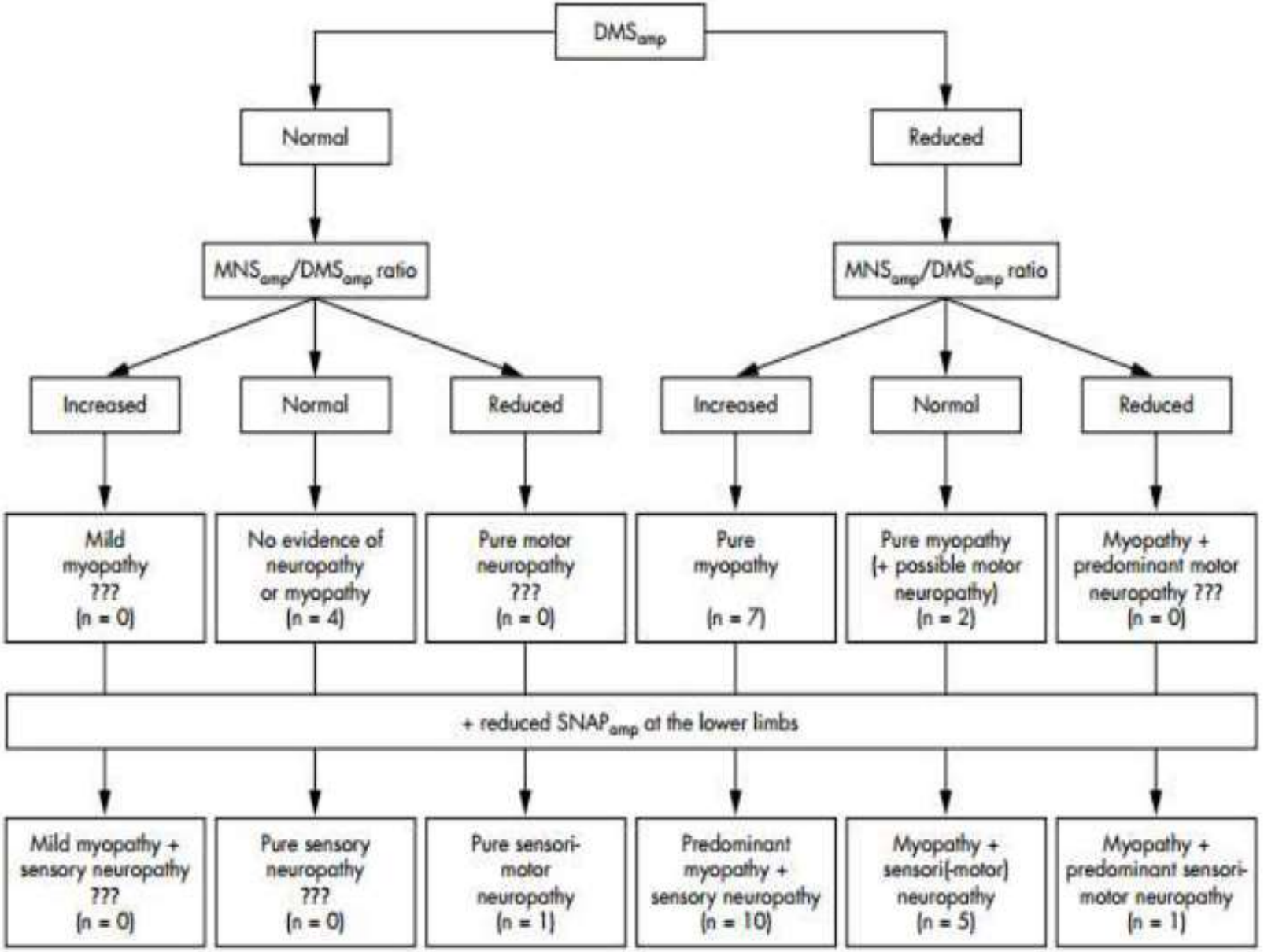
- Direct muscle stimulation enables the investigation of electrical **excitability/inexcitability** of muscle membrane

- Both the stimulating and the recording electrodes are placed in the muscle distal to the end-plate zone

- Using the **ratio of compound muscle action potential amplitude evoked by nerve stimulation to that evoked by direct muscle stimulation, the CIP is diagnosed if the ratio is less than 0.5, whereas CIM is diagnosed if the ratio is more than 0.5**

- Direct muscle stimulation is useful to differentiate CIM from CIP in the ICU setting, however, despite its apparent simplicity, it is technically demanding and requires thorough practice to obtain reliable results.

Latronico et al. Crit Care Med 2009 Vol. 37, No. 10 (Suppl.)



Lefaucher eta J Neurol Neurosurg Psychiatry 2006;77:500–506

BIOPSY

- The definitive diagnosis of muscle involvement requires examination of muscle tissue by biopsy.

➢ **Light-microscopic findings**

✓ Muscle fiber atrophy (preferentially type II fibers),

✓ Occasional fiber necrosis, regeneration, and

✓ Decreased or absent reactivity in myofibrillar adenosine triphosphatase staining, corresponding to a selective loss of myosin filaments

Schweickert et al chest 2007; 131:1541–1549

BIOPSY

- **On electron microscopy**
- ✓ Preferential loss of thick filaments with splitting of A band and loss of normal sarcomeric structure.
- ✓ Mitochondria were often abnormal in size, shape, and distribution, and even in fibers where there appeared to be no loss of myofilaments, mitochondria tended to be elongated in the long axis of muscle fibers

Schweickert et al chest 2007; 131:1541–1549

SDS PAGE ELECTROPHORESIS

- Sodium dodecyl sulfate polyacrylamide gel electrophoresis
- Proposed as a rapid method to diagnose CIM in early stages
- The mean value of Myosin/Actin ratio considered to be diagnostic is **0.37± 0.17** for CIM

Stibler et al. Intensive Care Med (2003) 29:1515–1527

USG EVALUATION OF PERIPHERAL MUSCLE

- Neuromuscular ultrasound (NMUS) is a **new technique to diagnose muscle disorders**
- Can **detect muscle atrophy as well as changes in muscle architecture**
- Muscle **echo intensity may increase** due to an increase in fat and fibrous tissue
- Nerve cross-sectional area (CSA) and echo intensity can be quantified using USG
- Recent studies have shown that **muscle CSA decreases and echogenicity increases with duration of ICU stay**
- But they have not compared these parameters between those with ICUAW and those without ICUAW

Witteveen *et al. Ann. Intensive Care (2017) 7:40*

STUDY DESIGN	PROSPECTIVE - OBSERVATIONAL STUDY (Puthucheary et al)	PROSPECTIVE OBSERVATIONAL STUDY (Cartwright et al)
Objective	Using neuromuscular ultrasound (NMUS) to measure rectus femoris CSA	Assess muscle thickness and echogenicity in critically ill patients
Subjects	63 critically ill patients who were expected to be mechanically ventilated greater than 48 hours, have an ICU length of stay greater than 7 days,	16 patients admitted to the ICU with acute respiratory failure
Method	USG was done to assess CSA of RF on days 1, 3, 7 and 10	Serial USG were done from day 1 to day 14 to assess for echogenicity and thickness
Results	CSA **decreased significantly from days 1 to 7** (−12.5**%; P = .002**) and continued to decrease to day 10 (−17.7%; P < .001). Additionally, **increasing organ failure score correlated with change in rectus femoris CSA (P < .001**).	A **significant increase was found in the gray-scale** mean of the tibialis anterior (138.29 to 166.39, ***P=0.027)*** indicating increased muscle echogenicity. **No significant change in muscle thickness (p > 0.773)** was found in any of the study muscles.

Muscle Nerve. 2015 November ; 52(5): 701–708

GRADES OF ECHOGENICITY

Heckmatt Score

Grade I - Normal (Starry appearance)

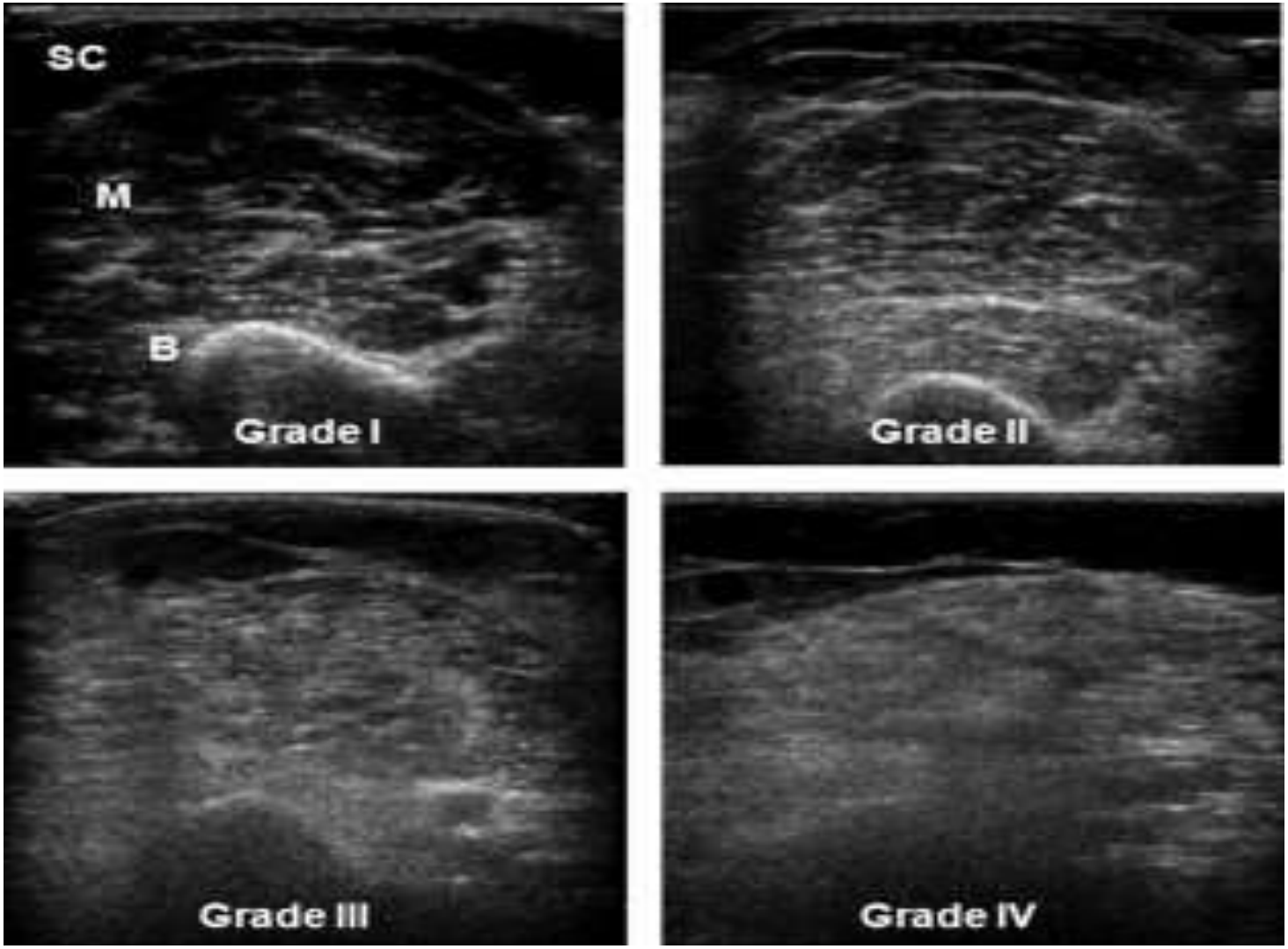
Grade II - Increased muscle echo intensity with distinct bone echo

Grade III - Marked increased muscle echo with reduced bone echo

Grade IV - Very strong muscle echo and complete loss of bone echo

Heckmatt et al. J. Pediatr (101) 5: 656-660

MUSCLE ECHOGENICITY GRADING



ROLE OF USG

STUDY	cross-sectional observational study
Subjects	Consecutive, newly admitted ICU patients, who **were mechanically ventilated for ≥48 h (total 71 patients)**
Place	AMSTERDAM, NETHERLANDS
Objective	Diagnostic accuracy of neuromuscular ultrasound for diagnosing ICU-AW
Method	Patients who got awake were subjected to USG examination **of BB, TA, RF, FCR, median nerve and peroneal nerve** and MRC muscle testing as well
Conclusion	A **single neuromuscular ultrasound at the moment a patient awakens does not discriminate between patients with and without ICU-AW.**

Witteveen et al. Ann. Intensive Care (2017) 7:40

	No ICU-AW	ICU-AW	*P* value	ROC–AUC (95% CI)
Thickness				
BB thickness [mean cm (SD)]	2.6 (0.6)	2.2 (0.5)	0.002*	68.0 (55.4–80.7)
FCR thickness [mean cm (SD)]	1.1 (0.2)	1.0 (0.2)	0.035*	64.5 (50.4–78.7)
RF thickness [mean cm (SD)]	3.1 (0.9)	2.8 (0.8)	0.258	55.6 (41.8–69.4)
TA thickness [mean cm (SD)]	2.2 (0.4)	2.1 (0.4)	0.558	54.3 (40.3–68.3)
Z-score thickness				
BB *z*-score thickness [mean (SD)]	0.1 (0.6)	−0.3 (0.5)	0.011*	66.7 (53.7–79.6)
FCR *z*-score thickness [mean (SD)]	−0.7 (1.2)	−1.3 (0.9)	0.033*	65.5 (51.3–79.7)
RF *z*-score thickness [mean (SD)]	−0.5 (0.7)	−0.6 (0.8)	0.656	53.2 (39.4–67.1)
TA *z*-score thickness [mean (SD)]	−0.4 (0.7)	−0.4 (1.0)	0.818	51.3 (37.5–65.1)
Echo intensity				
BB absolute echo intensity [mean gray scale level (SD)]	76.2 (14.1)	79.1 (16.4)	0.434	57.6 (44.0–71.3)
FCR absolute echo intensity [mean gray scale level (SD)]	62.3 (12.6)	67.7 (13.6)	0.095	63.2 (49.6–76.9)
RF absolute echo intensity [mean gray scale level (SD)]	77.2 (17.0)	83.9 (14.8)	0.094	60.2 (46.4–74.0)
TA absolute echo intensity [mean gray scale level (SD)]	88.6 (12.4)	94.6 (12.1)	0.046*	60.8 (47.4–74.1)
Z-score echo intensity				
BB *z*-score echo intensity [mean (SD)]	0.5 (1.4)	0.7 (1.9)	0.519	56.3 (42.8–69.9)
FCR *z*-score echo intensity [mean (SD)]	1.4 (1.6)	1.9 (2.0)	0.207	59.2 (45.2–73.2)
RF *z*-score echo intensity [mean (SD)]	1.0 (1.6)	1.6 (1.8)	0.137	58.7 (45.0–72.4)
TA *z*-score echo intensity [mean (SD)]	1.0 (1.2)	1.5 (1.4)	0.118	59.4 (45.9–72.9)
Echo intensity SD				
BB echo intensity SD [mean gray scale level(SD)]	29.0 (4.0)	28.5 (4.4)	0.585	53.3 (39.6–67.0)
FCR echo intensity SD [mean gray scale level(SD)]	21.3 (3.1)	20.8 (3.9)	0.573	56.2 (42.2–70.2)
RF echo intensity SD [mean gray scale level(SD)]	24.2 (3.3)	23.5 (3.5)	0.398	55.9 (42.0–69.8)
TA echo intensity SD [mean gray scale level (SD)]	25.8 (3.6)	26.2 (3.9)	0.698	54.4 (40.5–68.3)
Z-score echo intensity SD				
BB *z*-score echo intensity SD [mean (SD)]	0.3 (1.5)	0.1 (1.5)	0.746	53.3 (39.6–67.0)
FCR *z*-score echo intensity SD [mean (SD)]	0.8 (1.4)	0.6 (1.7)	0.716	55.0 (41.0–69.1)
RF *z*-score echo intensity SD [mean (SD)]	0.1 (1.6)	0.04 (1.4)	0.890	54.2 (36.9–65.5)
TA *z*-score echo intensity SD [mean (SD)]	−0.3 (1.1)	−0.2 (1.4)	0.777	55.0 (41.1–68.9)

Witteveen et al. Ann. Intensive Care (2017) 7:40

	No ICU-AW	ICU-AW	*P* value	ROC–AUC (95% CI)
Median nerve				
CSA wrist [mean mm^2 (SD)]	10.7 (3.5)	8.9 (2.1)	0.020*	66.7 (53.6–79.9)
CSA proximal [mean mm^2 (SD)]	7.3 (1.8)	7.6 (1.7)	0.445	52.5 (38.6–66.4)
Thickness proximal [mean mm (SD)]	2.4 (0.4)	2.4 (0.4)	0.977	51.0 (37.2–65.2)
Intraneural vascularization proximal (%)[a]	6 (20.0)	10 (25.6)	0.793	
Peroneal nerve				
CSA fibular head [mean mm^2 (SD)]	10.8 (3.5)	11.7 (5.0)	0.504	53.1 (35.6–70.7)
CSA knee fold [mean mm^2(SD)]	8.2 (3.3)	8.2 (3.0)	0.999	52.4 (36.9–67.9)
Thickness knee fold [mean mm (SD)]	2.2 (0.4)	2.3 (0.4)	0.505	54.6 (38.9–70.2)
Intraneural vascularization proximal (%)[a]	3 (12.0)	4 (14.3)	1.000	

Witteveen et al. Ann. Intensive Care (2017) 7:40

WHY DISCREPANCY?

- A diagnosis of ICU-AW before awakening (before muscle strength measurements are possible) is more desirable, because an early diagnosis is a prerequisite for any future preventive measure or treatment to be implemented

- Since diagnostic accuracy of NMUS at awakening was poor, it is less likely that differences in thickness and echo intensity will be more noticeable before this time point

- Muscle thickness and echo intensity can be influenced by **confounding factors, like excessive fluid administration, often present in the first days after ICU admission, impairing the use of NMUS for early diagnosis of ICU-AW**.

Witteveen et al. Ann. Intensive Care (2017) 7:40

FUTURE PROSPECTS

- The rate at which muscle size decreases or echo intensity increases can discriminate between ICU-AW and no ICU-AW.
- This would require serial assessments with ultrasound in the first few days after ICU admission to acquire an early diagnosis

Witteveen et al. Ann. Intensive Care (2017) 7:40

USG FOR PERIPHERAL NERVE ASSESSMENT

- It is hypothesized that nerve damage in ICU-AW may be caused by increased vascular permeability causing endoneurial edema and subsequent hypoxia
- To compensate, perineural veins may dilate and cause hyperemia and hyper vascularization, which could be detected by NMUS
- However, there were **no differences between patients with and without ICU-AW**.

Witteveen et al. Ann. Intensive Care (2017) 7:40

QUALITATIVE USG FOR ECHOGENICITY

- Skeletal muscle function depends not only on its quantity but its quality, which may be adversely affected and **hence USG can detect these qualitative changes at an earlier timepoint** than quantitative USG
- **Early stages of CIM (1-3 days)** - edema, neutrophil infiltration, and fibrin deposition, macrophage-rich cellular fasciitis extending deeper within the muscle fascicles
  - **USG shows increased fascial echogenicity**
- **Late stages (7- 10 days)** - myofiber necrosis and muscle regeneration
  - **USG shows increased muscle echogenicity**

Puthucheary et al. Crit Care Med 2015; 43:1603–1611

QUALITATIVE USG

Study	Prospective two center observational study.
Observer	Puthucheary et al
Subjects	30 critrically ill patients on MV
Method	Muscle biopsy of Vastus lateralis and facial and muscle echogenicity of RF muscle tested on day 1 and day 10
Results	Change **in fascial echogenicity correlated better with change in RF echogenicity** (r2 = 0.22 [95% CI, 0.116–0.750]; p = **0.009**).

Puthucheary et al. Crit Care Med 2015; 43:1603–1611

ROLE OF CT MUSCLE VOLUMETRY SCAN

- Muscle volume is the strongest predictor of resting energy expenditure
- **An observational study was conducted on 7 patients > 40 years age admitted in ICU**
- CT muscle evaluation is useful to **compare the femoral muscle volume change with muscle volume changes in other body parts**

Sonoo et al., J Med Diagn Meth 2018, 7:1

CT VOLUMETRY SCAN

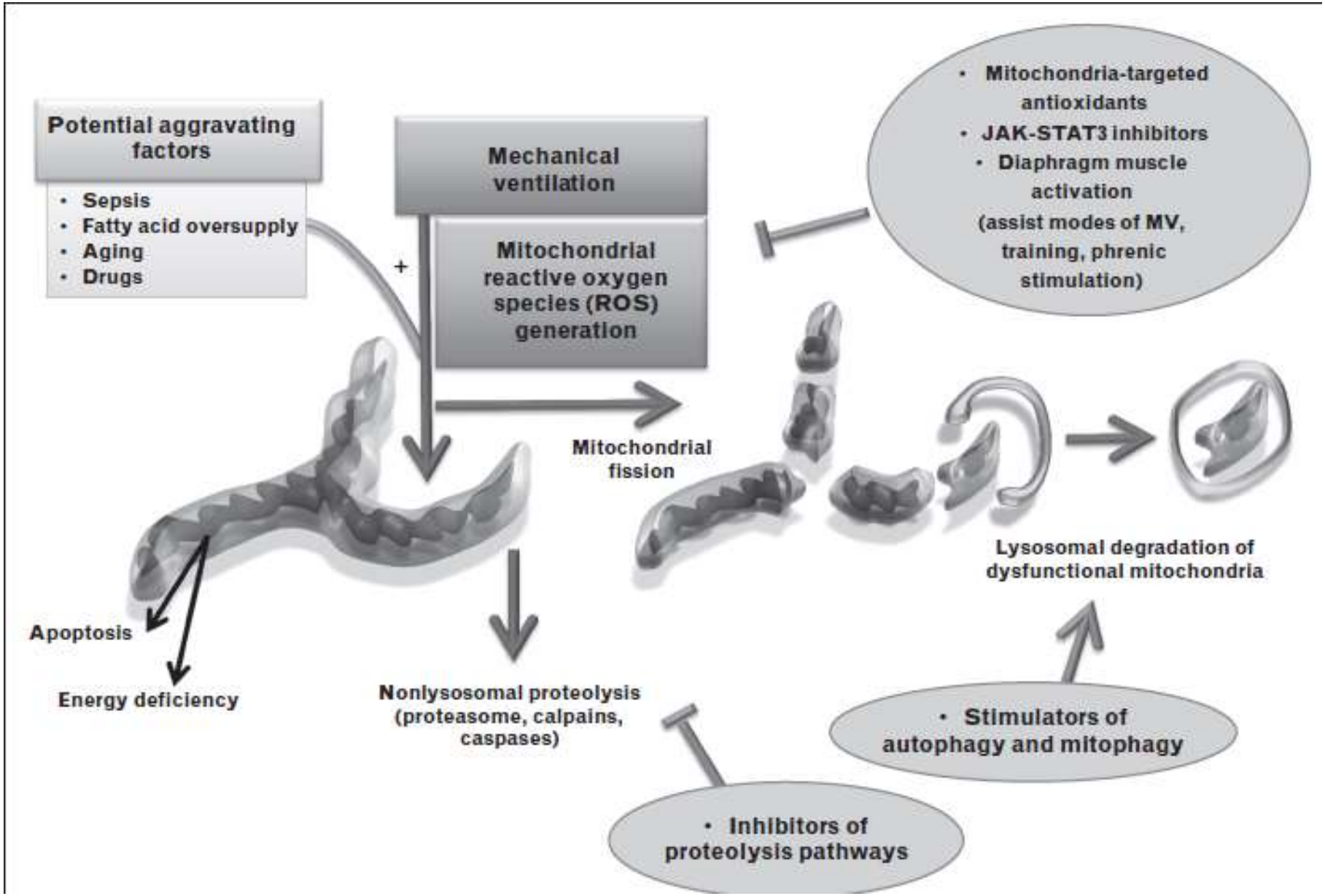
- Volumetric CT was done at admission and 2nd scan between 10- 14 days after admission
- Comparison made between Femoral muscles and psoas muscles
- **Femoral muscle volume declined considerably, by about 20%, from the baseline value (P= 0.001)**
- Regarding the psoas muscle, a slight but non-significant decreasing tendency was found **(P= 0.07)**
- **CT can be used as a reliable method of assessing for ICUAW**

Sonoo et al., J Med Diagn Meth 2018, 7:1

VIDD

- Ventilator induced Diaphragmatic dysfunction
- **Loss of Diaphragmatic force-generating capacity specifically related to the use of mechanical ventilation**
- VIDD has been documented to **occur as early as 24 hours after MV**
- During weaning the diaphragm becomes the major pathophysiological determinant of weaning failure or success.
- VIDD develops during **control modes of ventilation**, but **can occur in partial support modes as well**, when the support is excessive, but at a later time point
- **Longer the duration** of CMV, greater the degree of atrophy and contractile impairment.

Demoule et al. Am J Respir Crit Care Med. 2013 ;188(2):213-9
Sigala et al. Ann Transl Med 2017;5(4):79
Petrof et al. Curr Opin Crit Care 2016, 22:67–72



Petrof et al. Curr Opin Crit Care 2016, 22:67–72

METHODS OF ASSESSING DIAPHRAGMATIC WEAKNESS

- CXR
- Fluoroscope
- MIP
- Diaphragmatic EMG
- Transdiaphragmatic pressure
- Phrenic nerve stimulation
- USG
- Newer modalities

X RAY

- Conventional radiography can be used for evaluating the position (chest X-ray) and motion (fluoroscopy) of the diaphragm.
- The dome of **the right hemidiaphragm overlaps anteriorly with the fifth rib and posteriorly with the tenth rib**, and the dome of the left hemidiaphragm is one interspace lower than the right
- **Bilateral, smooth elevation of the hemidiaphragms and small lung volumes are usually seen,** and the costophrenic and costovertebral sulci are deep and narrow. The lateral view confirms a smooth contour and elevated diaphragmatic position.
- Non- specific

Kharma et al. Curr Opin Pulm Med 2013, 19:394–398

FLUOROSCOPE

- Compared with chest X-ray, fluoroscopy provides more **dynamic information** and can be used to detect unilateral diaphragm paralysis
- In weakness of one or both hemi-diaphragms, **excursion is reduced or delayed on quiet and deep inspiration.**
- In case of **severe weakness, paradoxical movement** is seen
- But its **utility is limited in ICU settings as usually CIN/CIM is associated with bilateral diaphragmatic weakness** and false negative test can be seen due to active contraction of the abdominal muscles during expiration, followed by abrupt relaxation of the abdominal muscles at the onset of inspiration, resulting in downward motion of the paralyzed diaphragm.

Kharma et al. Curr Opin Pulm Med 2013, 19:394–398

MIP- MAXIMUM INSPIRATORY PRESSURE

- MIP- (PI_{max}) can be measured in an intubated patient

➢ If conscious and on support mode of ventilation- ask to perform Mueller maneuver

➢ If sedated – give end expiratory pause of 20 seconds

- Expected- **more than 30 cmH2O negative pressure** predicts successful extubation

Doorduin et al. Am J Respir Crit Care Med. 2013 Jan : 187(1); 20–27

DIAPHRAGMATIC EMG

EMG of the diaphragm may be useful in distinguishing between **neuropathic and myopathic causes** of diaphragmatic dysfunction

Two methods

1. Esophageal catheter with electrodes
   - **Less affected by increased adiposity, artefacts**, and interference from adjacent muscles
   - The signals are amplified by a gain of 1000 and the root mean square is given which gives the number and rate of firing of the recruited motor units

Clin Sci (Lond). 2008 Oct;115(8):233-44

DIAPHRAGMATIC EMG

2. Needle EMG

- The EMG needle electrode is inserted under the costal margin behind the eighth, ninth, or tenth rib cartilage
- The presence of fibrillation potentials and positive sharp waves is strongly suggestive of neurogenic impairment

Clin Sci (Lond). 2008 Oct;115(8):233-44

ESOPHAGEAL CATHETER EMG

- Amplitude of the electrical activity of the diaphragm (EAdi) is recorded by the electrodes

3 implications :

➢ Respiratory muscle loading assessment :

- **The ratio of actual EAdi to maximum EAdi is a measure of the patient's effort to breath**, in which maximum EAdi can be defined as the peak activity observed during a 20-second inspiratory occlusion

Doorduin et al. Am J Respir Crit Care Med. 2013 Jan : 187(1); 20–27

ESOPHAGEAL CATHETER METHOD

- EAdi/max EAdi = if very low, **high ventilatory support**, poor diaphragm loading, **chance of diaphragm atrophy**
- EAdi/maxEAdi = if high, **low ventilatory support**, high diaphragm loading, distress and fatiguability

➢ <u>Patient-ventilator synchrony</u>

- Continuously monitoring the EAdi helps in better triggering and cycling synchrony

Doorduin et al. Am J Respir Crit Care Med. 2013 Jan : 187(1); 20–27

ESOPHAGEAL CATHETER EMG

- Neuroventilator and Neuromechanical efficiency:

- **NVE** (Vt/EAdi) – ratio of tidal volume and EAdi

  Higher the value, the better the chances of successful extubation

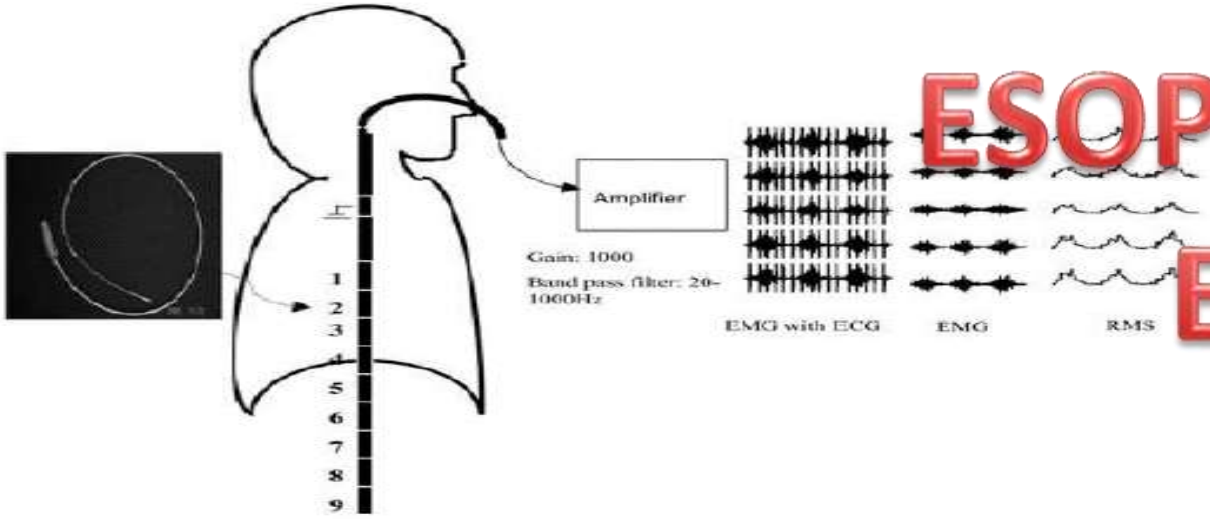
- **NME** (Pdi/EAdi) – ratio of transdiaphragmatic pressure to EAdi

  - A gradual decrease in NME over days indicates the development of diaphragm weakness, whereas an increase suggests recovery.

  - Also NME is not affected by diaphragmatic load

Doorduin et al. Am J Respir Crit Care Med. 2013 Jan : 187(1); 20–27

NEEDLE EMG



ESOPHAGEAL EMG

TRANSDIAPHRAGMATIC PRESSURE (PDI)

- A measurement of **maximal diaphragmatic force generating capacity is the gold standard to assess diaphragm muscle dysfunction**
- Pdi is the difference between abdominal and pleural pressure. In practice, the difference between esophageal (Pes) and gastric pressure (Pga) is used to calculate Pdi

  Tdi = Pga- Pes

N Engl J Med 2012;366:932-42

Doorduin. Am J Respir Crit Care Med jan 2013;187:20-27

TRANSDIAPHRAGMATIC PRESSURE (PDI)

- Obtained by having the patients inspire as forcefully as possible against a closed airway or by having the patient sniff forcefully
- **Gilbert index (DPga/DPdi)** can be used to determine the relative contribution of the diaphragm to inspiration
- Gilbert index **is directly proportional to inspiratory effort of the diaphragm**

Doorduin. Am J Respir Crit Care Med jan 2013;187:20-27

TRANSDIAPHRAGMATIC PRESSURE (PDI)

Three types of measurements

- Sniff Pdi: after maximal sniff maneuver
- Pdi max: Inspiring against closed glottis
- Twitch Pdi: after phrenic nerve stimulation

✓ **Sniff Pdi or Pdi max >80cmH2O (men) and >70cmH2O (women) rules out clinically significant diaphragmatic weakness**

- Twitch Pdi is effort independent and can assess each hemidiaphragm separately

✓ **Twitch Pdi >10 cmH2O with unilateral phrenic nerve stimulation or >20 cmH2O with bilateral phrenic nerve** simulation also rules out clinically significant diaphragmatic weakness

N Engl J Med 2012;366:932-42

TRANSDIAPHRAGMATIC PRESSURE (PDI)

- Pdi is influenced by positive pressure of the mechanical ventilator **and ideally should be measured during a trial of spontaneous breathing**
- Invasive and technically difficult procedure
- Hence difficult to be used routinely in ICU settings

N Engl J Med 2012;366:932-42

Doorduin. Am J Respir Crit Care Med Vol 187, Iss. 1, pp 20–27, Jan 1, 2013

PHRENIC NERVE STIMULATION

- Magnetic phrenic nerve stimulation allows non-voluntary evaluation of diaphragm strength
- Twitch transdiaphragmatic pressure and **CMAP** of the diaphragm can be recorded and phrenic nerve conduction velocity can be calculated
- Thus can be used to identify **phrenic nerve injuries and also diaphragmatic weakness**
- It is not applicable for routine bedside monitoring because of the fairly invasive nature, technical difficulties

Doorduin. Am J Respir Crit Care Med Vol 187, Iss. 1, pp 20–27, Jan 1, 2013

SIGNIFICANCE OF ULTRASOUND AS DIAPHRAGMATIC ASSESSMENT TOOL

- Easy applicability, low cost, non-invasiveness, fast learning curve

- Diaphragmatic ultrasound using **either excursion or thickening fraction has been demonstrated to perform at least equally or even better** to other established weaning indices like rapid shallow breathing index**-RSBI and maximum inspiratory pressure-PI,max**

Sigala et al. Ann Transl Med 2017;5(4):79

SIGNIFICANCE OF ULTRASOUND AS DIAPHRAGMATIC ASSESSMENT TOOL

- RSBI, or PI,max are an indirect (RSBI) or direct (PI,max) assessment of all respiratory muscles acting together-meaning that in case of diaphragmatic weakness tidal volume or pressure generation can be preserved with the **compensatory recruitment-increased work of the other inspiratory and accessory inspiratory muscles**. In contrast, ultrasound permits direct assessment of diaphragm function *per se.*

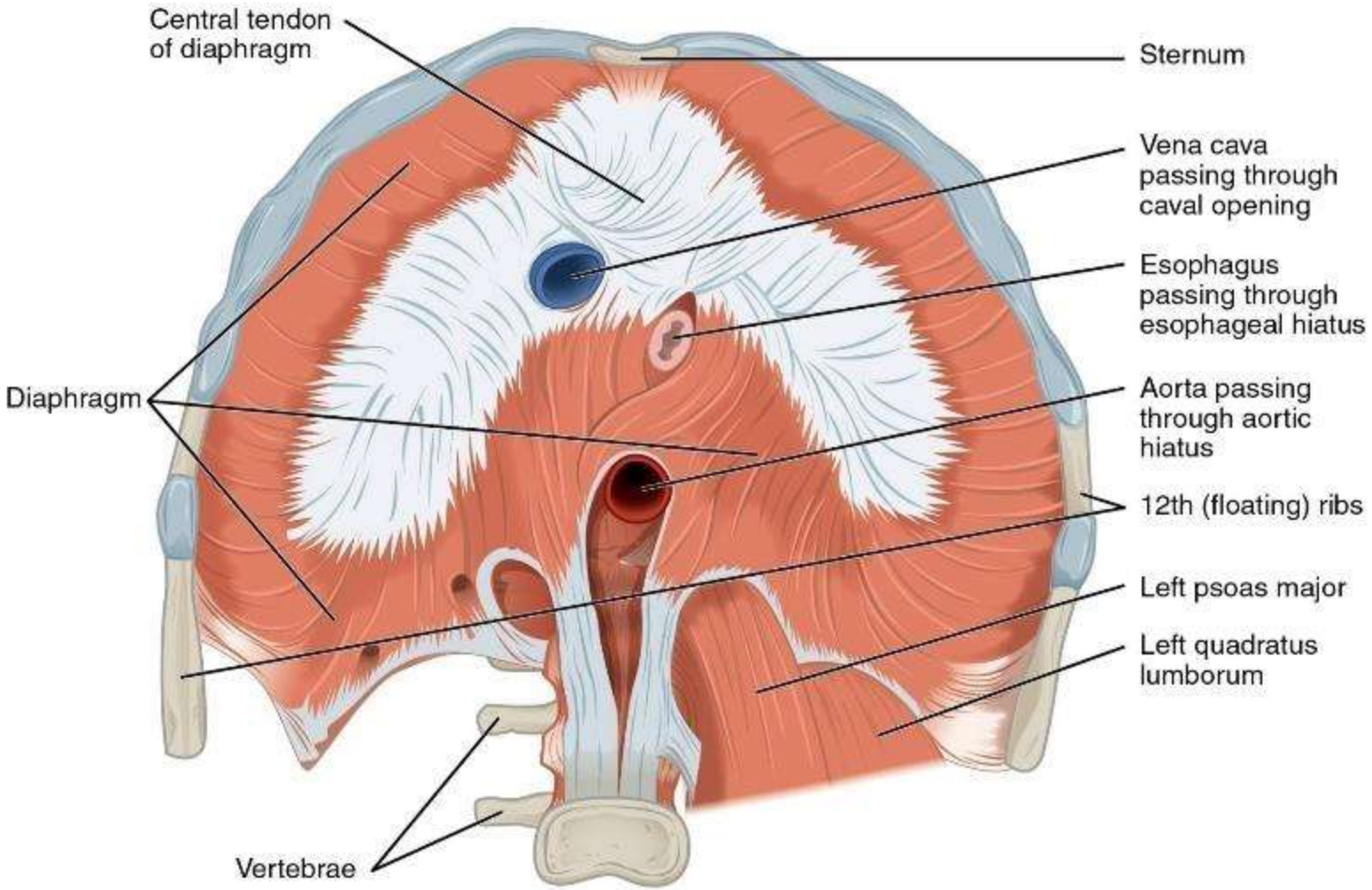
Sigala et al. Ann Transl Med 2017;5(4):79

USG APPEARANCE OF DIAPHRAGM

- The diaphragm is composed of 4 components: transverse septum (which is anterior and becomes the **central tendon** of the diaphragm), **pleuroperitoneal** folds**, esophageal mesentery**, and **muscular body wall laterally**

- Ultrasound focuses mainly on the posterior and lateral parts of the diaphragm, which are the muscular crural components **innervated by the phrenic nerve**, rather than the **anterior central tendon** seen in **fluoroscopy, which moves 40% less with respiration**

Muscle Nerve. 2013 March ; 47(3): 319–329



Diaphragm (inferior view)

USG TECHNIQUE

- **Supine position-**

✓ Diaphragm excursion is known to be greater

✓ Abdominal viscera more easily move the diaphragm in this position

✓ Exaggerates any paradoxical movement

- **Laterality-**

✓ The right diaphragm can be visualized through the liver window. Visualization of the left diaphragm is more difficult because of the smaller window of the spleen

✓ Excursion usually **greater on the left side hemidiaphragm than the right side** with the **difference in excursion less than 50 %**

Muscle Nerve. 2013 March ; 47(3): 319–329

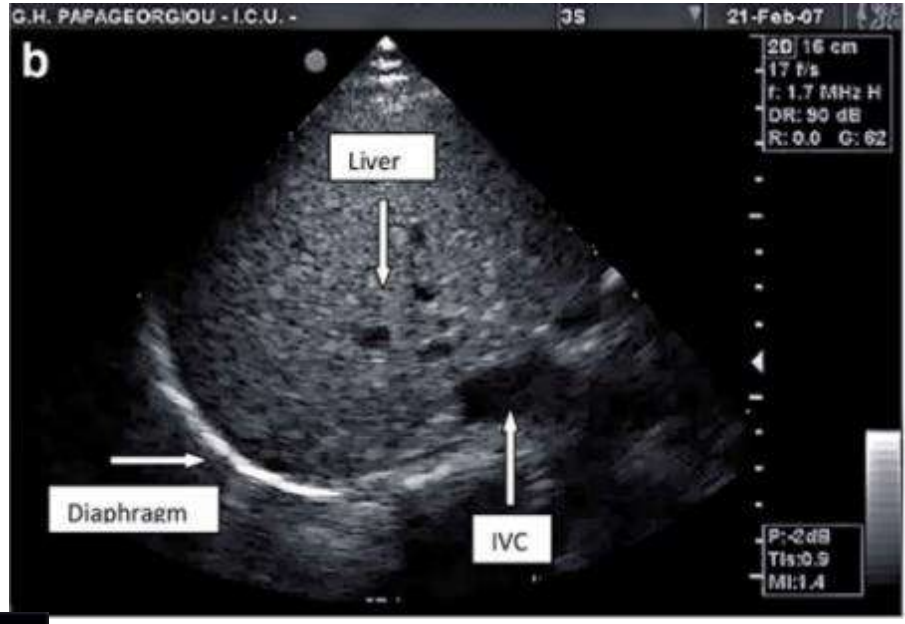
- Views
  - Intercostal view- challenging and difficult, cannot be done in deep inspiration as it is based only on the zone of apposition
  - **Anterior subcostal view- preferred method**
  - Posterior subcostal view- similar to the anterior subcostal view
  - Sub xiphoid view- useful in children

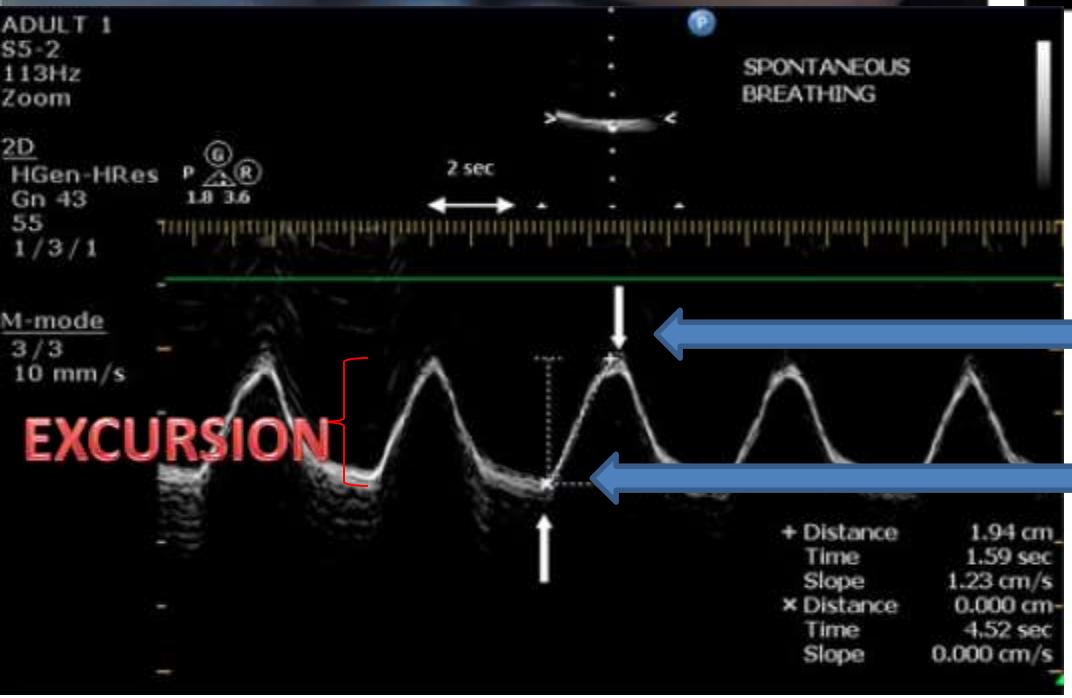
Muscle Nerve. 2013 March ; 47(3): 319–329

TECHNIQUE TO LOOK FOR EXCURSION

- Diaphragmatic sonography is performed using a **3.5–5 MHz** phased array probe
- It is placed immediately **below the right or left costal margin** in the **mid-clavicular line, or in the right or left anterior axillary line** and is directed cranially, medially and dorsally
- The two-dimensional **(2D) mode** is initially used to obtain the best approach and select the **exploration line**
- The **M-mode** is then used to display the motion of the anatomical structures along the selected line, so that the ultrasound beam reaches perpendicularly the posterior third of the corresponding hemi-diaphragm
- Normal inspiratory diaphragmatic movement is caudal

Matamis et al. Intensive Care Med
DOI 10.1007/s00134-013-2823-1





END OF INSPIRATION

END OF EXPIRATION

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TECHNIQUE

- Normal expiratory trace is cranial, as the diaphragm moves away from the probe
- The diaphragmatic excursion (displacement, cm), the speed of diaphragmatic contraction (slope, cm/s), the inspiratory time (Tinsp, s) and the duration of the cycle (Ttot, s) can be measured
- The values of diaphragmatic excursion in healthy individuals were reported to **be 1.8 ± 0.3, 7.0 ± 0.6 and 2.9 ± 0.6 cm for males, and 1.6 ± 0.3, 5.7 ± 1.0, and 2.6 ± 0.5 cm for females**, during quiet, deep breathing and voluntary sniffing, respectively

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TECHNIQUE- FOR MEASURING THICKNESS

- The zone of apposition is the area of the chest wall where the abdominal contents reach the lower rib cage
- In this area, the diaphragm is observed as a structure made of three distinct layers : a non-echogenic central layer bordered by two echogenic layers, the peritoneum and the diaphragmatic pleurae
- **Linear high-frequency probe (10 MHz) is used**
- Diaphragmatic thickness can be measured during quiet spontaneous breathing and during a maximal inspiratory and expiratory effort
- **TF = thickness at end inspiration- thickness at end-expiration/thickness at end-expiration.**

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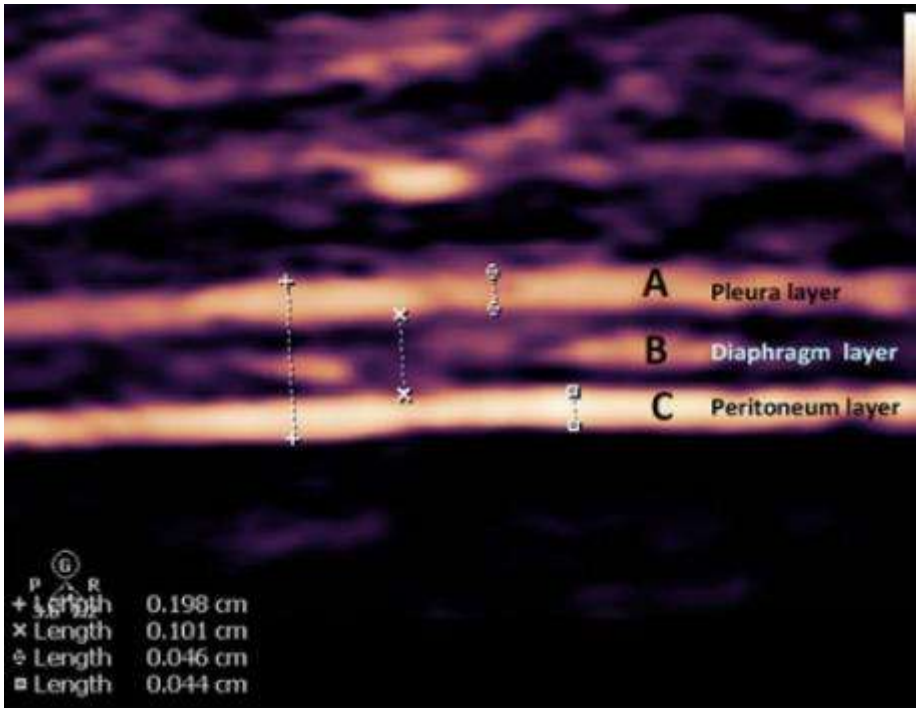
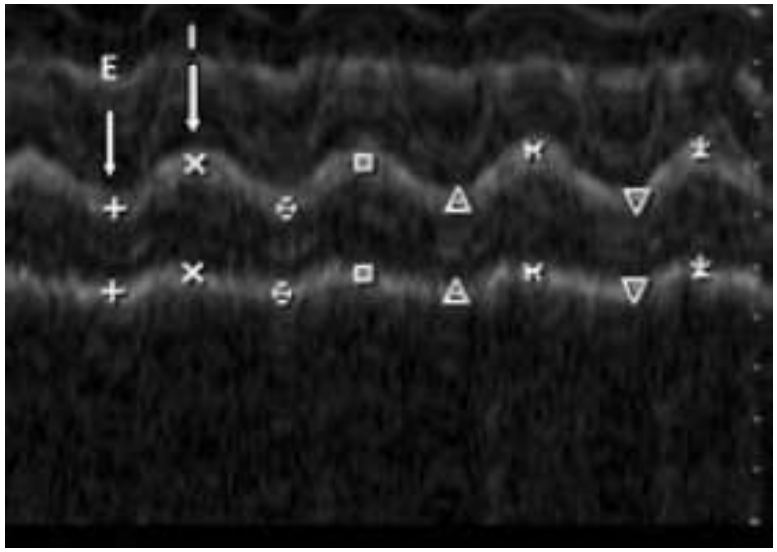


DIAPHRAGM THICKNESS



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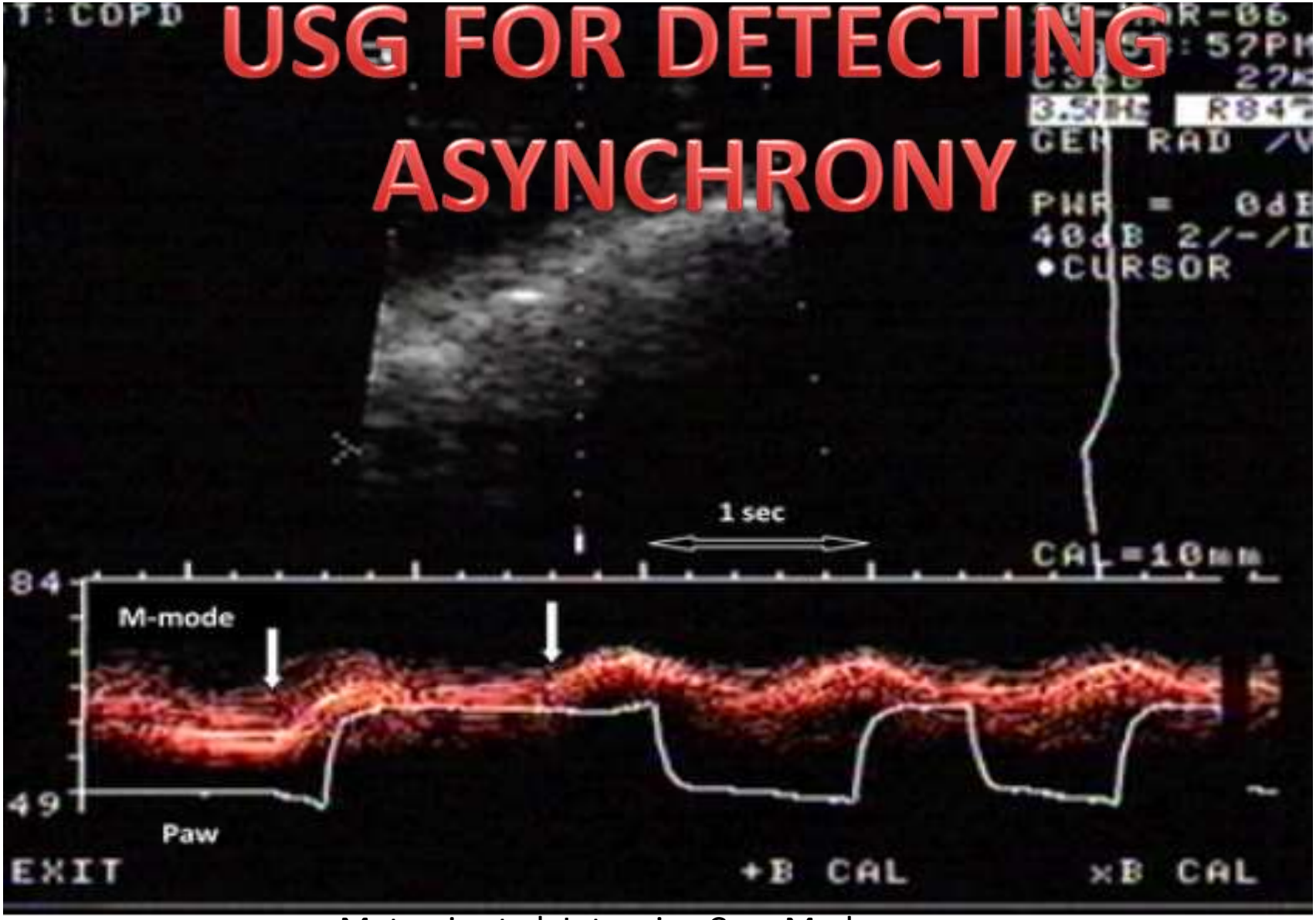
USG FOR DETECTING ASYNCHRONY



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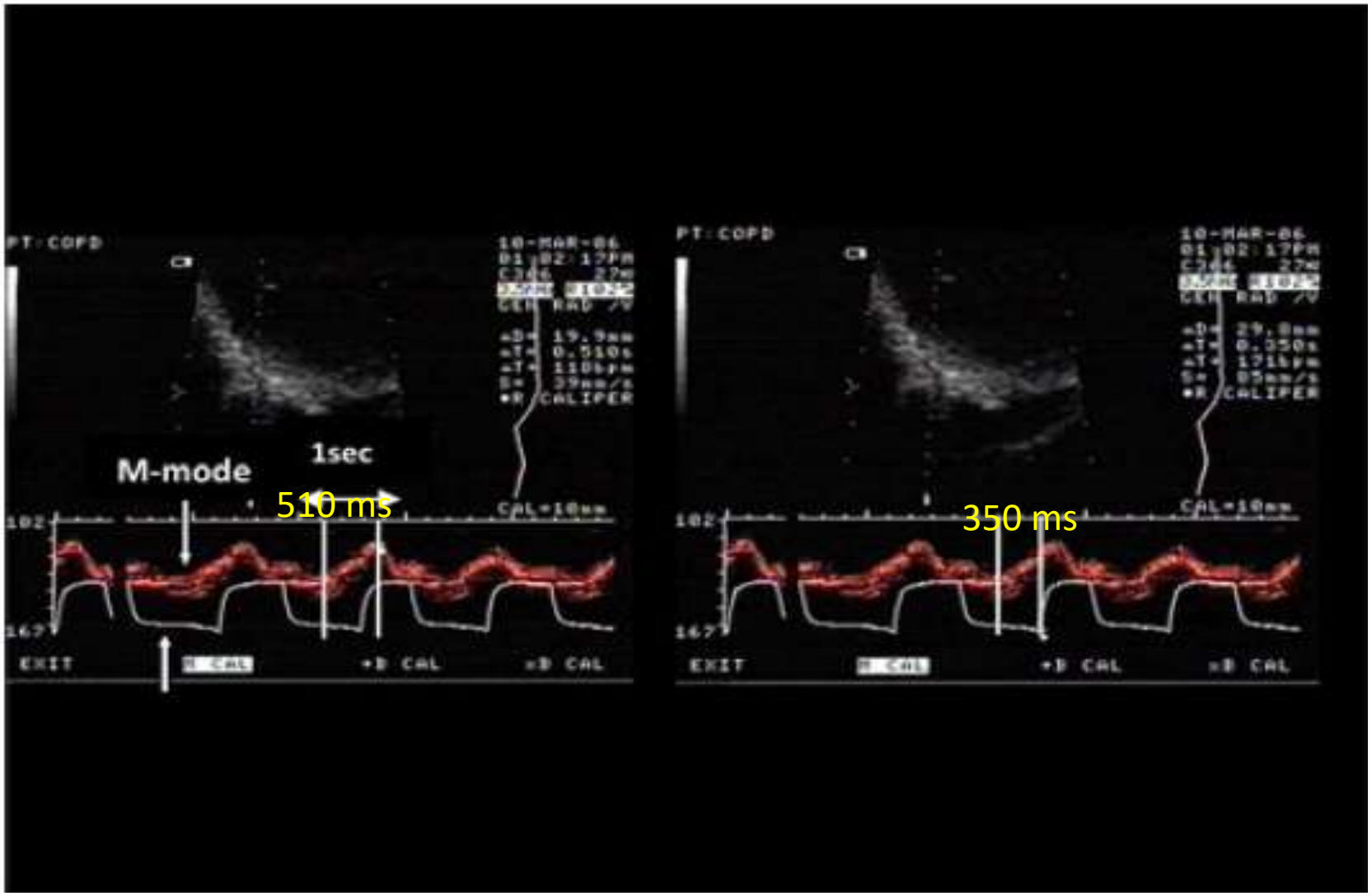

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ULTRASOUND IN DIAPHRAGMATIC ASSESSMENT

The mean thickness of diaphragm is **1.7 – 2** millimetre (mm) (95% CI: 1.7–2.0 mm) as evaluated in 109 healthy subjects when measured in the zone of apposition

In healthy individuals thickening has an extremely large range with values ranging from **24.5% to 53.2%** during normal breathing, up to 131% during forceful inspiration

There is a **decline in diaphragmatic thickness of 6% per day in MV patients**

Sigala et al. Ann Transl Med 2017;5(4):79

Haaksma et al. Intensive Care Med 2017;43:29-38

STUDY DESIGN	PROSPECTIVE STUDY
SUBJECTS	25 post surgery patients admitted in ICU fit for SBT
OBJECTIVE	Performance of ultrasonographic **respiratory excursion** and **thickening** in comparison to inspiratory muscle effort during assisted mechanical ventilation
METHOD	Patients fit for SBT were put on varying levels of pressure support (0, 5, 15) and excursion and thickness of right hemidiaphragm checked
RESULTS	Increasing levels of PS- Diaphragm **thickness (p< 0.001)** and Esophageal pressure time decreased significantly (**p< 0.001)** **No significant change in diaphragm excursion** and esophageal pressure time with increasing pressure support (p = 0.981 and p= 0.506)

Umbrello et al. Critical Care (2015) 19:161

STUDY	PROSPECTIVE OBSERVATIONAL STUDY
OBJECTIVE	To compare the USG indices (TFdi, EXdi and thickness) with gold standard Ptr, stim for diaphragm dysfunction
Subjects	112 patients in ICU expected to be on MV for > 24 hours
Method	At baseline and at the time of switch to pressure support mode, all the above parameters measured
Results	**Tfdi (p < 0.001)_and Exdi (p= 0.001)** correlated well with Ptr stim and thickness did not correlate (p= 0.28)

Dube et al. Thorax, BMJ Publishing Group, 2017, <10.1136/thoraxjnl-2016-209459>. <hal-01510951>

- At switch to PSV**, a TFdi <29%** (95% CI 25–30) could detect diaphragm dysfunction with a **sensitivity of 85% and specificity of 88%, with positive and negative values of 93% and 74%, respectively.**
- The advantage of Tfdi over diaphragm thickness is that it can detect even acute paralysis/weakness of the diaphragm

Dube et al. Thorax, BMJ Publishing Group, 2017, <10.1136/thoraxjnl-2016-209459>. <hal-01510951>

Matamis et al. Intensive Care Med DOI 10.1007/s00134-013-2823-1

APPLICATION OF USG IN THE PREVENTION OF VIDD

- A study was conducted on using diaphragm thickness and excursion measured by ultrasound as a predictor of weaning outcome and to assess the **risk factors for VIDD in an adult intensive care unit (ICU) and evaluating the possible protective indices against VIDD.**
- It was a prospective study conducted on 60 MV patients with matched non- MV healthy individuals as controls
- Diaphragmatic thickness, DTF and excursion were measured daily until 14 days or until extubation/ death

Ali et al. Egyptian Journal of Chest Diseases and Tuberculosis 66 (2017) 339–351

- Results –
- **Significant decrease in the MDT, DTF and mean diaphragmatic excursion with increased length and duration of mechanical ventilation**. the maximum diaphragmatic changes occurred **early in the first 3 days after MV.** Cutoff values for diaphragmatic ultrasound predicting successful weaning were **MDT >2 mm, DTF >30% and DE >1.5 cm.**
- **Early switch from controlled MV to assist ventilation** (addition of PS and or PEEP) was associated with reversal of VIDD

Ali et al. Egyptian Journal of Chest Diseases and Tuberculosis 66 (2017) 339–351

Variables	Mechanically ventilated patients (N = 60)		Healthy control volunteers (N = 20)	P value
	Short duration of MV (25/60) (41.7%)	Long duration of MV (35/60) (58.3%)		
MDT(mean diaphragmatic thickness) (mm)	2.1 ± 12.33	1.3 ± 13.54	2.61 ± 17.33	0.01
DTF (diaphragmatic thickness fraction) (%)	45 ± 20.51	37 ± 21.67	50 ± 29.35	0.01

Variables	Mechanically ventilated patients (N = 60)		Healthy control volunteers (N = 20)	P value
	Short duration of MV (25/60) (41.7%)	Long duration of MV (35/60) (58.3%)		
MDT(mean diaphragmatic excursion) (cm)	2.0 ± 17.23	1.5 ± 19.33	2.4 ± 11.12	0.01

Variables	Cutoff value	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
MDT (mean diaphragmatic thickness) (mm)	>2 mm	79.3%	77.7%	89%	69.9%	85%	0.01
DTF (diaphragmatic thickness fraction) (%)	> 30%	97.3%	85.2%	94.4%	90.6%	91.9%	<0.001
DE (Mean diaphragmatic excursion) (cm)	>1.5 cm	88.7%	84.3%	92.6%	81.3%	87.9%	<0.001

Ali et al. Egyptian Journal of Chest Diseases and Tuberculosis 66 (2017) 339–351

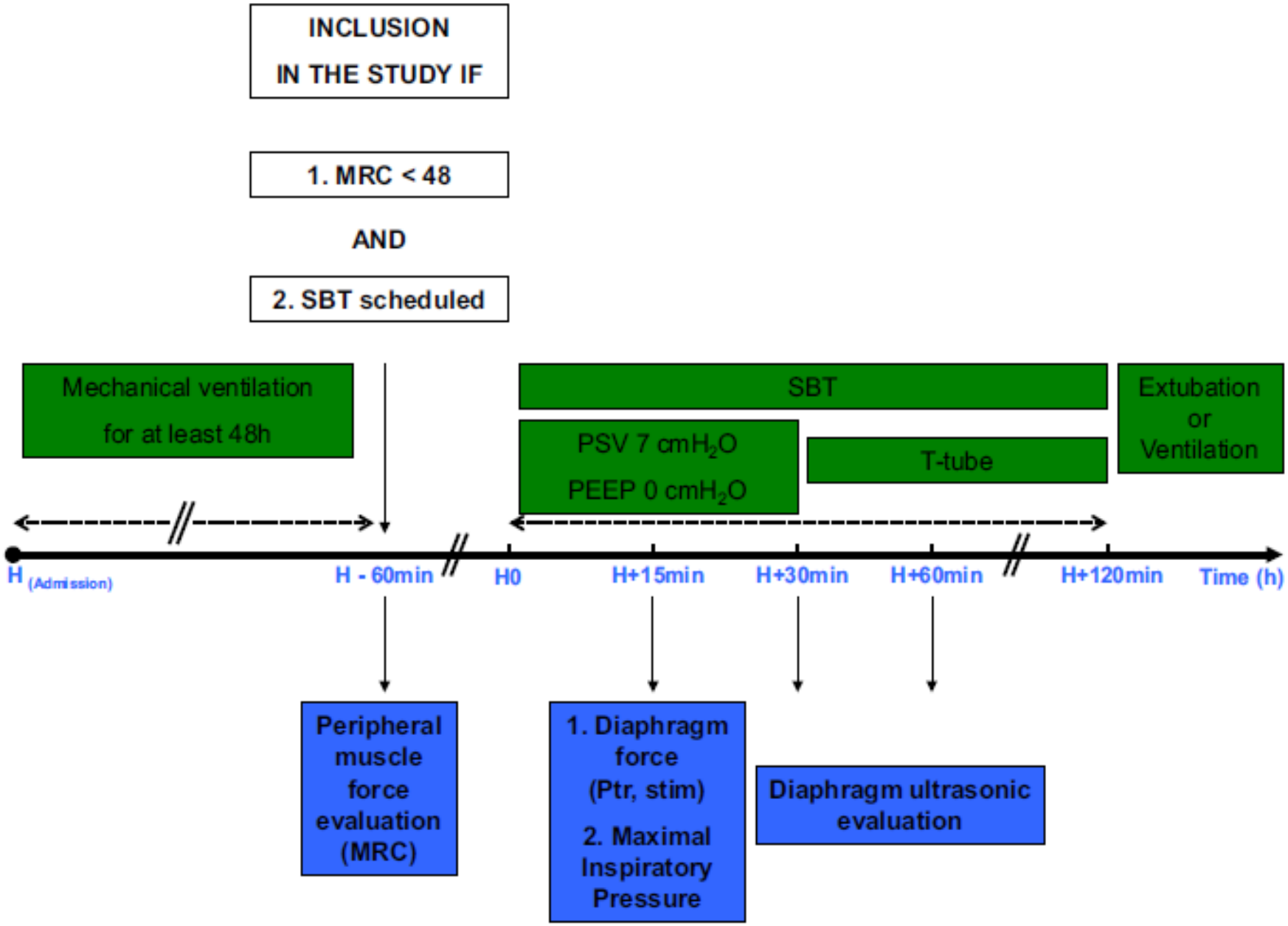
Ventilator parameters	MDT (mm) (Mean ± SD)	P value	DTF (%) (Mean ± SD)	P value	DE (cm) (Mean ± SD)	P value
TV (tidal volume)						
Low TV	2.2 ± 1.4	<0.001	52.6 ± 13.2	<0.001	1.93 ± 1.10	0.01
High TV	1.4 ± 2.2		26.2 ± 11.4		1.14 ± 1.13	
RR (respiratory rate)						
Low RR	1.1 ± 5.2	<0.001	29.2 ± 1.23	<0.001	1.22 ± 1.68	0.01
High RR	2.1 ± 3.4		50.7 ± 1.27		1.89 ± 1.75	
PEEP (positive end expiratory pressure)						
With PEEP	2.1 ± 5.2	<0.001	52.7 ± 15.9	<0.001	1.99 ± 1.70	0.01
Without PEEP	1.1 ± 3.6		28.2 ± 9.9		1.12 ± 1.98	
PS (pressure support) Time for switch from CV (controlled ventilation) to AV (assist ventilation)						
Early (Rapid) switch	2.4 ± 1.21	<0.001	51.9 ± 15.1	<0.001	1.44 ± 1.30	0.01
Late switch	1.1 ± 5.28		31.2 ± 14.3		1.10 ± 1.24	
Value of PS						
No PS (PS 0)	1.1 ± 5.8		19.0 ± 13.2		1.24 ± 1.98	
Low PS <12 (5–12)	2.4 ± 9.7	<0.001	54.7 ± 15.2	<0.001	1.92 ± 1.70	0.01
High PS >12	1.3 ± 4.4		26.4 ± 12.4		1.35 ± 1.73	

Ali et al. Egyptian Journal of Chest Diseases and Tuberculosis 66 (2017) 339–351

DIAPHRAGMATIC DYSFUNCTION IN ICUAW

STUDY DESIGN	Prospective observational study
Subjects	Diagnosed for ICUAW [Medical Research Council (MRC) Score\48], mechanically ventilated for at least 48 h and were undergoing a spontaneous breathing trial (**n= 85)**
Objective	The aim of the present study was to **evaluate the diaphragm function and the outcome using a multimodal approach in ICUAW patients**
Method	MIP, Phrenic nerve stimulation, USG diaphragm thickness
Results	•**Diaphragm dysfunction was observed with ICUAW in 32 patients (80 %).** MIP correlates with change in (p = 0.005) endotracheal pressure. TF correlates with change in endotracheal pressure (p=0.02)

Jung et al. Intensive Care Med (2016) 42:853–861



Jung et al. Intensive Care Med (2016) 42:853–861

	All patients ($n = 40$)	Weaning success ($n = 20$)	Weaning failure ($n = 20$)	p
Age (years)	58 (51–67)	56 (50–65)	63 (55–76)	0.1
Male (sex)	25 (63)	11 (55)	14 (70)	0.5
Body mass index (kg/m^2)	25 (22–28)	27 (23–29)	25 (21–26)	0.1
IGSII	51 (42–60)	47 (41–55)	55 (49–63)	0.07
SOFA	10 (7–14)	8 (6–13)	11 (9–15)	0.1
Comorbidities				
Arterial hypertension	10 (25)	5 (25)	4 (10)	1
Coronaropathy	2 (5)	1 (5)	1 (5)	1
Myocardial insufficiency	4 (10)	1 (5)	3 (15)	1
COPD	5 (13)	1 (5)	4 (20)	0.3
Cancer	12 (30)	5 (25)	7 (35)	0.7
Liver cirrhosis	16 (40)	9 (45)	7 (35)	0.7
Upon ICU admission				
Recent surgery	29 (73)	14 (70)	15 (75)	1
Septic shock	35 (88)	16 (80)	19 (95)	0.3
ICU LOS, days	25 (15–35)	28 (14–33)	24 (15–37)	0.9
Reason for mechanical ventilation				
Acute respiratory failure	26 (65)	11 (55)	15 (75)	0.3
Coma	4 (10)	2 (10)	2 (10)	1
Other	10 (25)	7 (35)	3 (15)	0.3
Physiological measurements				
Ptr,Stim (cmH_2O)	6.5 (3.5–10.0)	6.8 (4–13)	4.3 (3–9)	0.08
MRC score	31 (20–36)	35 (30–38)	26 (18–33)	0.03
Pulmonary function tests				
TV (ml)	440 (360–604)	405 (348–508)	499 (398–619)	0.2
RR (c/min)	23 (17–27)	23 (17–30)	23 (18–25)	0.9
RR/TV (c/min/ml)	50 (33–69)	53 (33–80)	46 (33–61)	0.5
MIP (cmH_2O)	18 (13–25)	20.5 (14–27)	16 (13–23)	0.3
Ultrasound diaphragm assessment				
End-expiration thickness (mm)	2.2 (1.9–2.9)	2.2 (2–3)	2.2 (2–3)	1
Thickening fraction in PSV (%)	15 (10–22)	20 (7–33)	9 (2–13)	0.008
Thickening fraction in T-tube (%)	16 (12–23)	20 (13–35)	12 (6–15)	0.008

Jung et al. Intensive Care Med (2016) 42:853–861

DISADVANTAGES OF USG

- A **poor acoustic window** has been reported to occur in **2-10 percent of individuals**
- When measuring diaphragmatic excursion, the **sonographer should be as perpendicular** as possible to the diaphragmatic excursion line, otherwise the accuracy and the repeatability of the diaphragmatic excursion measurements can be seriously affected
- Diaphragmatic excursion can be used only on **spontaneously breathing patients**
- But patients **on control modes** can be subjected to USG to **check ventilator- patient interactions** including triggering delay.

Matamis et al. Intensive Care Med
DOI 10.1007/s00134-013-2823-1

NEWER USG MODALITIES

- 3D USG
  - Changes in functional anatomy of the diaphragm in different postures and consequently, respiratory mechanics
- Speckle Tracking
  - uses naturally occurring **speckle patterns** to provide information on **tissue's deformation and motion**
  - Evaluate **Diaphragm strain** which is a value that describes active shortening of a given segment related to the length at a previous time point, as a new parameter of diaphragm function.
  - **Crura and zone of apposition-** strain present, **Domes** – strain absent
  - Allow us to **evaluate the diaphragm during controlled modes of ventilation**, during which parameters such as thickness and motion are not well correlated to diaphragm activity.

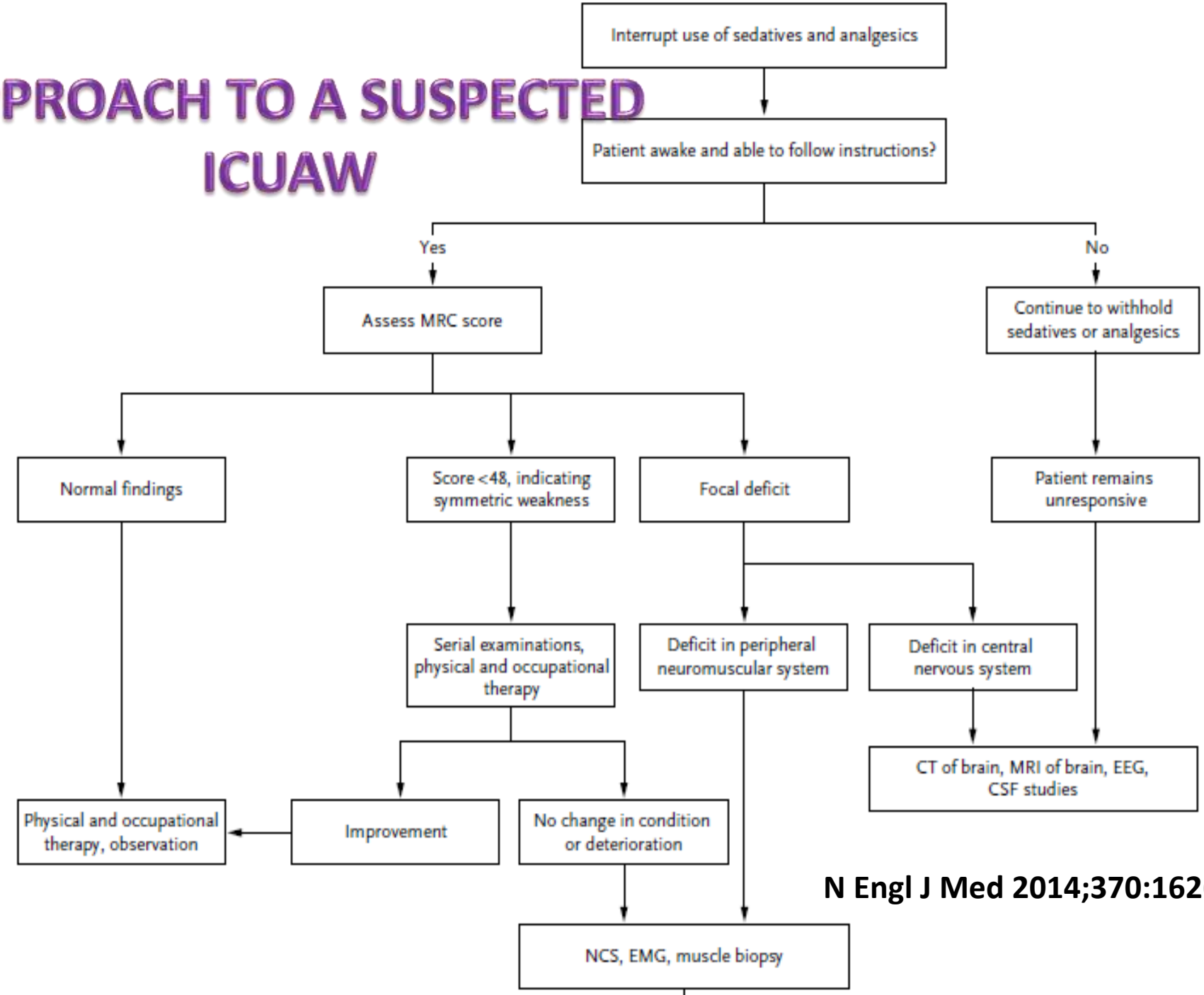
Haaksma et al. Intensive Care Med 2017;43:29-38

CONTRAST ENHANCED USG

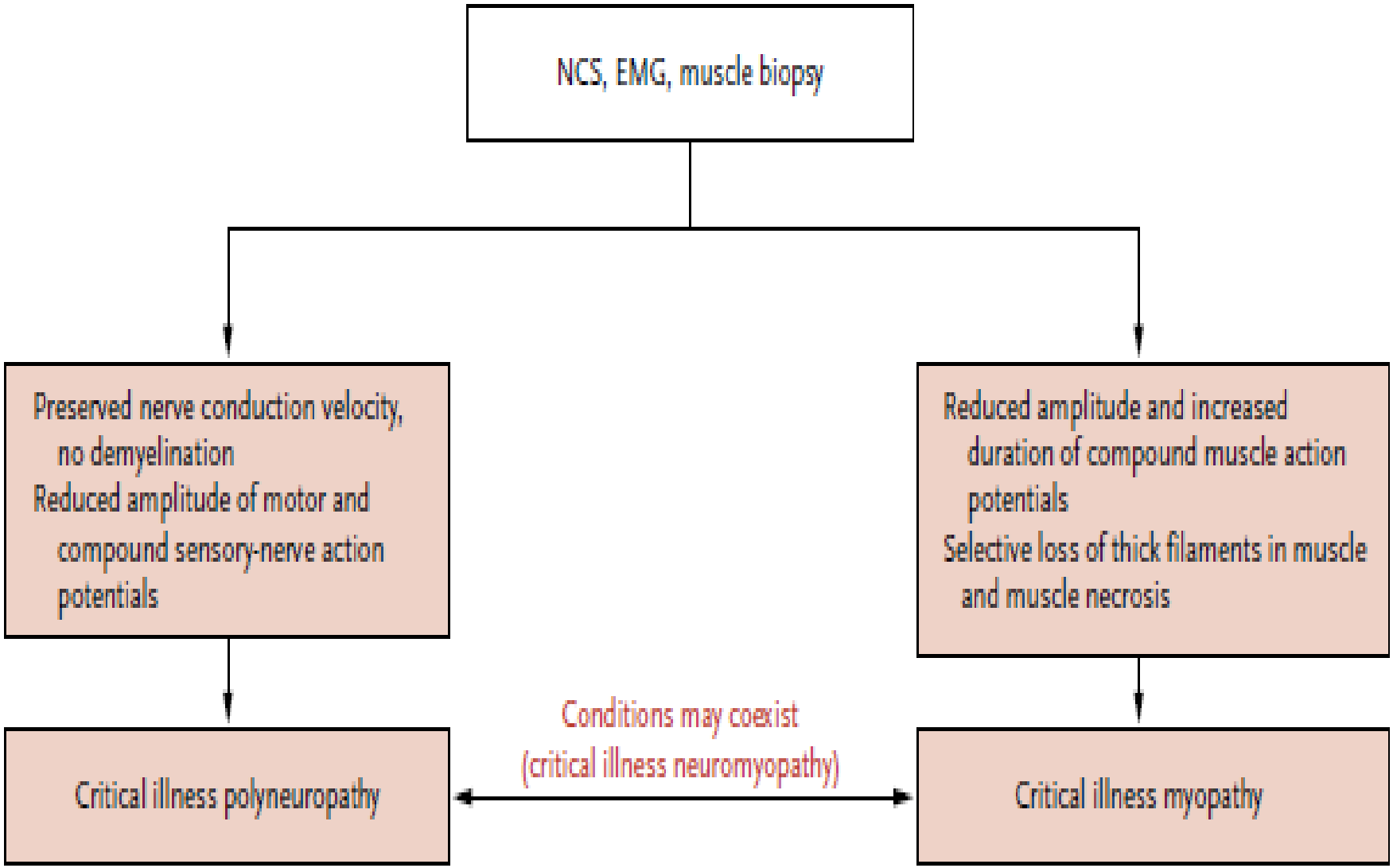
- Microbubbles are **gas-liquid emulsions,** surrounded by a shell that prevents leakage and aggregation, with a size of 1 to 4 microns
- The gaseous part creates a strong echogenic response which results in a high contrast-tissue ratio

Haaksma et al. Intensive Care Med 2017;43:29-38

APPROACH TO A SUSPECTED ICUAW



N Engl J Med 2014;370:1626-35



N Engl J Med 2014;370:1626-35

TAKE HOME MESSAGE

- ICUAW is a significant contributor to ICU related morbidity and mortality
- Have high suspicion in those with significant risk factors and difficult weaning
- Exclude mimics of ICUAW
- Traditional methods of assessing for ICUAW like MMS still play a significant role in diagnosing this condition
- But these cannot be applied on sedated patients

TAKE HOME MESSAGE

- All the more, MMS testing diagnose ICUAW at a later time period
- Earlier diagnosis of ICUAW requires EPS which helps in targeted therapy like NMES which might prevent significant morbidity
- But EPS is an invasive and highly technically demanding method
- USG has evolved to become a simple, non-invasive tool to assess for ICUAW

TAKE HOME MESSAGE

- A single USG assessment of peripheral muscles doesn’t not help in differentiating those with and without ICUAW
- Serial USG assessment might help in differentiating the two sub-population

TAKE HOME MESSAGE

- (VIDD) Diaphragm dysfunction has been a major problem in long term ventilated patients especially those on controlled modes of ventilation
- VIDD can occur earlier than peripheral muscle weakness
- USG can be used in patients on MV at the time of switching to support modes of ventilation to optimise the pressure support and to prevent VIDD
- USG indices can also be used to predict weaning success
- Among USG indices, thickness fraction has been found to be the best indicator of diaphragmatic function

TAKE HOME MESSAGE

- Minimise the duration of use of control modes of ventilation
- Shift to support modes of ventilation as soon as possible
- Use USG indices to optimise ventilator settings
- Using Low TV, optimal PEEP, optimal pressure support and minimising muscle relaxants and steroid usage helps in preventing VIDD

THANK YOU