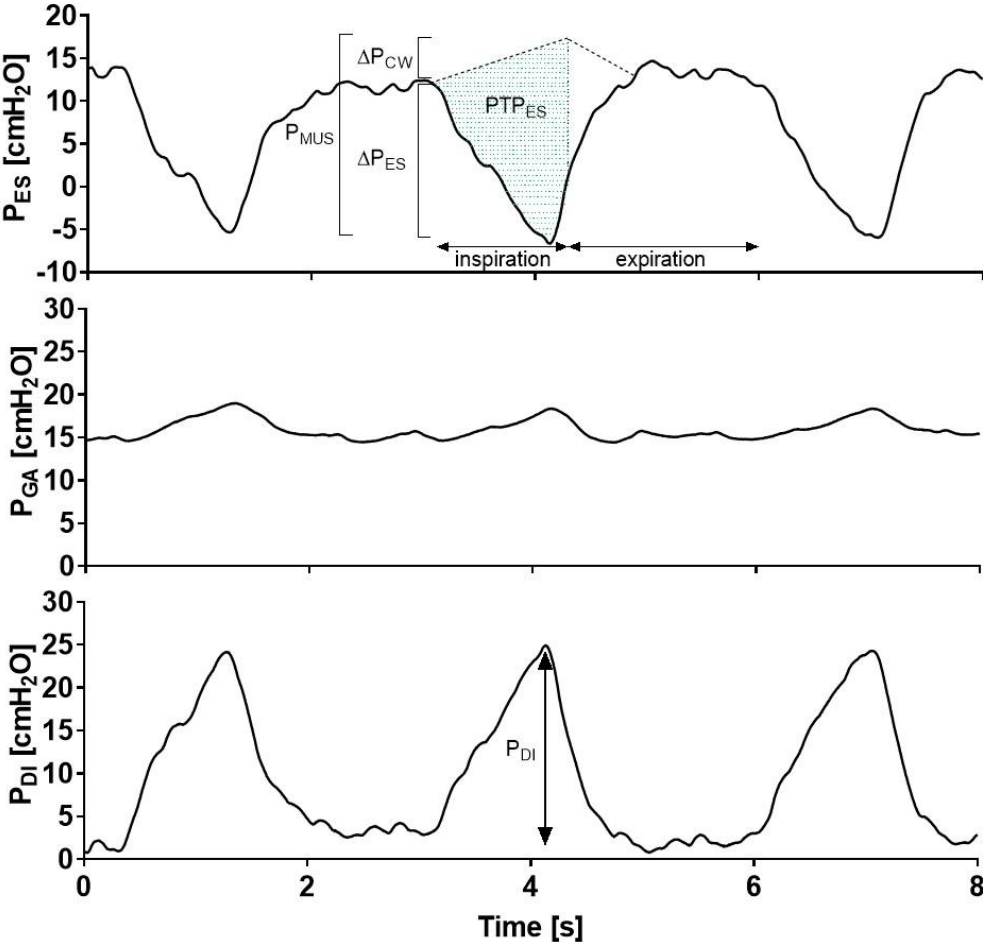


# Supplementary materials

eFigure 1. Esophageal, gastric, and transdiaphragmatic pressure traces over the respiratory cycle.



**Top panel – Pes Trace.**

Esophageal pressure (Pes) serves as a surrogate for pleural pressure and reflects inspiratory effort.

$\Delta P_{es}$  represents the swing in Pes from the end-expiratory baseline during inspiration.  $\Delta P_{cw}$  refers to the chest wall recoil pressure, estimated as the product of chest wall elastance ( $E_{cw}$ ) and lung volume.  $P_{mus}$ , the pressure generated by the respiratory muscles, is theoretically defined as:

$$P_{mus} = E_{cw} \times V(\Delta P_{es}) - \Delta P_{es},$$

where  $V(\Delta P_{es})$  is the inspired volume at the time of peak  $\Delta P_{es}$ .

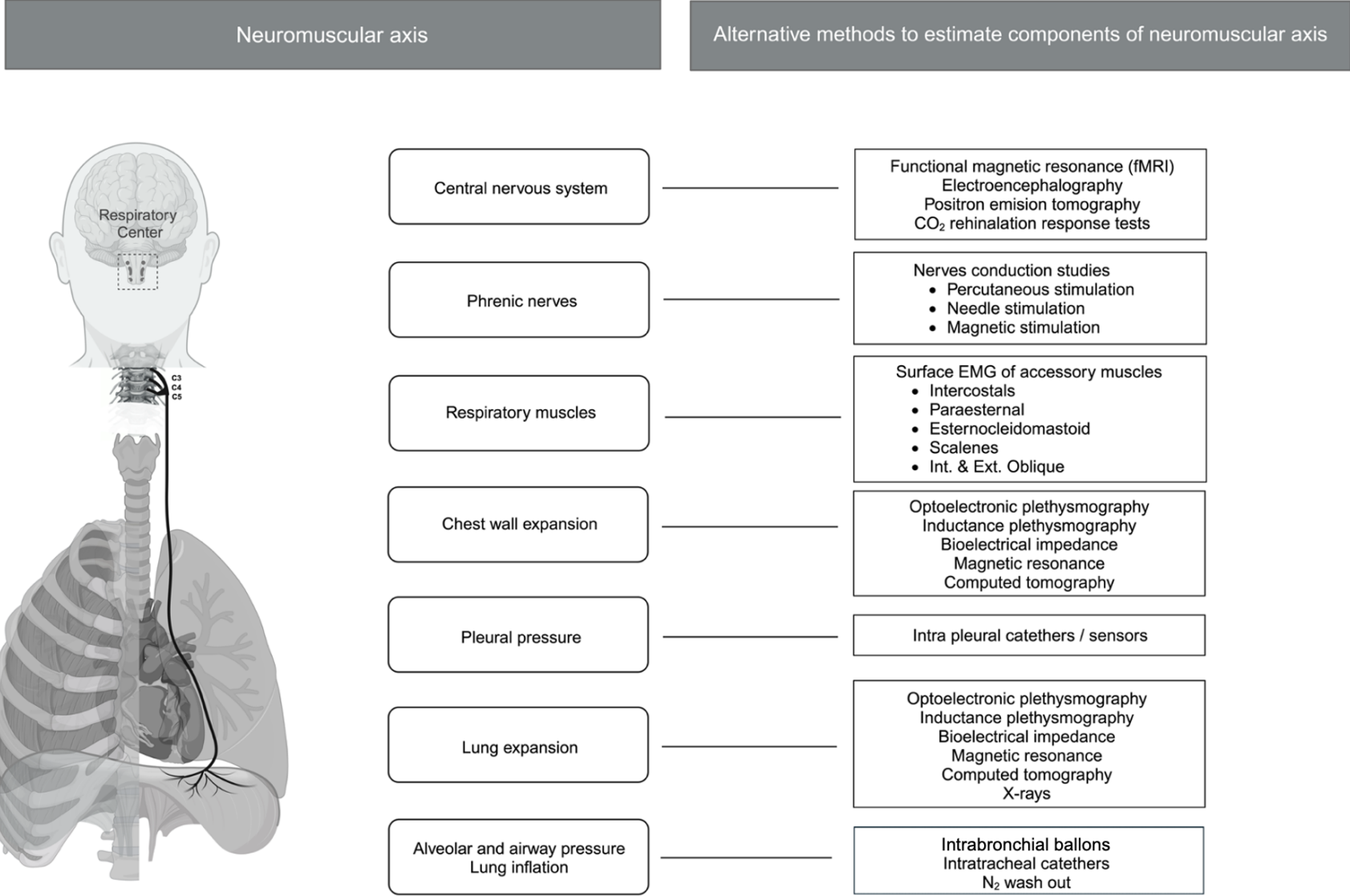
Since  $\Delta P_{es}$  usually precedes end-inspiration,  $V_t$  overestimates  $V(\Delta P_{es})$ ; nonetheless, the simplified equation  $P_{mus} \approx E_{cw} \times V_t - \Delta P_{es}$  is often used at the bedside, as the approximation is clinically acceptable. The shaded area represents  $PTP_{es}$ , the pressure–time product calculated from the esophageal pressure trace during inspiration.

**Middle panel – Pga Trace.** Gastric pressure ( $P_{ga}$ ) is measured using a double-balloon catheter, allowing simultaneous recording with Pes. It provides insight into abdominal muscle activity and its contribution to respiratory effort.

**Bottom Panel – Pdi Trace.** Transdiaphragmatic pressure ( $P_{di} = P_{ga} - P_{es}$ ) represents the pressure generated specifically by the diaphragm, serving as a direct measure of diaphragmatic effort. The peak inspiratory  $P_{di}$  reflects the intensity of diaphragmatic contraction.

Pes, esophageal pressure;  $\Delta P_{es}$  esophageal pressure swing;  $P_{ga}$ , gastric pressure;  $P_{di}$ , transdiaphragmatic pressure;  $P_{mus}$ , respiratory muscles pressure;  $P_{cw}$ , chest wall recoil pressure;  $V_t$ , tidal volume;  $E_{cw}$ , chest wall elastance

eFigure 2. Alternative methods to estimate respiratory effort and its impact on the components of the neuromuscular axis.



Even though many of these tools lack accessibility in clinical practice or are overly invasive, they offer valuable insights into the individual components of the neuromuscular axis. Some methods may be considered for use in complex clinical scenarios, where a deeper understanding is required. However, their application should carefully balance the potential benefits of the information gained against the risks associated with implementing these measurements.

fMRI, functional magnetic resonance; Int. internal; Ext. external; EMG, electromyography; CO<sub>2</sub>, carbon dioxide; N<sub>2</sub>, nitrogen

**eTable 1. Scores proposed for non-invasive monitoring in patients with acute respiratory failure under HFNC and NIV.**

	<b>Variables required</b>	<b>Relevant thresholds</b>	<b>Limitations</b>
<b>ROX index<sup>A</sup></b>	SpO <sub>2</sub> /FiO <sub>2</sub> /respiratory rate	< 2.85 at 2 h of HFNC initiation predicts HFNC failure < 3.85 at 12 h of HFNC initiation predicts HFNC failure	Validated only for HFNC Poorly correlated with effort (it predicts HFNC failure, which may be due to excessive effort or other causes)
<b>HACOR score<sup>B</sup></b>	Heart rate, Acidosis (arterial pH), Consciousness (GCS), Oxygenation (PaO <sub>2</sub> /FiO <sub>2</sub> ), and Respiratory rate	> 5 at 1 h of NIV predicts NIV failure	Validated only for NIV Poorly correlated with effort (it predicts NIV failure, which may be due to excessive effort or other causes)
<b>HACOR score updated<sup>C</sup></b>	Original HACOR score + 0.5 × SOFA + 2.5 if pneumonia is diagnosed – 4 if CPE is diagnosed + 3 if pulmonary ARDS is present + 1.5 if immunosuppression is present + 2.5 if septic shock is present	≤ 7 low risk for NIV failure 7.5–10.5 moderate risk for NIV failure 11–14 high risk for NIV failure > 14 very high risk for NIV failure	Time consuming Validated only for NIV Poorly correlated with effort (it predicts NIV failure, which may be due to excessive effort or other causes)
<b>VOX index<sup>D</sup></b>	SpO <sub>2</sub> /FiO <sub>2</sub> divided by Vt (ml/kg PBW), where Vt is measured during a short NIV test at PS = 5 cmH <sub>2</sub> O and PEEP = 5 cmH <sub>2</sub> O	< 20.91 at 2 h of HFNC predicts HFNC failure < 22.67 at 6 h of HFNC predicts HFNC failure	Evaluated in a single study Requires a temporary switch from HFNO to NIV Poorly validated as a direct marker of effort (it predicts HFNC failure, which may be due to excessive effort or other causes)

ROX, respiratory rate-oxygenation; HACOR, heart rate, acidosis, consciousness, oxygenation, respiratory rate; SpO<sub>2</sub>, peripheral oxygen saturation; FiO<sub>2</sub>, fraction of inspired oxygen, HFNC, high flow nasal cannula; NIV, non-invasive mechanical ventilation; GCS, Glasgow coma scale; SOFA, sequential organ failure assessment score; CPE, cardiogenic pulmonary edema, ARDS, acute respiratory distress syndrome; Vt, tidal volume

**eTable 2. BREF model equations and thresholds**

Purpose	Population	Model	Input	Equation	Output
Estimate the strength of the inspiratory effort	Without COVID-19	Linear	BEa, RR, PaO <sub>2</sub> /FiO <sub>2</sub>	$\Delta P_{es} = 14.25 - 0.52 \times BEa + 0.36 \times RR - 0.05 \times PaO_2/FiO_2^E$	Estimated $\Delta P_{es}$ (in cmH <sub>2</sub> O)
Estimate the strength of the inspiratory effort	With COVID-19	Linear	BEa, RR, PaO <sub>2</sub> /FiO <sub>2</sub>	$\Delta P_{es} = 3.52 - 0.52 \times BEa + 0.36 \times RR - 0.01 \times PaO_2/FiO_2^E$	Estimated $\Delta P_{es}$ (in cmH <sub>2</sub> O)
Estimate the risk of strong inspiratory effort	All	Logistic complete	BEa, RR, PaO <sub>2</sub> /FiO <sub>2</sub>	Probability = $1 / [1 + \exp(-(0.461 - 0.145 \times BEa + 0.075 \times RR - 0.014 \times PaO_2/FiO_2))]^E$	The probability of $\Delta P_{es}$ being >10 cmH <sub>2</sub> O
Estimate the risk of strong inspiratory effort	All	Logistic simplified	BEa, RR, PaO <sub>2</sub> /FiO <sub>2</sub>	BREF score = $33.7 - 10.6 \times BEa + 5.5 \times RR - PaO_2/FiO_2^E$	Score = 0 → 50% risk of $\Delta P_{es}$ >10 cmH <sub>2</sub> O Score < 0 → <50% risk of $\Delta P_{es}$ >10 cmH <sub>2</sub> O Score > 0 → >50% risk of $\Delta P_{es}$ >10 cmH <sub>2</sub> O

$\Delta P_{es}$ , esophageal pressure swing; BEa: arterial base excess; RR: respiratory rate; PaO<sub>2</sub>/FiO<sub>2</sub>, ratio of arterial oxygen partial pressure to inspired oxygen fraction

**eTable 3. Scales for assessing dyspnea**

Scale	Relevant thresholds	Limitations
<p><b><i>Dyspnea-Visual Analog Scale (VAS)</i></b><sup>F</sup>                      From 0 (no dyspnea or respiratory discomfort) to 100 mm (worst imaginable dyspnea or respiratory discomfort)</p>	<p>Dyspnea-VAS &gt; 3 defines a clinically relevant dyspnea<sup>G</sup></p>	<p>Patients need to be communicative                      Patients who report dyspnea have a higher P0.1<sup>H</sup></p>
<p><b><i>Dyspnea-Numerical rating scale (NRS)</i></b><sup>I</sup>                      From 0 (no dyspnea or respiratory discomfort) to 10 (worst imaginable dyspnea or respiratory discomfort)</p>	<p>Dyspnea-NRS ≥ 4 defines a clinically relevant dyspnea<sup>G</sup></p>	<p>Patients need to be communicative                      Patients who report dyspnea have a higher P0.1<sup>J</sup></p>
<p><b><i>IC-RDOS</i></b><sup>K</sup>                      Use of neck muscles, paradoxical motion of the abdomen, need for oxygen, heart rate, and facial expression of fear</p>	<p>IC-RDOS of 6.3 predicted D-VAS ≥ 4</p>	<p>Correlation with effort has not been assessed</p>
<p><b><i>MV-RDOS</i></b><sup>L</sup>                      Heart rate, respiratory rate, paradox breathing, use of neck muscles, and facial expression of fear</p>	<p>MV-RDOS of 2.3 predicted a D-VAS &gt;3</p>	<p>Correlation with effort has not been assessed</p>

IC-RDOS, Intensive Care - Respiratory Distress Observation Scale; MV-RDOS; Mechanical Ventilation Respiratory Distress Observation Scale; VAS, visual analog scale; NRS, numerical rating scale

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