Diaphragm Neurostimulation to optimize Biventricular Performance during Invasive Mechanical Ventilation for Acute Respiratory Failure

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Disclosure of Relevant Financial Relationships

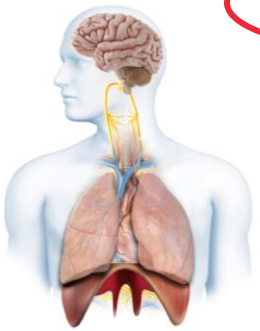
Within the prior 24 months, I, Thiago Bassi, have had a financial relationship with a company producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients:

Nature of Financial Relationship	Ineligible Company
Senior Research Scientist	Lungpacer Medical Inc.

All relevant financial relationships have been mitigated.
Faculty disclosure information can be found on the app

Hemodynamic Effects of Mechanical Ventilation

Spontaneous Breathing



Inspiratory effects on cardiac loading conditions

Increase in RV preload
Due to negative inspiratory intrathoracic pressure

Small increase in LV afterload
Due to inspiratory increase in transpulmonary pressure

Increase in RV filling at inspiration

Increase in RV stroke volume at inspiration

Pulmonary transit time

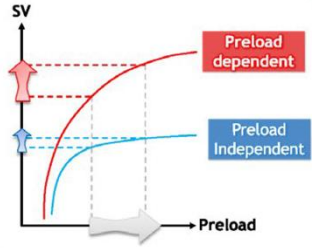
Increase in LV filling at expiration

Increase in LV stroke volume at expiration

Decrease in LV preload
Compared to expiration

Small increase in LV afterload
Due to negative inspiratory intrathoracic pressure

If RV preload dependency



If LV preload dependency

Decrease in RV preload
Due to increase in intrathoracic pressure

Small increase in RV afterload
Due to increase in intrathoracic pressure

Decrease in RV filling at insufflation

Decrease in RV stroke volume at insufflation

Pulmonary transit time

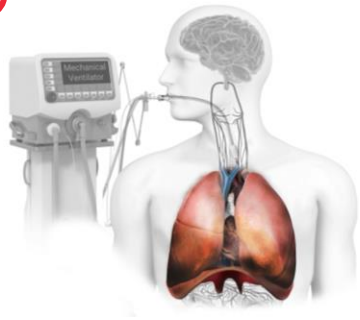
Decrease in LV filling at expiration

Decrease in LV stroke volume at expiration

Increase in LV preload
Compared to expiration

Small decrease in LV afterload
Due to increase in intrathoracic pressure

Mechanical Ventilation



Effects of mechanical insufflation on cardiac loading conditions

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Jozwiak, M., Teboul, JL. Heart–Lungs interactions: the basics and clinical implications. *Ann. Intensive Care* **14**, 122 (2024).

Why Does It Matter?

- Positive pressure ventilation may impair cardiovascular performance by:
  - Decreasing RV preload and increasing RV afterload.
  - Increasing pulmonary vascular resistance.
- Consequences:
  - Exacerbates shock states.
  - Contributes to organ dysfunction.
- Potential solution: Diaphragm neurostimulation

Cor pulmonale is a major cause of death in AHRF

STIMULUS Phase 1 - Study Design

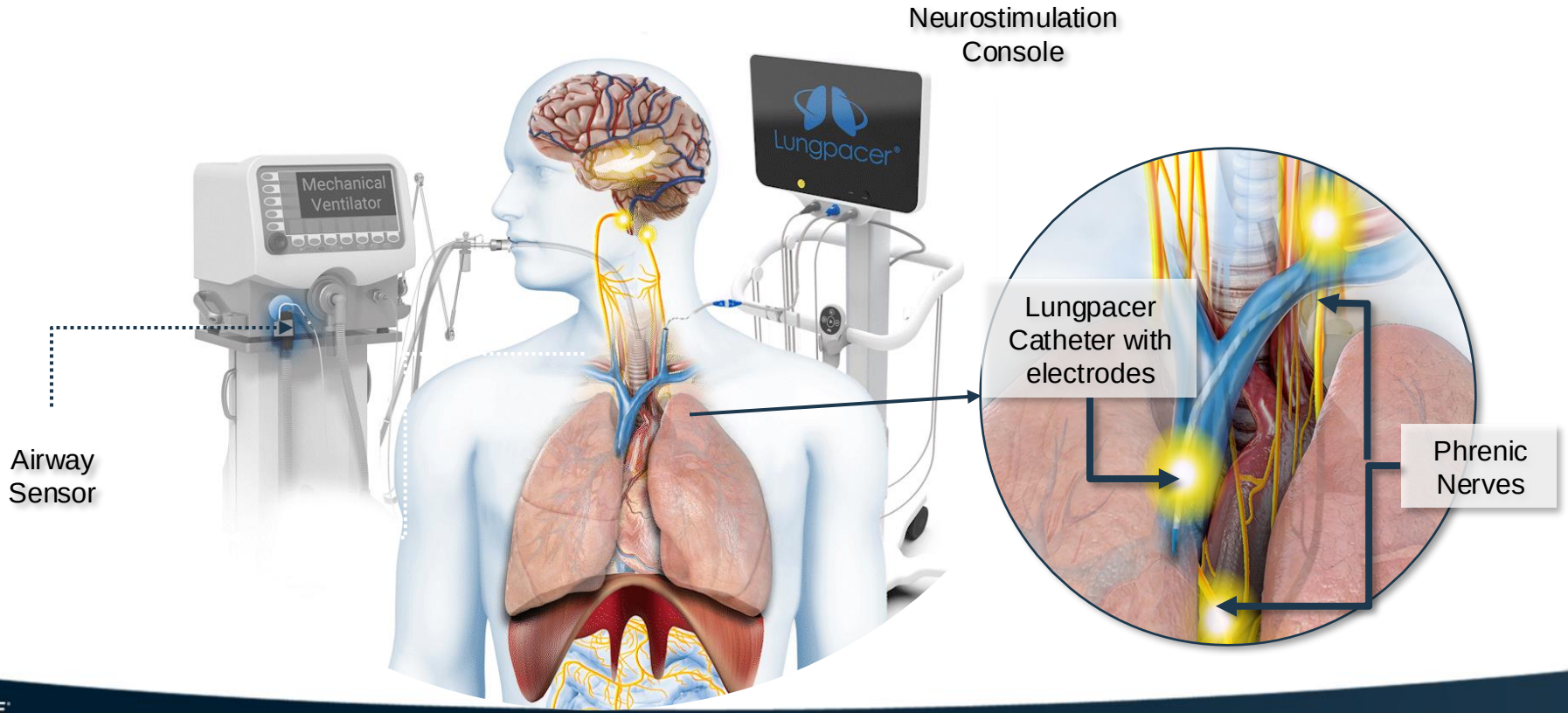
- Patients:
  - Mechanically ventilated with acute hypoxemic respiratory failure or post-thoracic surgery.
- Intervention:
  - Continual bilateral transvenous phrenic nerve stimulation using Lungpacer System investigational device.
- Measurements:
  - Hemodynamic measurements during passive ventilation.
  - Cardiac output, pulmonary artery pressures, in those with an established clinical indication for monitoring.
  - **Nested Titration Study (NTS):** Three levels of stimulation (quantified by the expiratory occlusion pressure) at two randomly ordered levels of positive end-expiratory pressure (PEEP), at least 5 cm H_2O apart.

Who Was Studied?

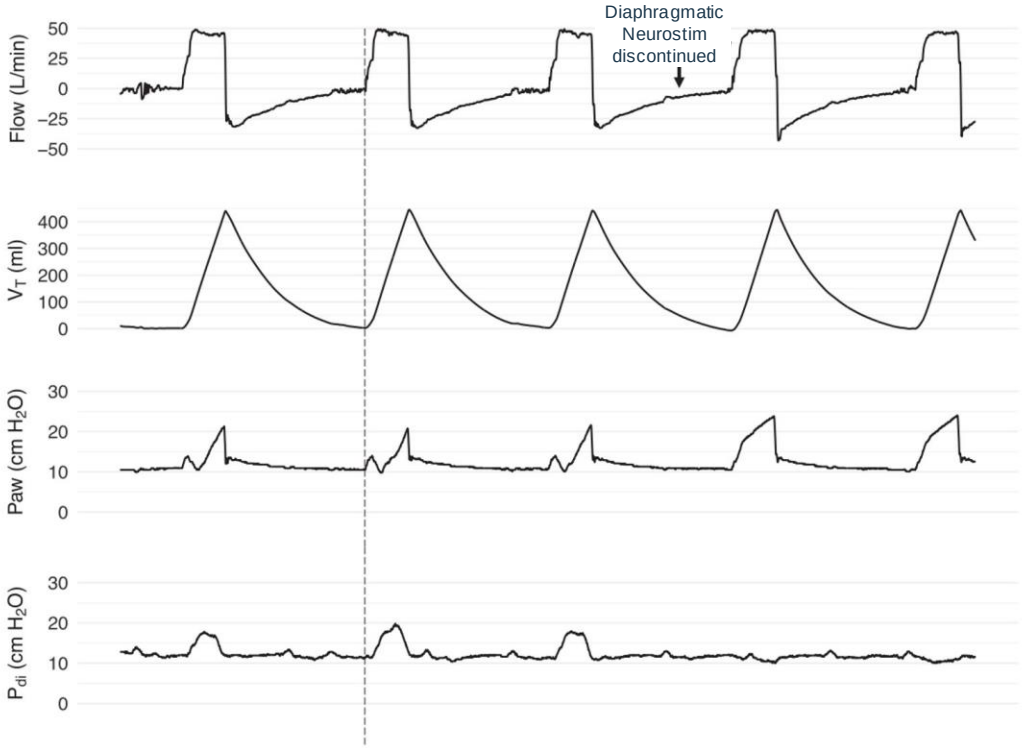
- Total Patients: 19 enrolled, 16 underwent titration procedure.
- 12/16 (75%) pre-existent cardiac dysfunction
- 9/16 (56%) documented RV dysfunction and/or pulmonary hypertension
- Pulmonary artery pressures were available in all participants with right heart disease

	All NTS patients (n=16)	Available PAC data (n=11)	Available CO data (n=8)
Age (years):	60 (49, 64)	60 (48, 65)	54 (45, 61)
Sex (male):	13 (81%)	8 (73%)	6 (75%)
BMI (kg/m^2):	27 (25, 35)	26 (24, 31)	27 (26, 35)
Known cardiac disease: Isolated PHtn RV dysfunc (+/- Phtn) Other	12 (75%) 3 (19%) 6 (38%) 3 (19%)	10 (91%) 4 (%) 6 (%) 0 (0%)	8 (100%) 3 (38%) 5 (62%) 0 (0%)
PaO_2/FiO_2 (mmHg)*:	237 (144, 329)	296 (231, 302)	267 (206, 323)
ARF type: Surgical AHRF	 11 (69%) 5 (31%)	 11 (100%) 0 (0%)	 8 (100%) 0 (0%)
NTS PEEP (cmH_2O): High Low	 15 (10, 16) *n=16* 7 (5, 10) *n=15*	 12 (10, 15) 7 (5, 10)	 15 (10, 16) 8 (5, 10)
NTS Tidal Volume (ml/kg PBW):	6 (6, 7)	7 (6, 7)	7 (7, 7)
NTS vasoactive agents: Nil Single agent Two or more agents	 2 (12%) 11 (69%) 3 (19%)	 0 (0%) 8 (73%) 3 (27%)	 0 (0%) 5 (62%) 3 (38%)

Lungpacer Diaphragmatic Neurostimulation System



Diaphragmatic Neurostimulation



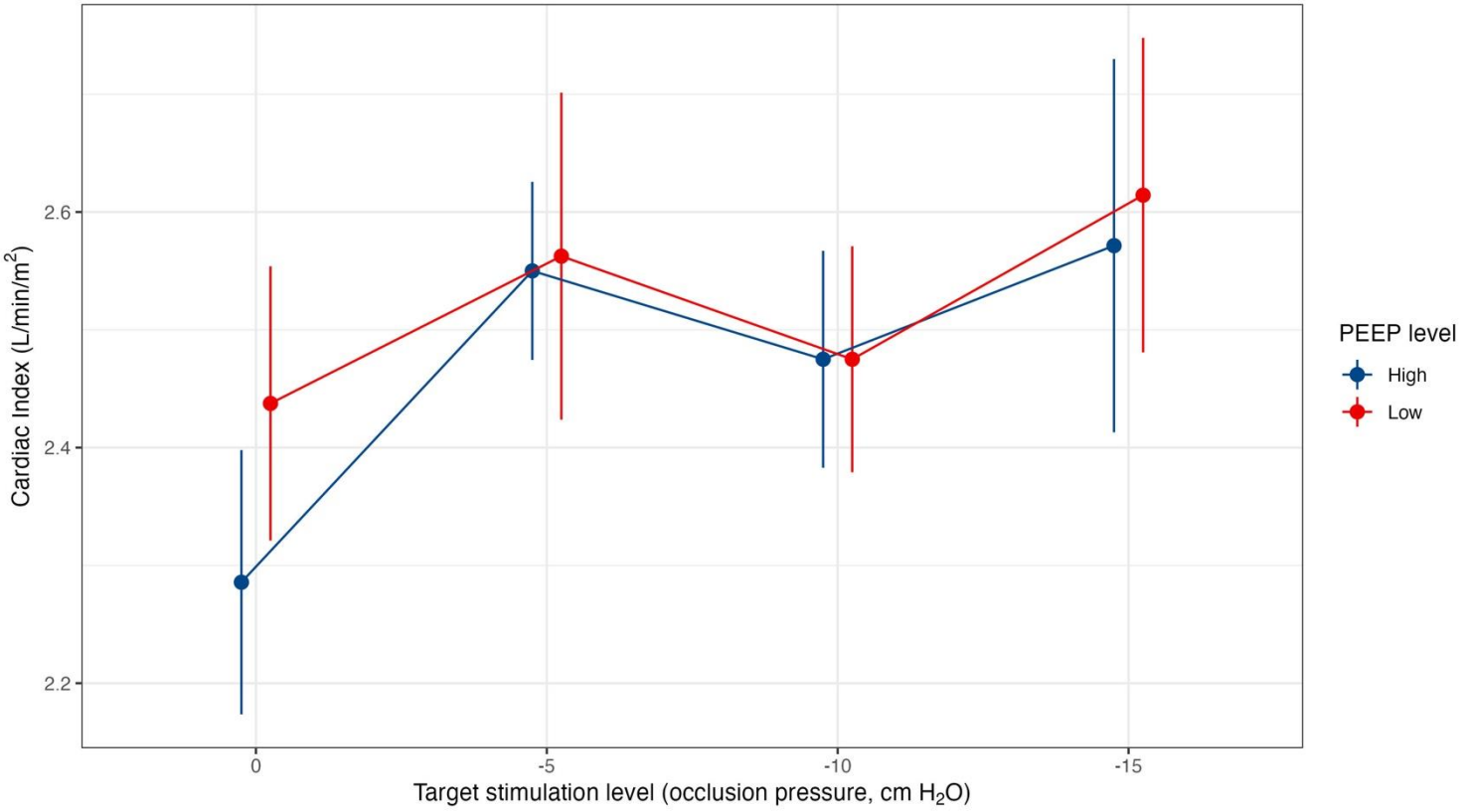
Morris et al. AJRCCM 2023

Key Results

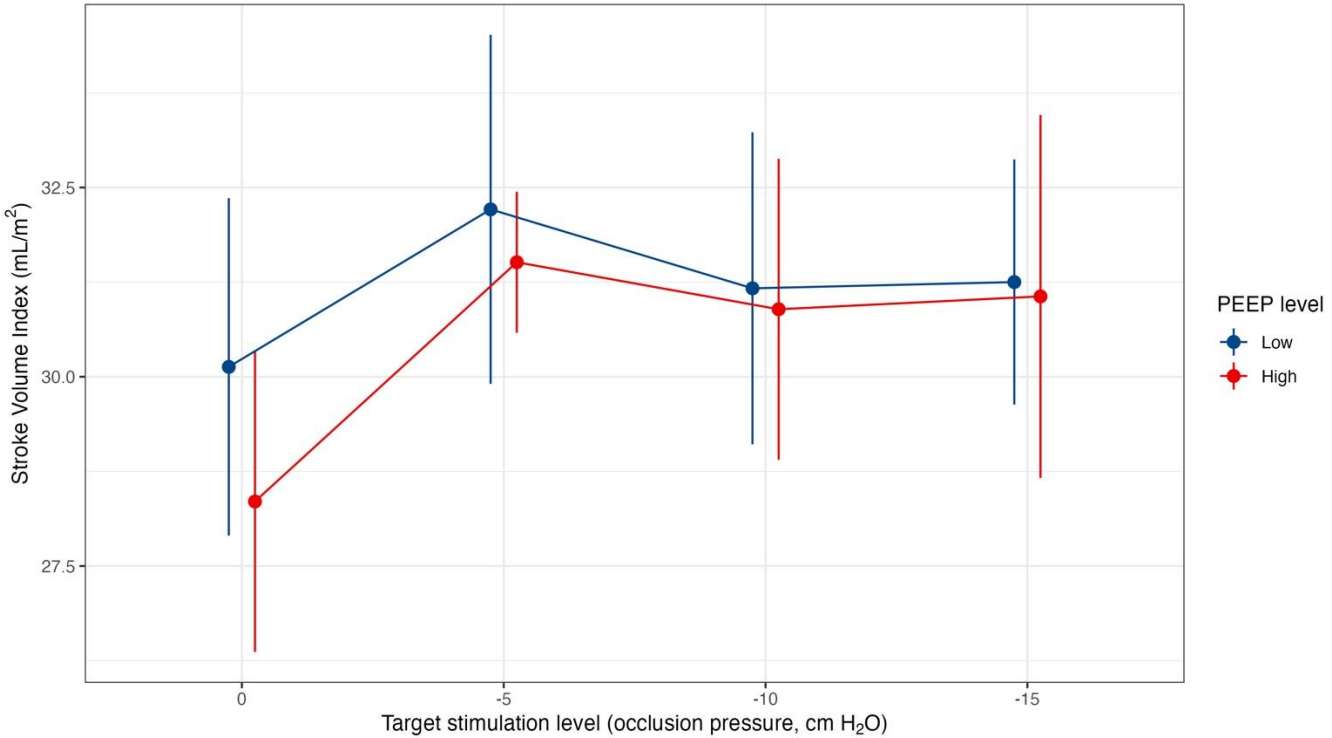
- With Increasing Diaphragm Neurostimulation*:
  - Cardiac Index: Increased (p=0.003).
  - Stroke Volume Index: Increased (p=0.016).
  - Mean Arterial Pressure: Increased (p=0.002).
  - Mean Pulmonary Artery Pressure: Decreased (p<0.001).
  - Indicates reduction in pulmonary vascular resistance.

*p-values from the comparison between the mean values across the nested titration study

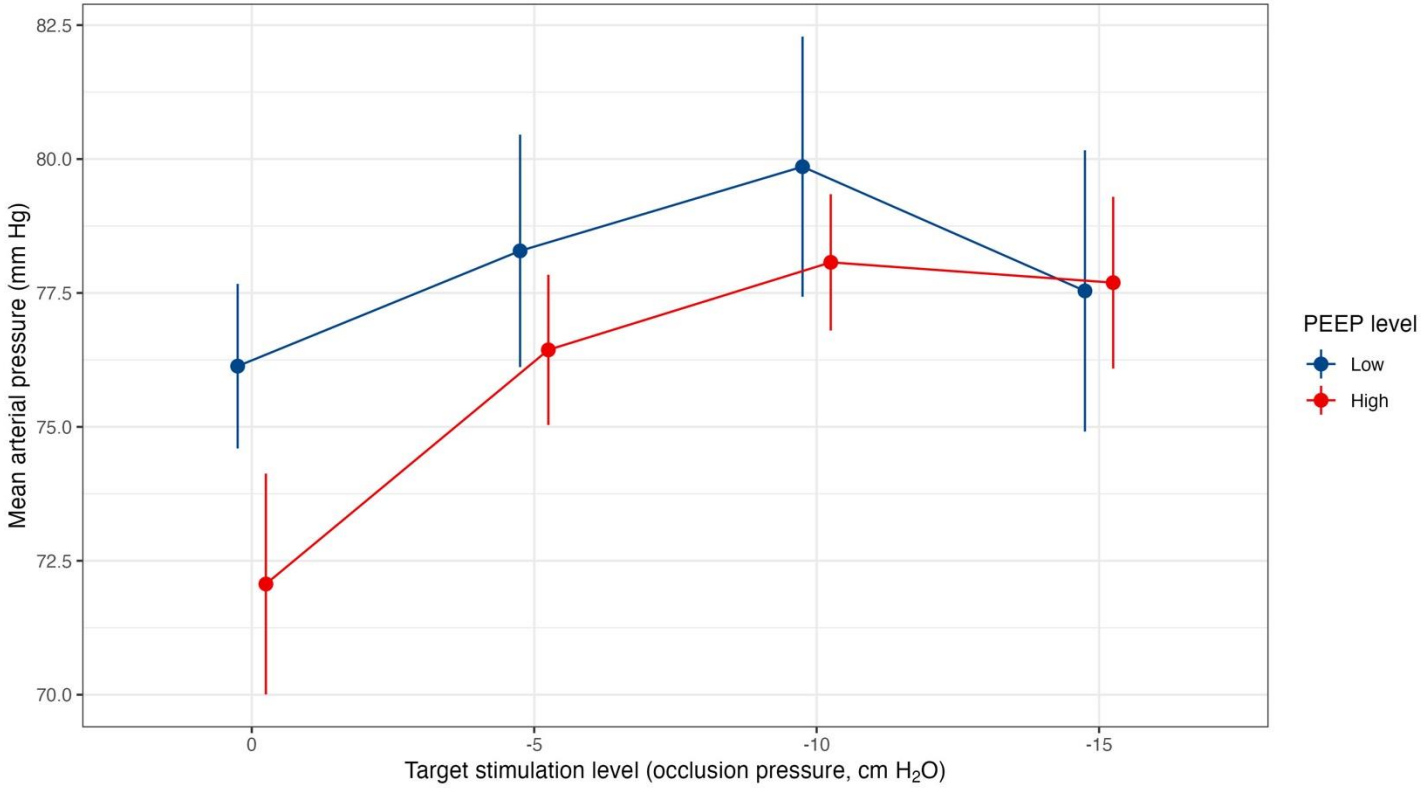
Increase in Cardiac Index



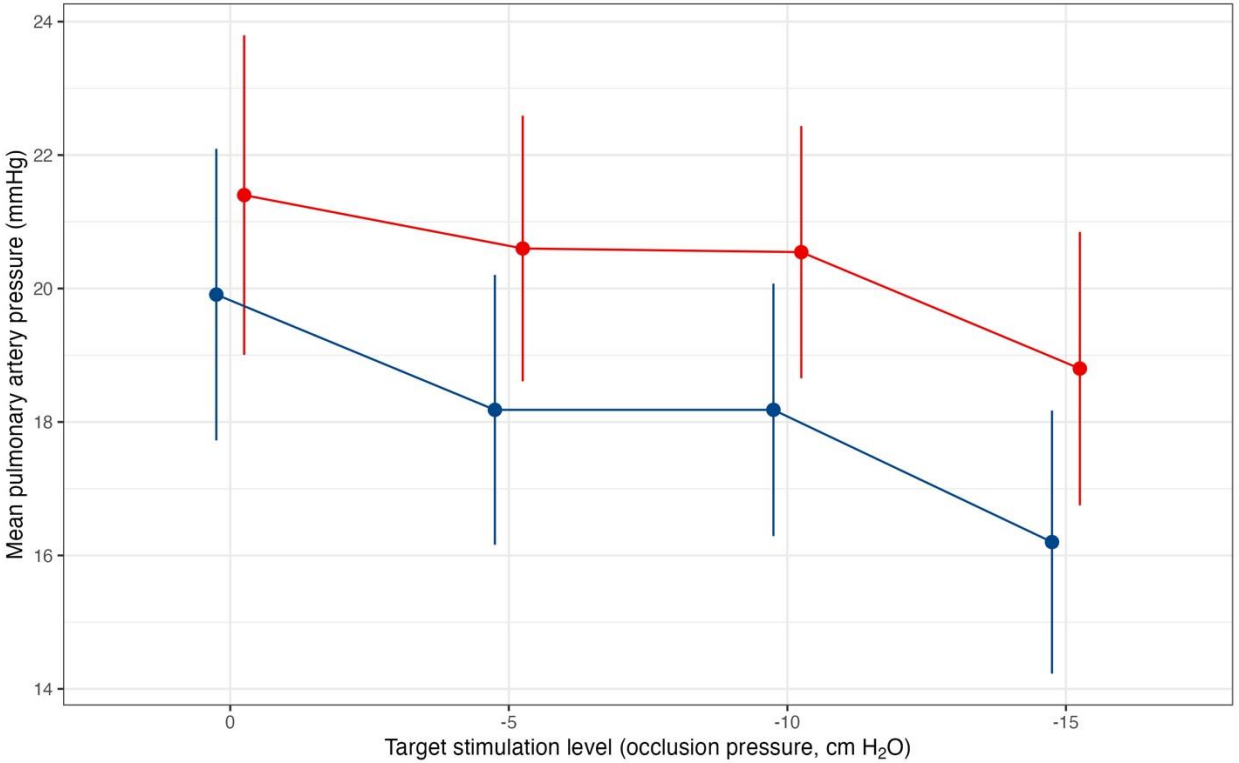
Increase in Stroke Volume Index



Increase in Mean Arterial Pressure



Reduction in Mean Pulmonary Artery Pressure



An increase in the cardiac index suggests pulmonary vascular resistance was significantly reduced (pulmonary capillary wedge pressure and thereby, direct measurement was precluded in surgical patients)

Key Takeaways

Diaphragm neurostimulation in a dose-response fashion (across the range of physiological levels of inspiratory effort):

- Increases cardiac output and stroke volume.
- Reduces pulmonary artery pressure.
- Mitigates adverse hemodynamic effects of positive pressure ventilation.
- Supports further exploration in mechanically ventilated patients.

Thank you!

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