Diaphragmatic dysfunction

Clinical approach and therapeutic options
Figure 1. Anatomical Arrangement of the Diaphragm with the Rib Cage and Abdomen.

The cylindrical region of the diaphragm that apposes the lower rib cage is referred to as the zone of apposition of the diaphragm.
Diaphragmatic dysfunction

- Paralysis
- Weakness
- Eventration
Eventration

- Although some authors use the term “eventration” to mean elevated diaphragm of any cause, true eventration is a **congenital** developmental defect in the muscular portion of the diaphragm.
- Eventrated part of diaphragm consists predominantly of fibroelastic tissue and has a paucity of muscle fibers.
- Eventration can be bilateral, unilateral, total or localized.
Etiology
Causes of Diaphragmatic Dysfunction (According to Level of Impairment)

Multiple sclerosis
Stroke
Arnold–Chiari malformation

Quadriplegia
Amyotrophic lateral sclerosis
Poliomyelitis
Spinal muscular atrophy
Syringomyelia

Guillain–Barré syndrome
Tumor compression
Neuropathic neuropathy
Critical-illness polyneuropathy
Chronic inflammatory demyelinating polyneuropathy
Charcot–Marie–Tooth disease
Idiopathic

Hyperinflation (COPD, asthma)

Myasthenia gravis
Lambert–Eaton syndrome
Botulism
Organophosphates
Drugs

Muscular dystrophies
Myositis (infectious, inflammatory, metabolic)
Acid maltase deficiency
Glucocorticoids
Disuse atrophy
Diaphragmatic paralysis

• Unilateral diaphragmatic paralysis (UDP) is commonly caused by ipsilateral phrenic nerve palsy, the most common cause of which is open heart surgery.
• Bilateral diaphragmatic paralysis (BDP) occurs most often in the context of severe generalized weakness from motor neuron disease or myopathy.
Clinical features
Symptoms

• UDP
  • Usually asymptomatic
  • May have dyspnea on exertion and exercise limitation

• BDP
  • Dyspnea at rest, on exertion, on assuming supine posture, on bending, when immersed in water above waist-level
  • Diagnosis is usually delayed by an average of 2 years as patients are usually mistaken to have CHF and undergo extensive cardiac evaluation.
Diaphragmatic paralysis and sleep-disordered breathing (SDB)

• Patient with BDP are at increased risk of hypoventilation during sleep (esp. REM sleep).

• REM sleep is associated with generalized atonia which includes extradiaphragmatic inspiratory muscles. Hence diaphragm assumes a major role during REM sleep.

• Initial symptoms of diaphragmatic weakness may include fatigue, hypersomnia, depression, morning headaches, and frequent nocturnal awakenings.

Neurology 2004;62:134–137
SDB occurs even in unilateral palsy/weakness

- N = 11 patients + 11 controls
- Patients either had unilateral diaphragmatic palsy or weakness (both had unilateral twitch Pdi <6cmH2O)
- Thoracoabdominal paradox only occurred in patients with a unilateral twitch Pdi <5 cmH2O (n = 8), and all such patients had SDB. This physical sign may serve to identify patients at risk of SDB.

**FIGURE 1.** Mean ± sem respiratory disturbance index (RDI) for patient (●) and control groups (■). There was a significant increase in RDI in rapid eye movement (REM) sleep compared with non-REM (NREM) sleep in patients with unilateral diaphragm paralysis. The intergroup difference was significant for REM sleep. NS: nonsignificant. #: p<0.0001.
Signs

- Poor sensitivity and specificity
- Use of accessory muscles of respiration during quiet breathing
- Decreased chest expansion on affected side
- Paradoxical inward movement of abdomen during inspiration
- Decreased excursion of diaphragm on tidal percussion

In one study of 30 patients with varying degrees of diaphragm weakness, orthopnoea and abdominal paradox were always present when sniff Pdi was <30 cmH2O. Am Rev Respir Dis. 1988 Apr;137(4):877-83
Investigations

• Non-invasive
  • PFT
  • MIP, SNIP
  • CXR
  • Fluoroscopy
  • USG

• Invasive
  • Transdiaphragmatic pressure
  • Diaphragmatic EMG
Non-invasive assessment
PFT

• Restrictive pattern
  • UDP: Mild (TLC 70-79% of predicted)
  • BDP: moderate to severe (TLC 30-50% of predicted)

• Fall in VC on assuming supine posture
  • Normal <10%
  • UDP 10-30%
  • BDP 30-50%

• FRC & RV: Unaffected in UDP; decreased in BDP

MIP, MEP & SNIP

• MIP and SNIP are mildly reduced in UDP (60-70% of predicted) and severely diminished in BDP (<30% of predicted)

• MEP is usually normal in isolated diaphragmatic dysfunction.

• Significant reduction MEP along with MIP suggests a more generalized process which involves respiratory muscles other than diaphragm as well.

Figure 3. The sniff manoeuvre, using a nasal bung and an adapted pressure meter.

Imaging
CXR

- UDP: Elevated hemidiaphragm on the affected side
  - Sensitivity 90%, specificity 44% (Ref 1)
- BDP: Smooth elevation of both hemidiaphragms
  - Commonly be mistaken for poor-inspiratory effort
- Other features:
  - Accentuated dome configuration
  - Abnormally deepened costophrenic and costovertebral angles
  - Basal subsegmental atelectasis
- DD:
  - Lung collapse, pleural adhesions, subpulmonic effusion, causes of elevated abdominal pressure (ascites, ileus, organomegaly), poor chest wall compliance (obesity)

Fluoroscopic sniff test

• Brisk downward diaphragmatic movement on the normal side and paradoxic upward movement of the affected hemidiaphragm are seen in >90% of patients who have UDP.

• At least 2 cm of paradoxical upward motion is considered abnormal.

• Unilateral/bilateral false positive results (paradoxical upward movement) can occur in 9% and 2 % of normal subjects respectively (n = 776).

• False negative results can occur in BDP due to passive descent of diaphragm after relaxation of abdominal wall muscles which have contracted during previous expiration.

Clin Radiol. 1966 Jan;17(1):79-83
USG assessment of the diaphragm

• Thickness
• Excursion
• Velocity
• Side-to-side comparison
FIGURE 2. (A) Transducer placement for an intercostal view, with the transducer positioned on the ninth intercostal space in the anterior axillary line. (B) Diaphragm visualization at the zone of apposition using this approach. (C) Corresponding B-mode ultrasonography image, with the left side of the image being cranial. In (D), the patient is inspiring and the diaphragm is seen ‘peeling away’ from the chest wall. The downward displacement of the lung can also be appreciated.
USG diaphragmatic thickness: Normal

- Relationship between lung volume and Tdi was studied in 9 healthy subjects by obtaining diaphragm images at the five target lung volumes [25% increments from RV to TLC]
- A 7.5MHz transducer was placed in the midaxillary line over the right 8th or 9th intercostal space (whichever gave the clearest image).
- All subjects were standing and breathing quietly. They then performed at least three reproducible VC maneuvers while breathing into a wedge spirometer.

J Appl Physiol 1997;83:291-6
USG diaphragmatic thickness: UDP & BDP

- 30 subjects (5 BDP, 7 UDP, 3 with inspiratory weakness but normally functioning diaphragms, and 15 healthy controls)
- A 7.5-10.0 MHz transducer was placed over the lower rib cage in the mid-axillary line.
- The thickness of the diaphragm (tdi) was measured to the nearest 0.1 mm at FRC (TdiFRC) and TLC (TdiTLC).
- Diaphragm thickening during inspiration (delta Tdi) was calculated as (TdiTLC - TdiFRC)/TdiFRC.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>UDP</th>
<th>BDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>TdiFRC (mm)</td>
<td>2.8</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Delta Tdi (%)</td>
<td>37</td>
<td>-8.5</td>
<td>-1</td>
</tr>
</tbody>
</table>
USG diaphragmatic thickness cut-off

• Tdi <2mm and Delta Tdi <20% with inspiration have been suggested as cut-offs for BDP

FIGURE 3. (A) Curvilinear transducer placement for the **anterior subcostal view**, with the transducer positioned below the costal margin in the midclavicular line. (B) Ultrasound beam and the path it travels to image the diaphragm. (C) B-mode view of the diaphragm with the anterior subcostal approach. (D) M-mode view of diaphragm motion with an anterior subcostal view. ‘a’ represents the amplitude of excursion during deep breathing, and ‘b’ represents the time-frame used for diaphragm contraction, which is used to calculate velocity of movement. Velocity = \( \frac{A \text{ [cm]}}{B \text{ [s]}} \).
**Figure 1.** Ultrasonographic approach of the right and left hemidiaphragms. The liver and spleen were used as acoustic windows. **Left, A:** For the right hemidiaphragmatic study, the probe was positioned below the right costal margin between the midclavicular and anterior axillary lines. The left diaphragmatic was studied from a low intercostal or subcostal approach. The probe was positioned between the midaxillary and anterior axillary lines. **Right, B:** The probe angled cranially so that the ultrasound beam reached perpendicularly the posterior part of the diaphragm.
**M-mode tracing**

1. Normal quiet breathing
2. Normal sniffing
3. Normal deep breathing

**Diaphragmatic paralysis**

Lack of movement of the diaphragm during deep breathing.

**Paradoxical movement**

Diaphragm moving away from the transducer during inspiration.

**Normal diaphragm movement** (anterior subcostal approach)

Diaphragm moving closer to the transducer with inspiration.

**Diaphragmatic paralysis**

Lack of movement of the diaphragm during deep breathing.
Diaphragmatic excursion

- 210 healthy adult subjects (150 men, 60 women) from France were investigated with M-mode USG of diaphragm.
- Normal values of both diaphragmatic excursions were determined.
- Excursions were larger in men than in women.
- The lower limit values were:
  - During quiet breathing: 0.9 cm for women and 1 cm for men
  - During voluntary sniffing: 1.6 cm for women and 1.8 cm for men
  - During deep breathing: 3.7 cm for women and 4.7 cm for men
Invasive assessment
Transdiaphragmatic pressure (Pdi)

- Gold standard for diagnosis of diaphragmatic dysfunction
- \( Pdi = Pga - Pes \)
- 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 >80 cmH2O (men) and >70 cmH2O (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 stimulation also rules out clinically significant diaphragmatic weakness

Pdi = Pga - Pes

50 cm H₂O

Normal

Diaphragmatic Paralysis
Diaphragmatic EMG

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

• However it is limited by a number of technical issues, including the
  • Difficulty in proper placement of electrodes
  • Electromyographic “cross-talk” from adjacent muscles
  • Variable distances between muscles and electrodes that result from differences in subcutaneous fat among patients
Diaphragm EMG using esophageal catheter

- Unlike surface EMG, diaphragm EMG recorded from an esophageal electrode is less affected by obesity, power line artefact and cross-talk signals from adjacent muscles.
- The diaphragm EMG is recorded with an esophageal catheter with ten coils.
- EMG signals are amplified with a gain of 1000 and filtered.
- Root mean square (RMS) of the diaphragm EMG is generated after eliminating the ECG.
- RMS reflects the number and firing rate of the motor units recruited and thereby is a measure of diaphragm activity.

USG-guided needle EMG of diaphragm
Phrenic nerve stimulation studies

- Magnetic cervical coils
- Cervical needle electrodes

Phrenic nerve stimulation

- Assessment of electrical/mechanical response as a measure of diaphragmatic function
- Diaphragmatic action potential measurement (Diaphragmatic EMG) using esophageal or surface electrodes
- Transdiaphragmatic pressure (Twitch Pdi) measurements using esophageal and gastric balloons
Treatment
Natural history

• In post-traumatic or infectious diaphragmatic paralysis, spontaneous recovery occurs in approximately 2/3rd of patients but may take a considerable amount of time.
  • Regeneration of the phrenic nerve may take up to 3 years.
  • Recovery times may be somewhat shorter in patients who have diaphragmatic dysfunction after cardiac surgery.

• Prognosis is poor for patients who have diaphragmatic dysfunction after traumatic injury to the spinal cord and those with degenerative neuromuscular diseases.
Rx options

• Mechanical ventilation
• Diaphragmatic plication
• Diaphragmatic pacing
NIV in diaphragmatic dysfunction

• No RCTs are available.
• Evidence from observational studies suggest that it is effective.
• Night-time CPAP is usually enough to improve or reverse the hypoxic and hypercapnic respiratory failure.
Negative-pressure ventilators

Iron-lung

Portalung

Pneumowrap

Cuirass
Ventilators that displace the abdominal contents

A: Pneumobelt

B: Rocking bed
NIPPV: Indications

• Symptoms (such as fatigue, dyspnea, morning headache, etc) and one of the following physiologic criteria
  • PaCO2 ≥45 mmHg
  • Nocturnal oximetry demonstrating SpO2 ≤88% for 5 consecutive minutes
  • For progressive neuromuscular disease, MIP <60 cmH2O or FVC <50% predicted

AARC, ACCP, ATS Consensus conference report. Chest 1999;116;521-534
Diaphragmatic plication

- Diaphragm is sutured to become a taut, fixed, immobile structure.
- This transfixion eliminates the paradoxic movement of the diaphragm with inspiration, thereby improving the ability of the accessory muscles to create a negative inspiratory pressure.

Fig. 2. Technique of diaphragm plication. (A) Plication is performed with six to eight nonabsorbable U-shaped stitches placed in the diaphragm. (B) Diaphragm is taut and immobile after sutures are tied. (C) Redundant tissue is imbricated.
Diaphragm plication

- Plication is most commonly done for UDP. However, limited evidence suggests that it can be effective in BDP as well.
- Suggested indications:
  - Life-style limiting dyspnea
  - Evidence of significant impairment in upright and supine PFT
  - Progression/persistence of symptoms despite follow-up
- In general, a long period of observation (6 months - 3 years in various series) should be considered before plication is recommended because of the possibility of spontaneous recovery.
- VATS appears to produce results similar to open thoracotomy with a shorter hospital stay and lower complication rate.
Plication: Long-term results

Table 3. Functional Status at Six-Month Follow-Up for Patients Treated With Diaphragm Plication for Unilateral Diaphragm Paralysis

<table>
<thead>
<tr>
<th>Pulmonary spirometry</th>
<th>6 Months</th>
<th>48 Months</th>
<th>p Value</th>
</tr>
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<tbody>
<tr>
<td>FVC</td>
<td>+19%</td>
<td>+17%</td>
<td>0.62</td>
</tr>
<tr>
<td>FEV₁</td>
<td>+23%</td>
<td>+21%</td>
<td>0.68</td>
</tr>
<tr>
<td>FRC</td>
<td>+21%</td>
<td>+20%</td>
<td>0.82</td>
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<tr>
<td>TLC</td>
<td>+19%</td>
<td>+20%</td>
<td>0.81</td>
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<tr>
<td>MRC score</td>
<td>−2.0</td>
<td>−1.9</td>
<td>0.62</td>
</tr>
<tr>
<td>MRADL</td>
<td>+7</td>
<td>+8</td>
<td>0.12</td>
</tr>
<tr>
<td>Work status</td>
<td>+31</td>
<td>+29</td>
<td>0.8</td>
</tr>
</tbody>
</table>

- Patients with lifestyle-limiting dyspnea (MRC dyspnea score ≥3) from unilateral diaphragm paralysis present for at least 6 months were offered diaphragm plication.
- 41 patients who underwent plication of the hemidiaphragm through VATS (n = 30) or thoracotomy (n = 11).
- No deaths occurred in this series.

All pulmonary spirometry, Medical Research Council (MRC) dyspnea score, and Manchester respiratory activities of daily living questionnaire (MRADL) values are expressed as mean changes for each measurement.
Phrenic nerve pacing (PNP)

• PNP requires an intact phrenic nerve and diaphragm and hence is most commonly used in patients with complete respiratory paralysis due to high-level (above C3) spinal cord injury (SCI).
• Continuous PNP appears to be effective as a full-time and sole ventilation measure in such patients.
(Implanted subcutaneously)

(Externally placed over the subcutaneous receiver)

(Implanted within thorax by thoracotomy/thoracoscopy)

(Implanted subcutaneously)
Phrenic nerve pacing (PNP): Long term results

- 12 patients with high-level SCI who underwent PNP between 1981-1987 were evaluated after 15 years.
  - 6 were doing well with only PNP.
  - 2 were dead (one paced continuously for 10 years before his demise, one had stopped PNP after 1 year).
  - 4 shifted to ventilator/part-time use
- Despite theoretical concerns about long-term nerve damage, no patient lost the ability to pace the phrenic nerve.

Phrenic nerve pacing (PNP): Comparison with mechanical ventilation

• A retrospective analysis of 126 patients with high-level SCI (38 were on PNP and 88 were mechanically ventilated).
  • Paced patients had a longer age-adjusted survival and better social functioning measured as HRQL.
  • 74% of patients were able to use PNP as their only mode of respiratory support.
Intramuscular electrodes are placed on each hemidiaphragm laparoscopically. However, this technique requires localization of phrenic nerve motor points using a mapping procedure. Advantages:

- Avoids thoracotomy and its associated cost and complications
- Risk of phrenic nerve injury due to manipulation during electrode placement is greatly reduced

Wires from the electrode are brought out through a skin port and connected to a stimulator.

Chest. 2005 Feb;127(2):671-8
Mapping

- Mapping involves finding the point on the abdominal side of the diaphragm at which stimulation causes the greatest diaphragm excursion.
- The mapping instrument has a suction port that allows it to temporarily attach to the diaphragm and deliver an electrical stimulus.
- The stronger the stimulated contraction, the closer to the motor point of the phrenic nerve.

Mapping probe being used on patient’s left diaphragm. The blue marks indicate the locations at which the strongest contractions were found.
Laparoscopic diaphragm pacing: Results

- In a study summarizing the complete worldwide operative experience in laparoscopic diaphragm pacing a total of 88 patients (50 ventilator-dependent spinal cord injury (SCI) patients and 38 respiratory-compromised patients with amyotrophic lateral sclerosis (ALS)) were included.

- In the SCI patients 96% were able to use diaphragm pacing to provide ventilation replacing their mechanical ventilators and the ALS patients were able to delay the need for mechanical ventilation for up to 24 months.

Surg Endosc. 2009 Jul;23(7):1433-40
<table>
<thead>
<tr>
<th>Diagnostic Tools and Treatment</th>
<th>Bilateral Diaphragmatic Paralysis</th>
<th>Unilateral Diaphragmatic Paralysis</th>
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<tr>
<td>Presentation</td>
<td>Dyspnea at rest, unexplained dyspnea, exercise limitation, orthopnea, dyspnea when bending, constitutional symptoms, dyspnea when entering water, respiratory failure, prolonged mechanical ventilation</td>
<td>Asymptomatic, unexplained dyspnea; exercise limitation, incidental radiographic finding</td>
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<td>History</td>
<td>Neck or shoulder pain, chest or neck surgery, neck injury, manipulation of the cervical spine, neuromuscular disease</td>
<td>Neck or shoulder pain, chest or neck surgery, neck injury, manipulation of the cervical spine, neuromuscular disease</td>
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<td>Examination</td>
<td>Abdominal paradox</td>
<td>No abdominal paradox</td>
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<td>Laboratory tests</td>
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<td>Vital capacity (% of predicted value)</td>
<td>&lt;50</td>
<td>&gt;70</td>
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<tr>
<td>Decline in supine vital capacity (%)</td>
<td>30–50</td>
<td>10–30</td>
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<tr>
<td>MIP (% of predicted value)</td>
<td>&lt;30</td>
<td>&gt;60</td>
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<tr>
<td>Fluoroscopy</td>
<td>Not helpful</td>
<td>Sniff test positive</td>
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<tr>
<td>Thickening of diaphragm on inspiration†</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Pdi max (cm of water)</td>
<td>&lt;40</td>
<td>&gt;70</td>
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<tr>
<td>Twitch Pdi (cm of water)</td>
<td>&lt;20</td>
<td>&lt;10</td>
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<td>Complications</td>
<td>Frequent hypoventilation during sleep, atelectasis, pneumonia, respiratory failure</td>
<td>Occasional hypoventilation during sleep, atelectasis</td>
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<td>Treatment</td>
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<tr>
<td>Observation period for recovery (yr)</td>
<td>1.5–3</td>
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<td>Treatment for coexisting conditions</td>
<td>Yes</td>
<td>Yes</td>
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<td>Reversal of metabolic disturbance</td>
<td>Yes</td>
<td>Yes</td>
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<td>NIPPV</td>
<td>Often indicated</td>
<td>Usually not indicated</td>
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<td>Plication of diaphragm</td>
<td>Not indicated</td>
<td>May be helpful</td>
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<tr>
<td>Phrenic pacing</td>
<td>Yes, in patients with high SCI</td>
<td>No</td>
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Ventilator-induced diaphragm dysfunction (VIDD)
VIDD

• Loss of diaphragmatic force-generating capacity that is specifically related to the use of mechanical ventilation

Several infants and neonates who had received long-term ventilatory assistance had subnormal diaphragmatic muscle mass on autopsy.

J Pediatr. 1988 Dec;113(6):1074-7
<table>
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<tr>
<th>First Author (Ref.)</th>
<th>Year</th>
<th>Animal</th>
<th>n (CMV)</th>
<th>Duration</th>
<th>Control</th>
<th>Vt (ml/kg)</th>
<th>RR</th>
<th>PEEP</th>
<th>Force Decline (%)</th>
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<td>Le Bourdelles (16)</td>
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<td>48 h</td>
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<td>10</td>
<td>80</td>
<td>1</td>
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<td>Anzueto (13)</td>
<td>1997</td>
<td>Baboons</td>
<td>7</td>
<td>11 d</td>
<td>No</td>
<td>15</td>
<td>12</td>
<td>2</td>
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<td>Radell (14)</td>
<td>2002</td>
<td>Piglets</td>
<td>7</td>
<td>5 d</td>
<td>No</td>
<td>12–15</td>
<td>16–19</td>
<td>3.0–5.0</td>
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<td>Sassoon (15)</td>
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<td>Rabbits</td>
<td>30 (12)</td>
<td>1–3 d</td>
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<td>6–8</td>
<td>40–50</td>
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<td>Yang (18)</td>
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<td>Rats</td>
<td>9 (5)</td>
<td>44–93 h</td>
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<td>5</td>
<td>90</td>
<td>4</td>
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<td>Shanely (26)</td>
<td>2002</td>
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<td>38 (16)</td>
<td>18 h</td>
<td>Yes</td>
<td>10</td>
<td>80</td>
<td>1</td>
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<td>Powers (17)</td>
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<td>Rats</td>
<td>39 (15)</td>
<td>12–24 h</td>
<td>Yes</td>
<td>10</td>
<td>80</td>
<td>1</td>
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<td>Shanely (22)</td>
<td>2003</td>
<td>Rats</td>
<td>14 (6)</td>
<td>18 h</td>
<td>Yes</td>
<td>10</td>
<td>80</td>
<td>1</td>
<td>21</td>
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<td>Bernard (19)</td>
<td>2003</td>
<td>Rabbits</td>
<td>17 (7)</td>
<td>49 h</td>
<td>Yes</td>
<td>8</td>
<td>60</td>
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<td>24 h</td>
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<td>Gayan-Ramirez (20)</td>
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<td>Rats</td>
<td>31 (12)</td>
<td>24 h</td>
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<td>10</td>
<td>55–60</td>
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<td>Zergeroglu (30)</td>
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<td>Rats</td>
<td>52 (22)</td>
<td>3–18 h</td>
<td>Yes</td>
<td>10</td>
<td>80</td>
<td>1</td>
<td>NA</td>
</tr>
</tbody>
</table>

Definition of abbreviations: CMV = controlled mechanical ventilation; control = presence of control group; force decline = percent decline in diaphragmatic force production in mechanically ventilated animals versus control animals or baseline; NA = not available; PEEP = positive end-expiratory pressure; RR = respiratory rate.

* In vivo transdiaphragmatic pressure development in response to phrenic nerve stimulation.
Prolonged MV → Mitochondrial dysfunction → ROS

1. Activation of redox sensitive transcription factors (i.e., atrogin-1, murf-1)
2. Protease activation
   - Calpain
   - Caspase-3
   - Proteosome
3. Degradation of oxidized proteins → Oxidation of proteins

Atrogens → Atrogin-1, MuRF-1

Proteolysis
Rapid Disuse Atrophy of Diaphragm Fibers in Mechanically Ventilated Humans

• Biopsy specimens from the costal diaphragms of 14 brain-dead organ donors before organ harvest (cases) were compared with those of 8 patients who were undergoing surgery for either benign lesions or localized lung cancer (controls).
• Cases had diaphragmatic inactivity and underwent mechanical ventilation for 18 to 69 hours compared to controls where it was limited to 2 to 3 hours.
• As compared with diaphragm-biopsy specimens from controls, specimens from cases showed decreased cross-sectional areas of slow-twitch and fast-twitch fibers.
• Biopsy specimens from cases also showed increased concentrations of markers of proteolysis as compared to controls
Figure 1. Comparison of Representative Case and Control Diaphragm-Biopsy Specimens with Respect to Fiber Size.

The slow-twitch and fast-twitch fibers in the case specimens (Panels A, C, and E) are smaller than those in the control diaphragms (Panels B, D, and F). Panels A and B (hematoxylin and eosin) show that neither inflammatory infiltrate nor necrosis is present in case or control specimens. The sections in Panels C and D were preincubated with NOQ7.5.4D antibody,\textsuperscript{10,13} which is specific for the slow myosin heavy chain, whereas sections in Panels E and F were preincubated with the MY-32 antibody,\textsuperscript{10,14} which reacts with all fast myosin heavy chains. In addition, in each section, all fibers are outlined by an antibody reactive to laminin.\textsuperscript{10,15} In each of the sections, fibers reacting with the antibody appear orange-red, whereas fibers not reacting with the antibody appear black. In Panels C, D, E, and F, a representative slow-twitch fiber is indicated by an open circle and a fast-twitch fiber by an open square.
Does VIDD contribute to weaning difficulty?

• The diaphragm of 88 patients who were on mechanical ventilation for >48 hrs and met the criteria for a spontaneous breathing trial (SBT) were assessed using USG.

• Measurements were done in supine posture during SBT.

• Ultrasonographic diaphragmatic dysfunction (DD) was diagnosed if an excursion was <10 mm or negative (i.e. paradoxical movement)

• The prevalence of ultrasonographic diaphragmatic dysfunction among the eligible 82 patients was 29% (n = 24).

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Does VIDD contribute to weaning difficulty?

<table>
<thead>
<tr>
<th>Variables</th>
<th>DD Group</th>
<th>Non-DD Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ventilation time, hrs (IQR)</td>
<td>576 (374–850)</td>
<td>203 (109–408)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Weaning time, hrs (IQR)</td>
<td>401 (226–612)</td>
<td>90 (24–309)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Time to the spontaneous breathing trial, day (IQR)</td>
<td>4 (2.5–7.5)</td>
<td>4 (3.0–6.0)</td>
<td>.55</td>
</tr>
<tr>
<td>Primary weaning failure, no. (%)</td>
<td>20/24 (83)</td>
<td>34/58 (59)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Secondary weaning failure, no. (%)</td>
<td>10/20 (50)</td>
<td>10/46 (22)</td>
<td>.01</td>
</tr>
<tr>
<td>Died before weaning, no. (%)</td>
<td>4/24 (17)</td>
<td>12/58 (21)</td>
<td>.79</td>
</tr>
</tbody>
</table>

DD, diaphragmatic dysfunction; IQR, interquartile range.
Prevention and Rx of VIDD

• Animal studies indicate that VIDD is alleviated (but not completely prevented) when using partial support modes of mechanical ventilation.

• Whether any particular method of promoting diaphragmatic effort (SBT, PSV, NAVA) has any impact on VIDD is not clear at the moment.

• Emerging evidence suggests that inspiratory muscle training, designed to increase diaphragm strength and endurance, increases weaning success in patients who previously failed repeated weaning attempts by conventional methods.

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Conclusion

• Diaphragmatic paralysis should be looked for in any patient with unexplained dyspnea.
• Ultrasound examination of the diaphragm is emerging as an important non-invasive tool for assessment of diaphragm function.
• NIV is an important treatment option in patients with significant respiratory failure.
• Diaphragmatic pacing may help selected patients to avoid mechanical ventilation.
• VIDD appears to be an important contributor to weaning difficulty.