

Role of Spontaneous Breathing during Mechanical Ventilation in ARDS

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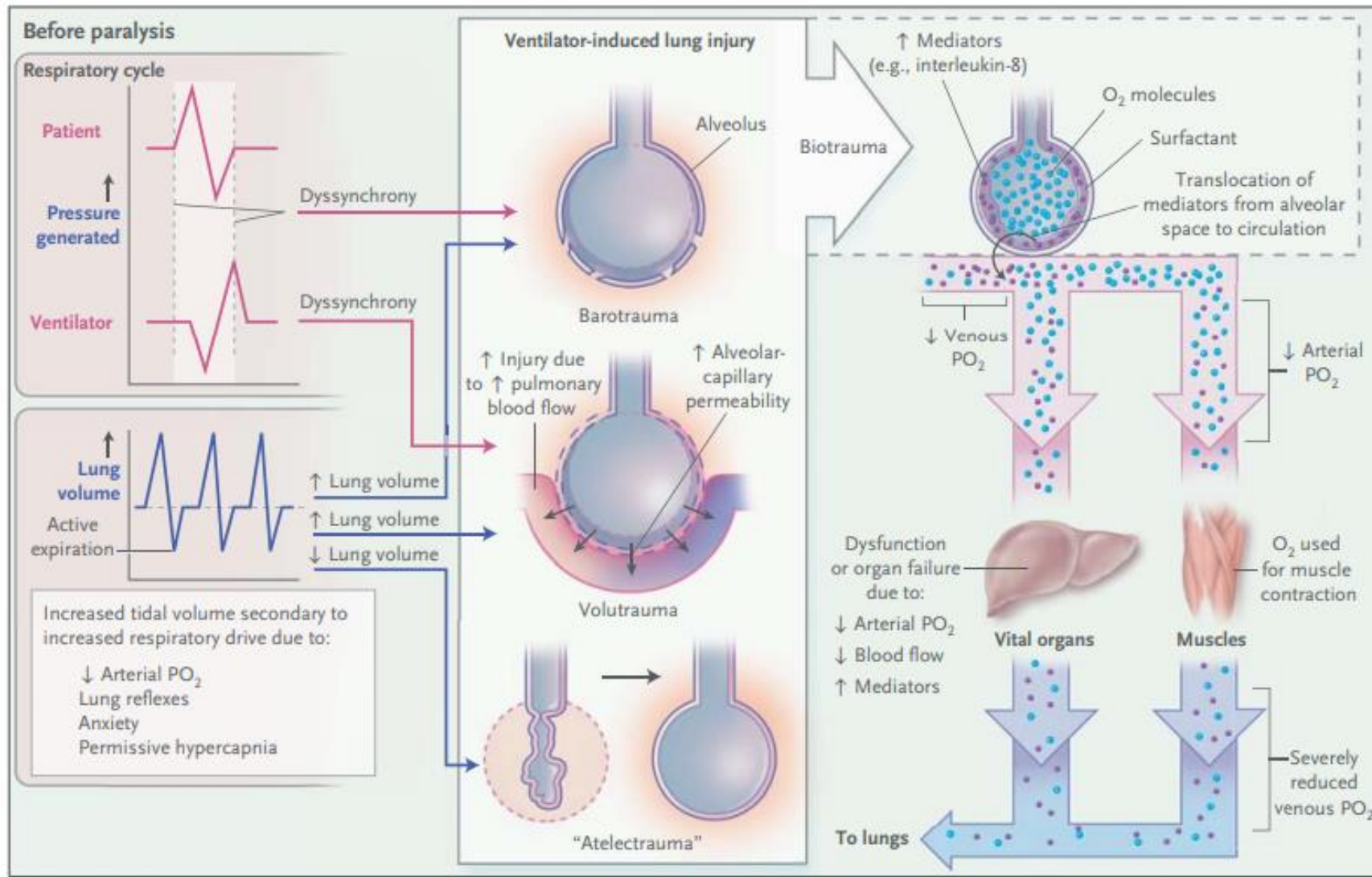
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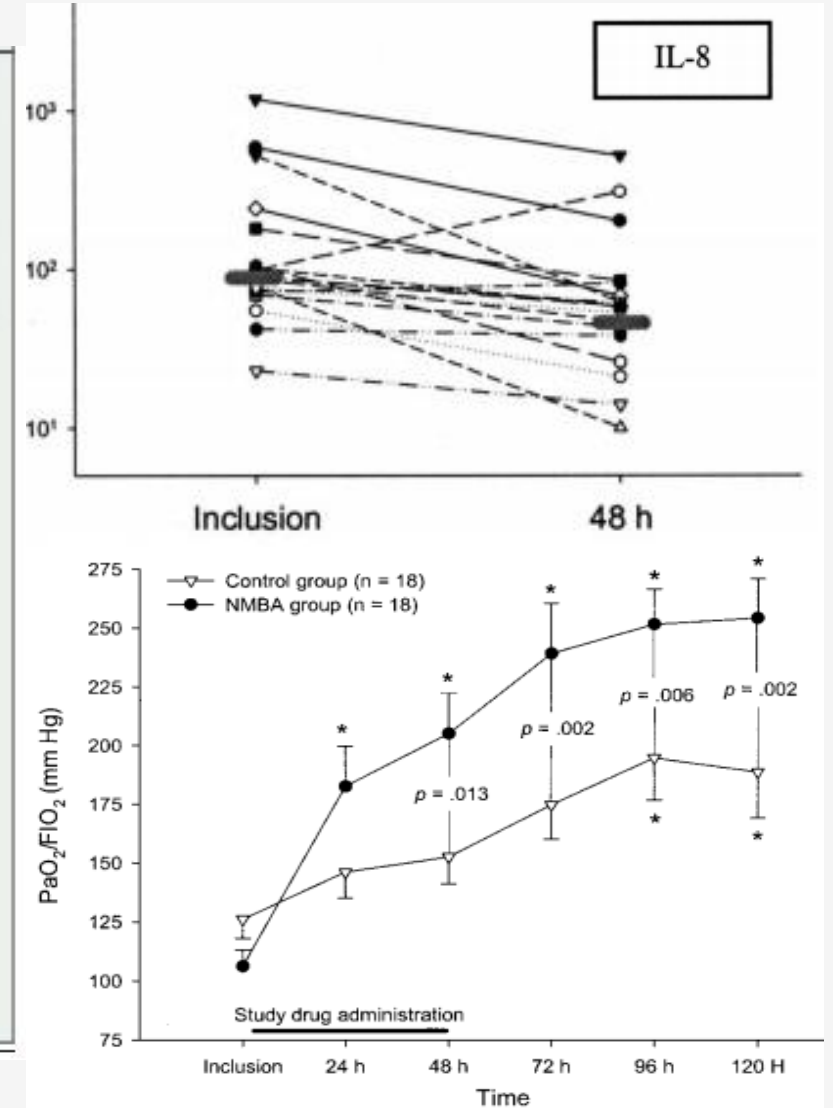
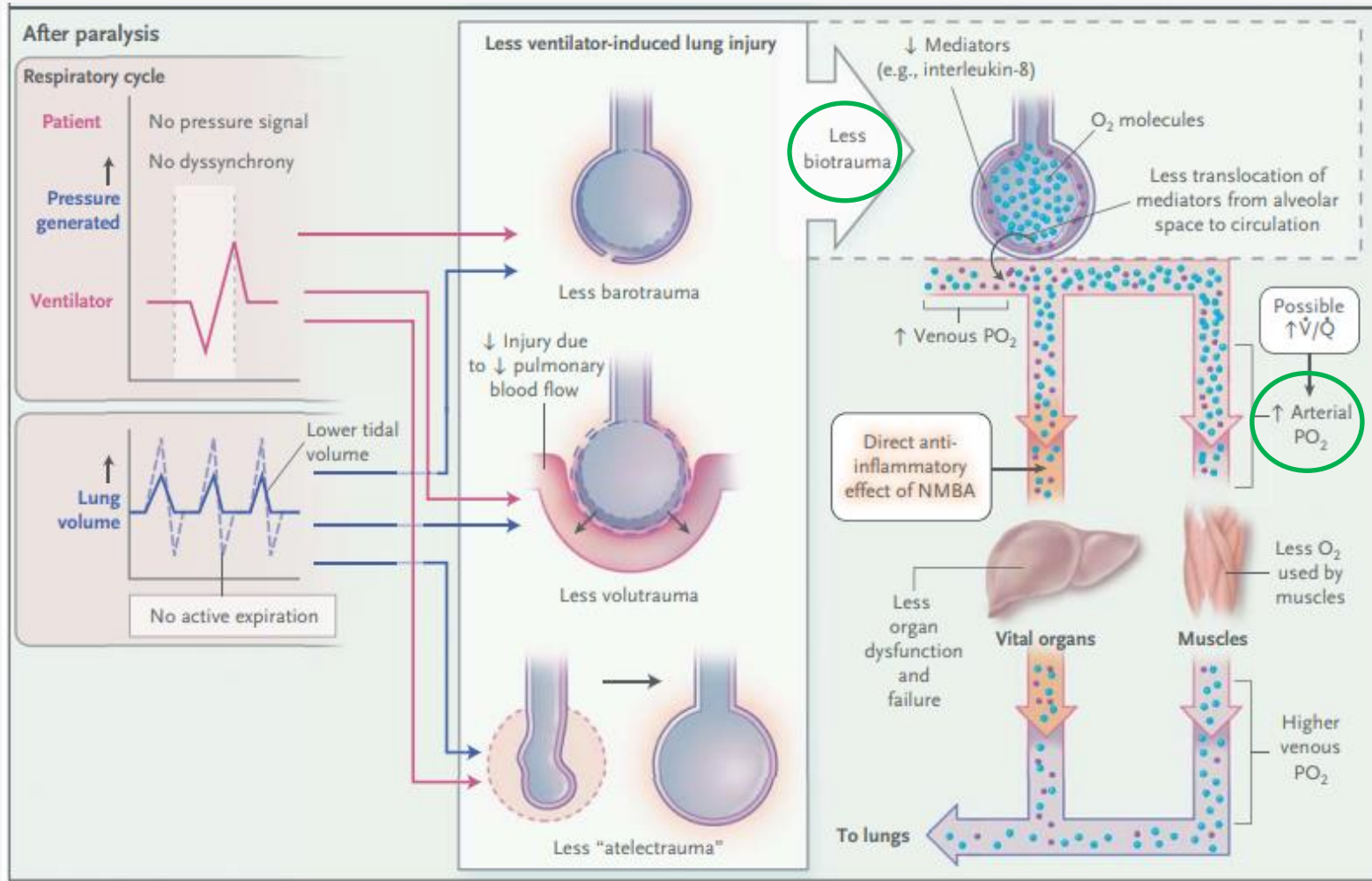
Patient Self-Inflicted Lung Injury (P-SILI)



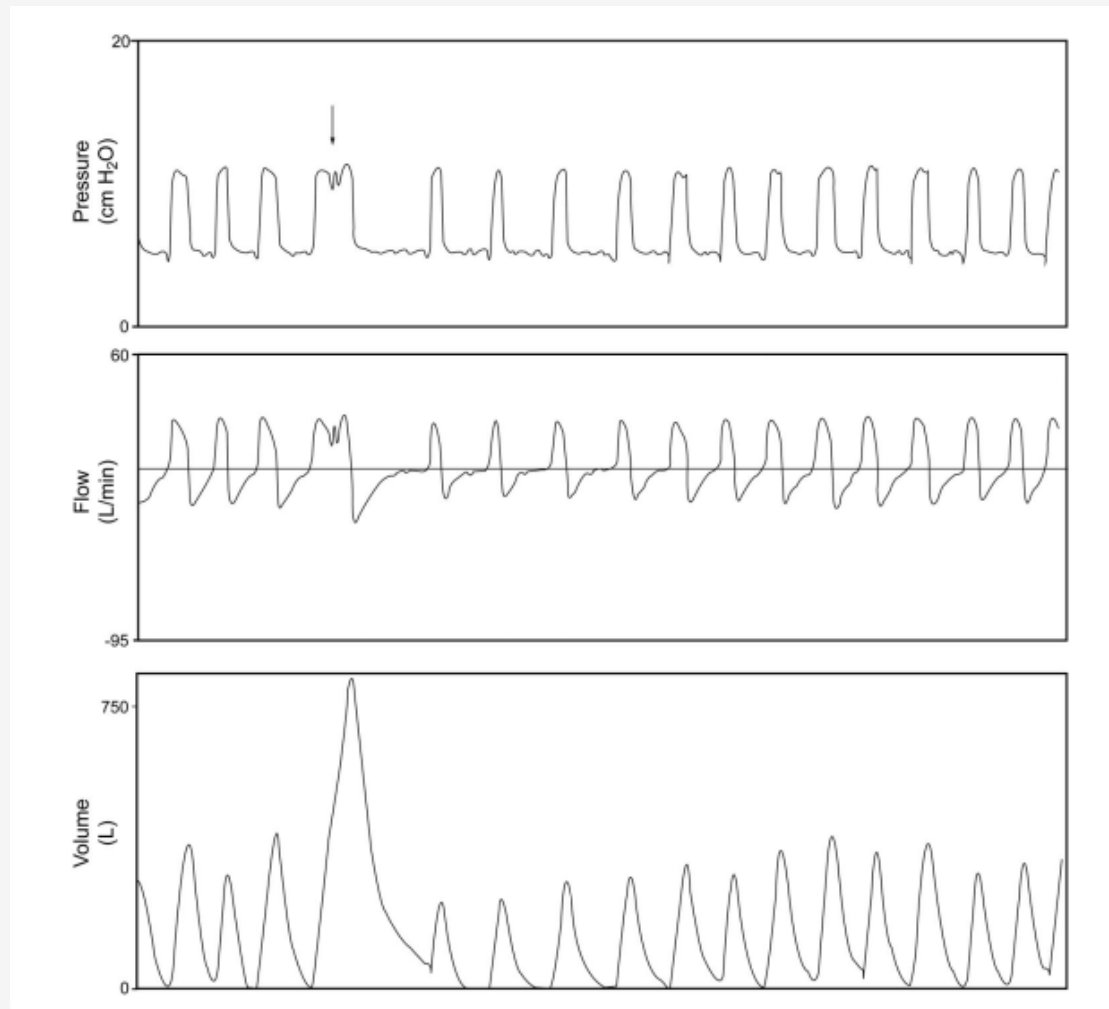
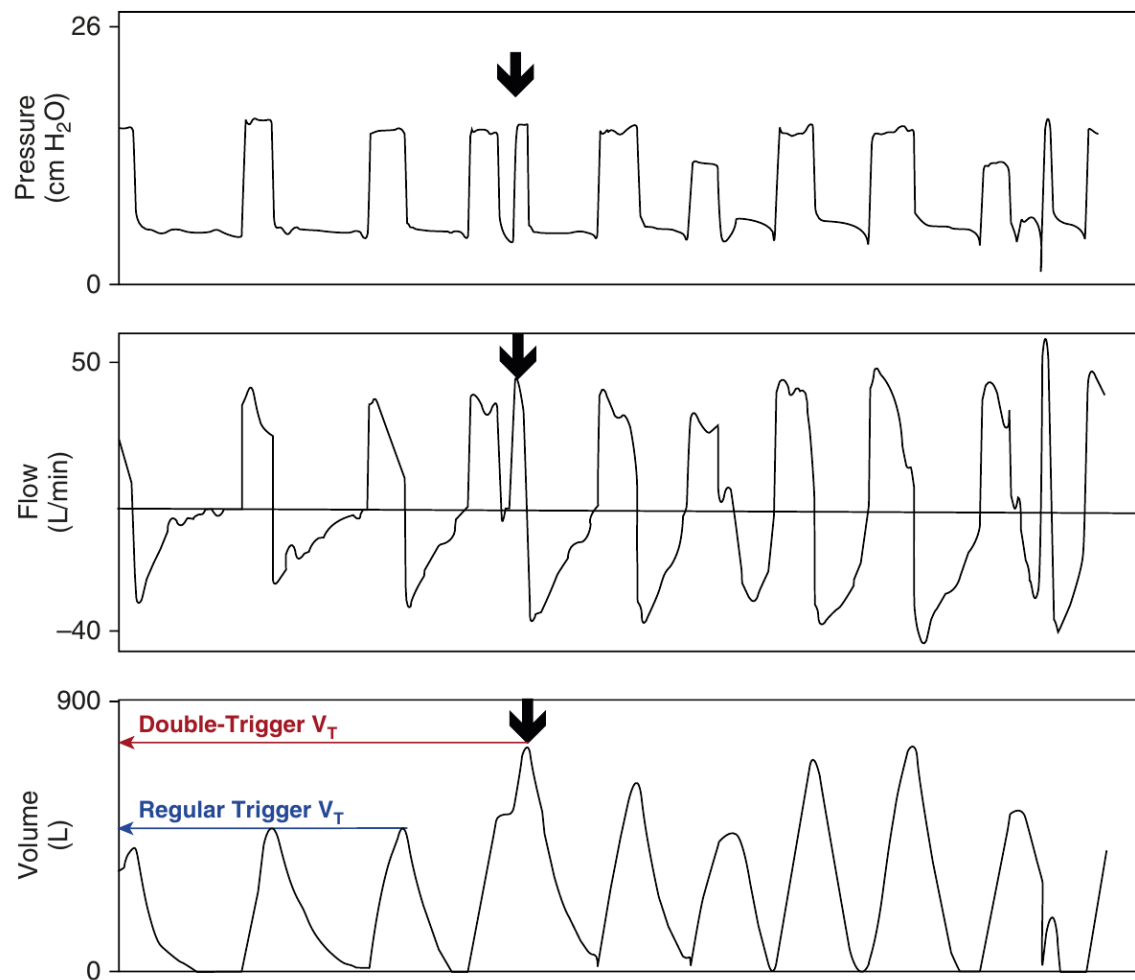
Ventilator induced lung injury (VILI) in ARDS



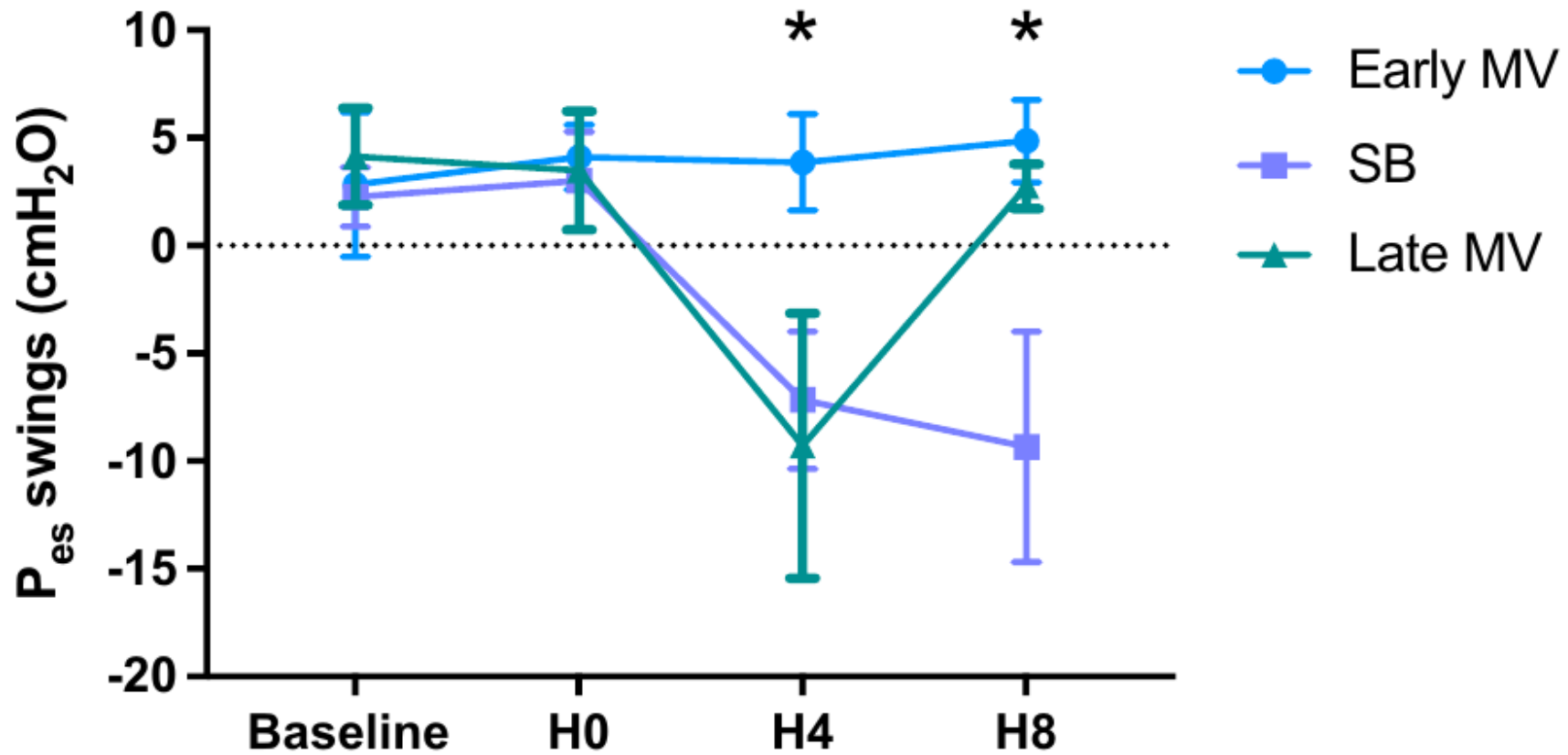
Neuromuscular blocker in ARDS



Patient–Ventilator Asynchrony



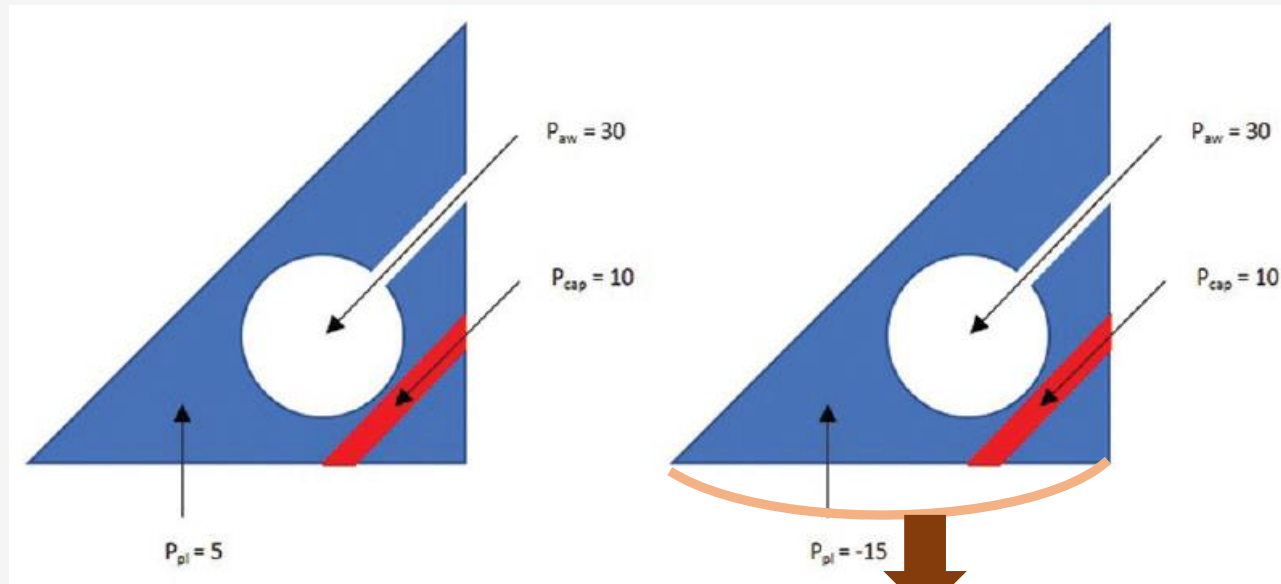
Increasing transpulmonary pressure



Spontaneous effort and transpulmonary and transvascular pressures

- Transpulmonary pressure & transvascular pressure

Paralysis



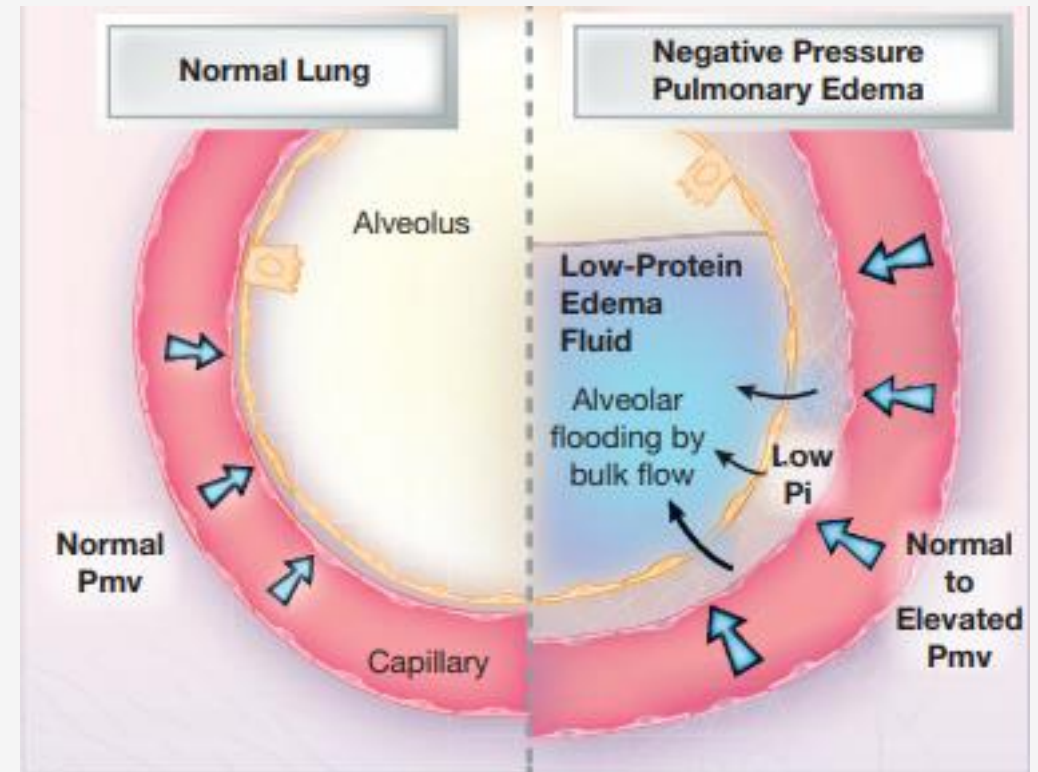
Transpulmonary Pr = $30 - 5 = 25$

Transvascular Pr = $10 - 5 = 5$

Spontaneous breathing

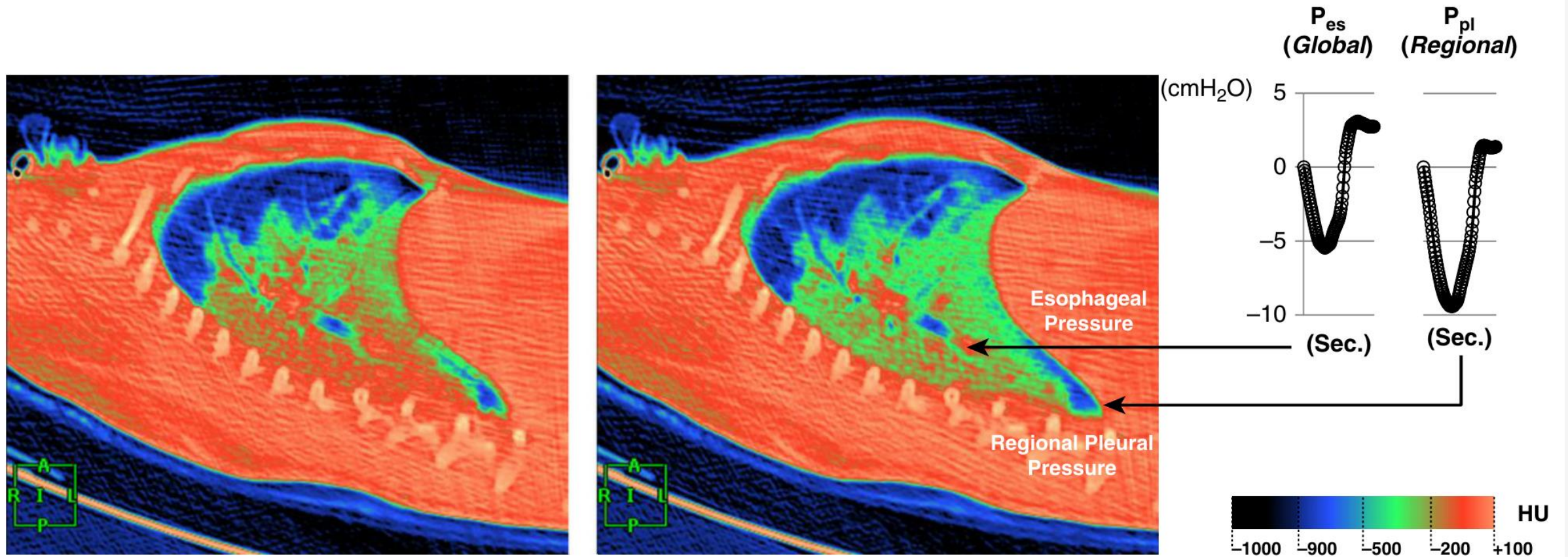
Transpulmonary Pr = $30 - (-15) = 45$

Transvascular Pr = $10 - (-15) = 25$

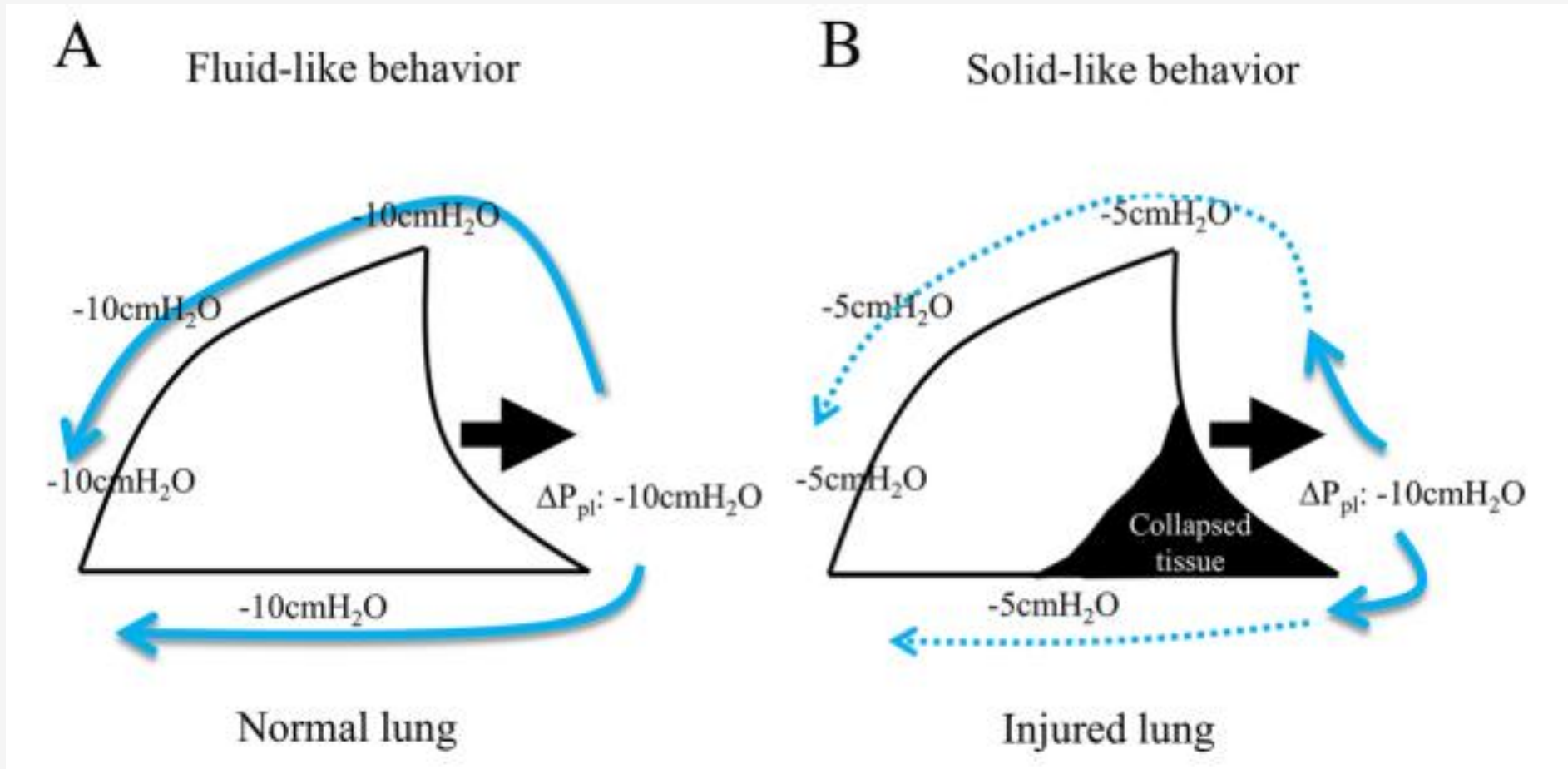


- Increase regional lung stress and strain
- Increase pulmonary edema

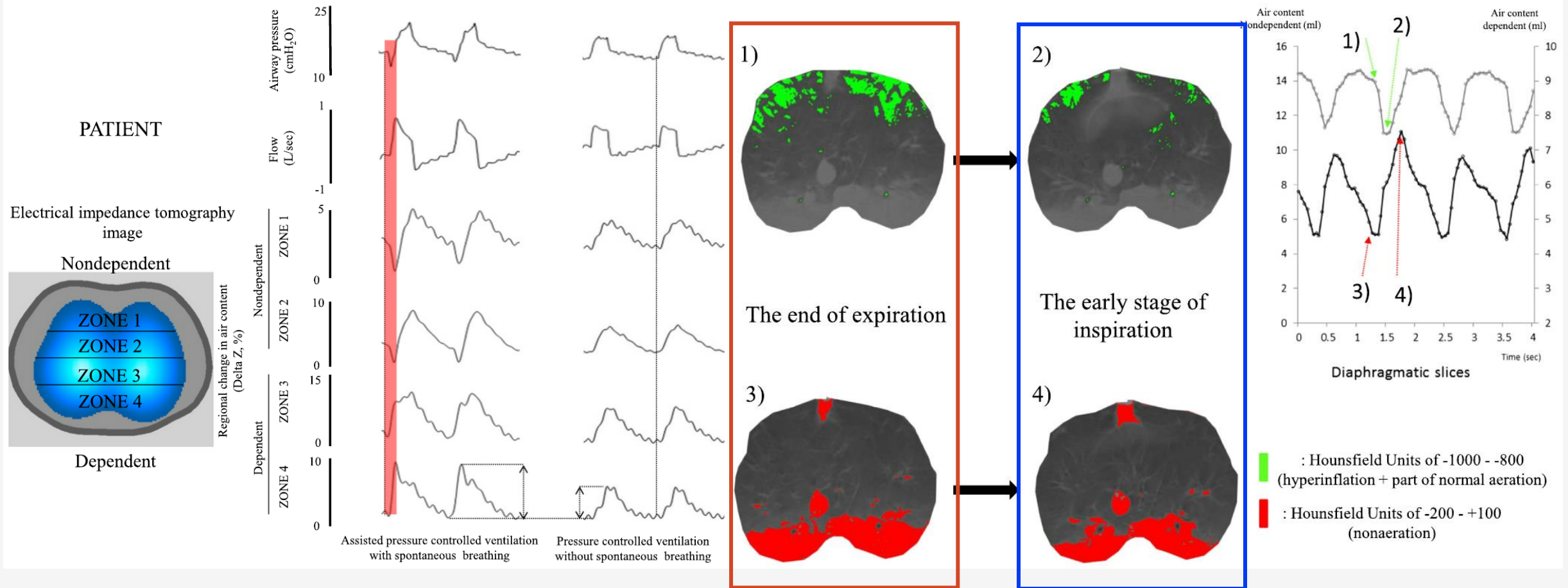
Spontaneous effort increase transpulmonary pressure in dependent lung



Occult-Pendelluft phenomenon

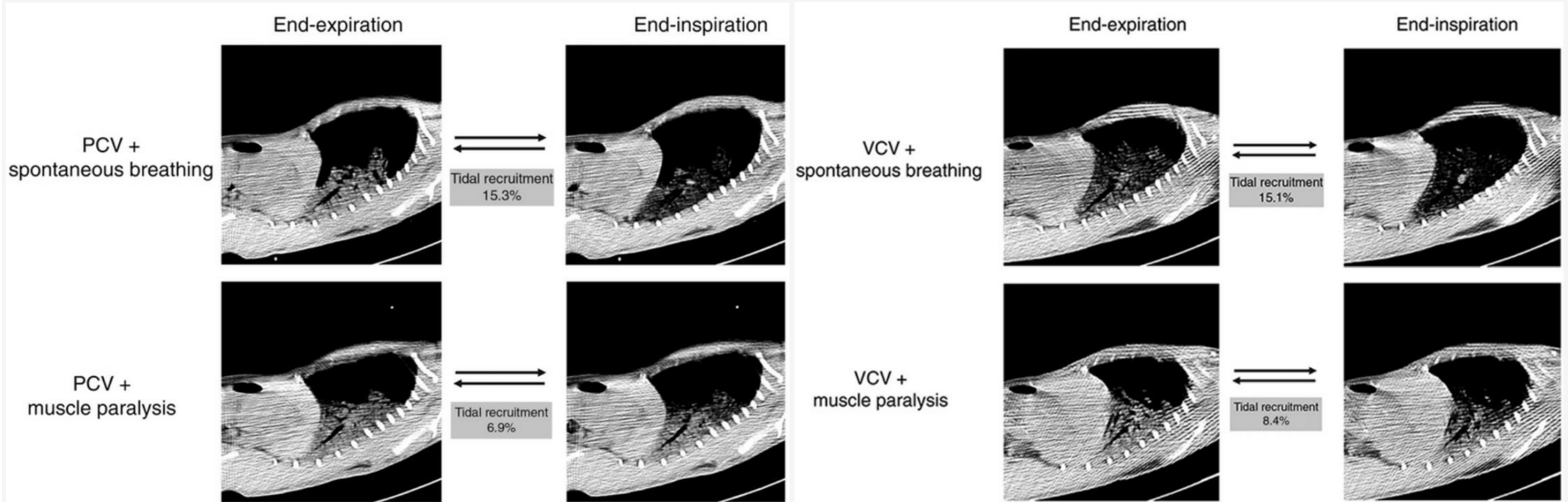


Pendelluft phenomenon



Regional tidal hyperinflation → Lung injury in dependent lung

Spontaneous effort increase atelectrauma in dependent region

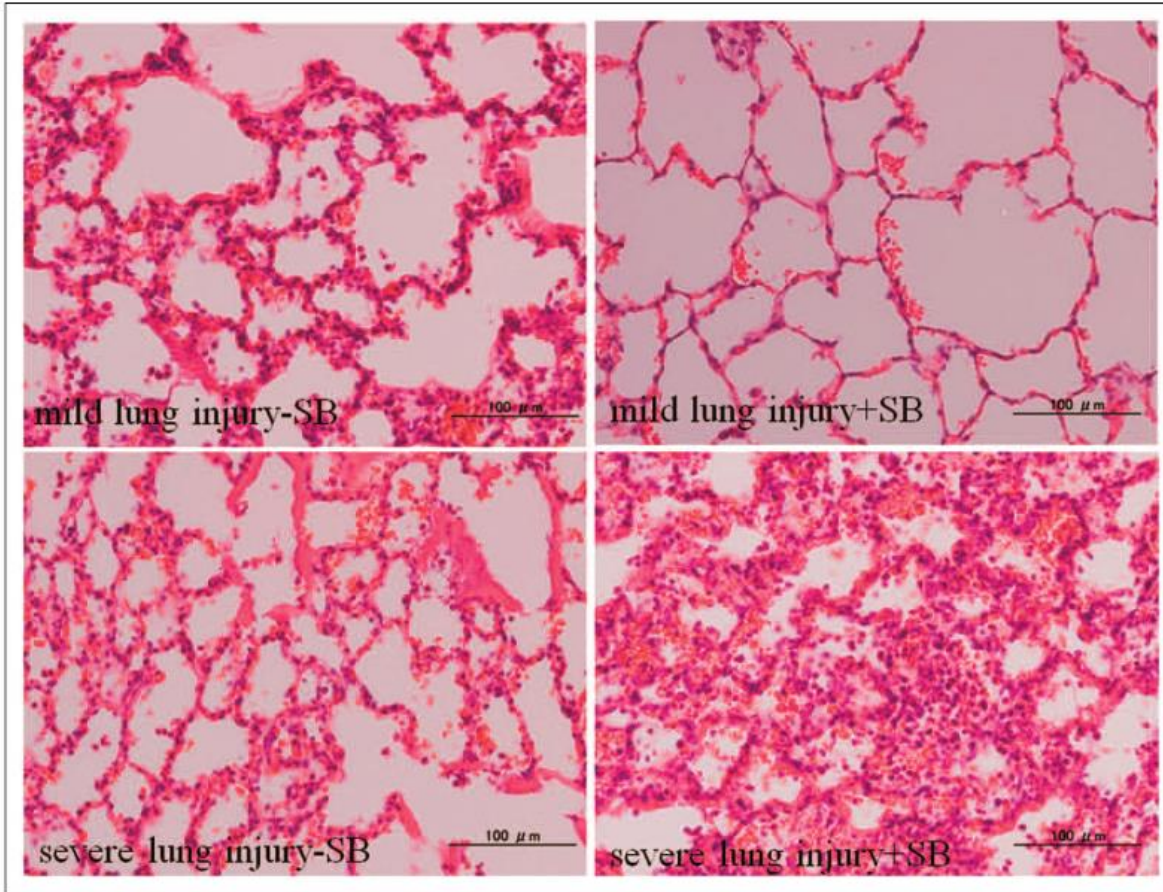


Spontaneous effort increase atelectrauma in dependent region

TABLE 4. Regional Distribution of Tidal Gas, Tidal Hyperinflation, and Cyclic Collapse

Injury	Spontaneous Breathing	Gas Distribution, %		Tidal Hyperinflation, %	Cyclic Collapse, %
		Nondependent Region of Interest	Dependent Region of Interest		
Mild	—	75.8 ± 7.9 ^a	24.1 ± 7.9 ^{a,b}	1.2 ± 1.4	1.5 ± 1.2
	+	42.2 ± 7.2	57.8 ± 7.2 ^b	0.1 ± 0.2	0.4 ± 0.3
Severe	—	54.7 ± 9.6	45.3 ± 9.6	0.1 ± 0.2	1.1 ± 1.4
	+	42.1 ± 9.7	57.9 ± 9.7 ^b	0.6 ± 0.8	8.2 ± 7.7 ^a

In severe lung injury, spontaneous breathing could worsen lung injury

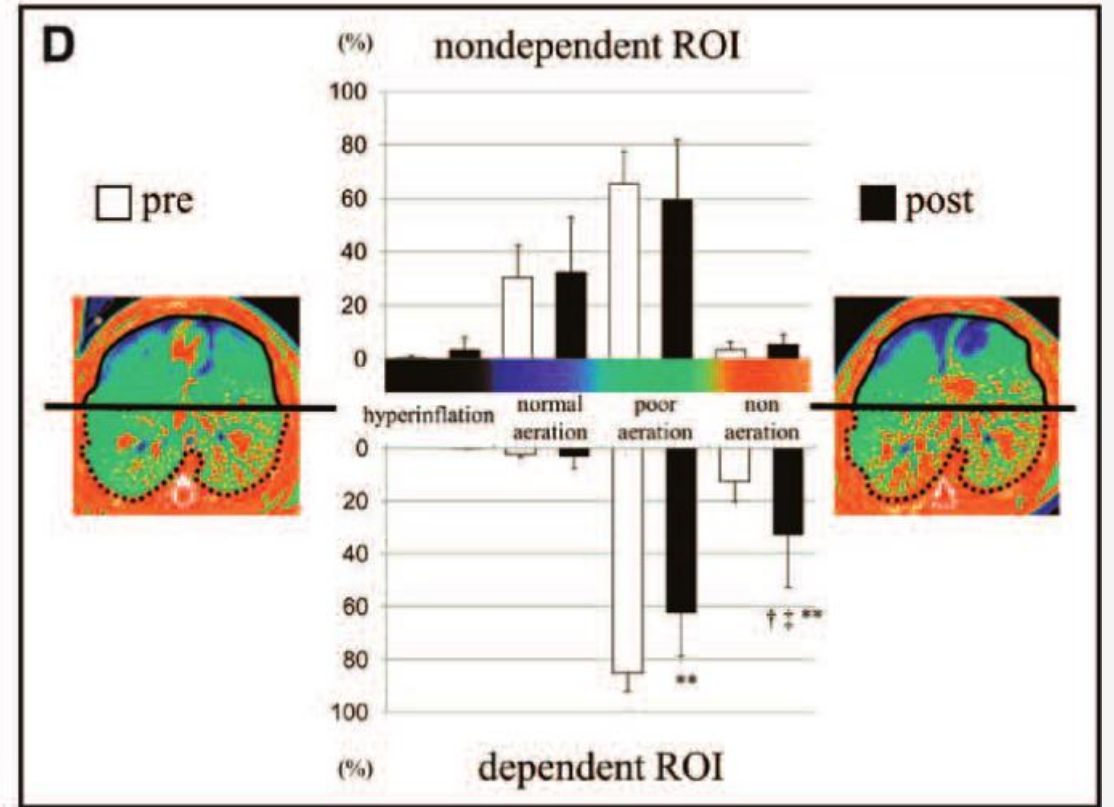
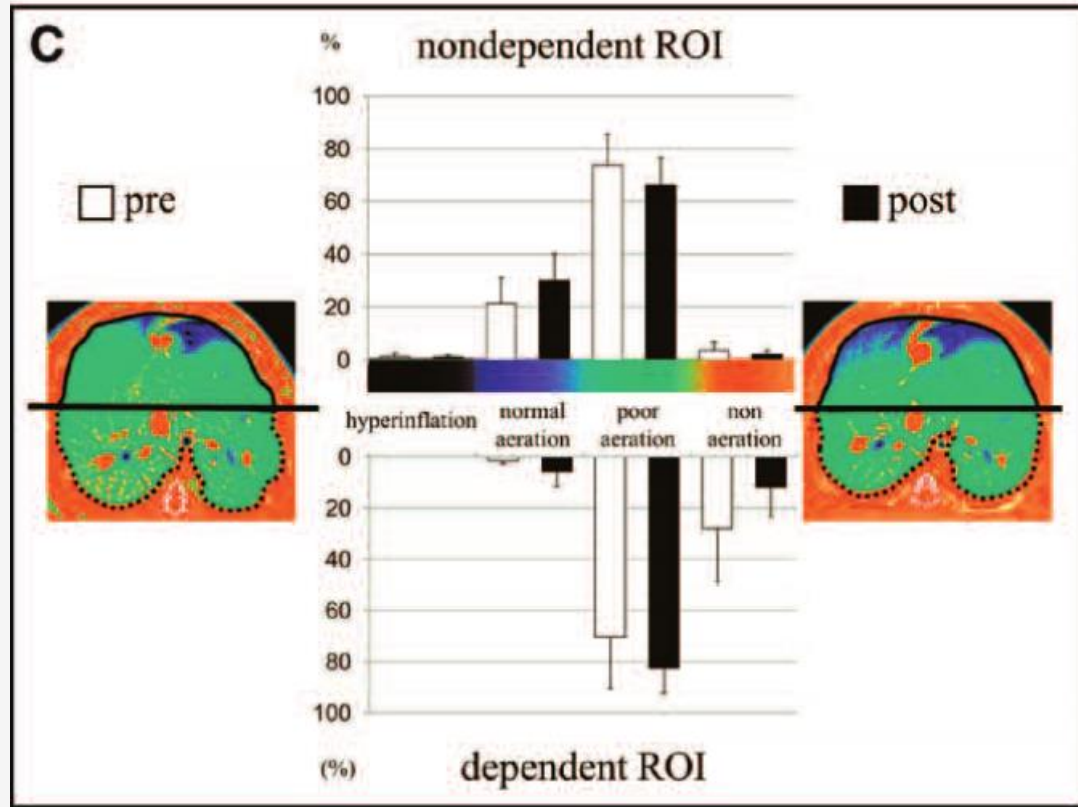


Injury	Spontaneous Breathing	Time After the Start of the Protocol				
		0	1 hr	2 hrs	3 hrs	4 hrs
Pao ₂ /Fio ₂ , mm Hg						
Mild	-	101 ± 39	158 ± 119	166 ± 109	129 ± 78	99 ± 29
	+	104 ± 35	174 ± 89	307 ± 105 ^{e,f}	347 ± 66 ^{a,d,f}	319 ± 63 ^{a,d,f}
Severe	-	51 ± 17 ^{a,b}	82 ± 45	149 ± 81	239 ± 140 ^{d,f}	240 ± 148 ^{a,d,f}
	+	51 ± 10 ^{a,b}	138 ± 118 ^f	121 ± 84	79 ± 48	76 ± 31

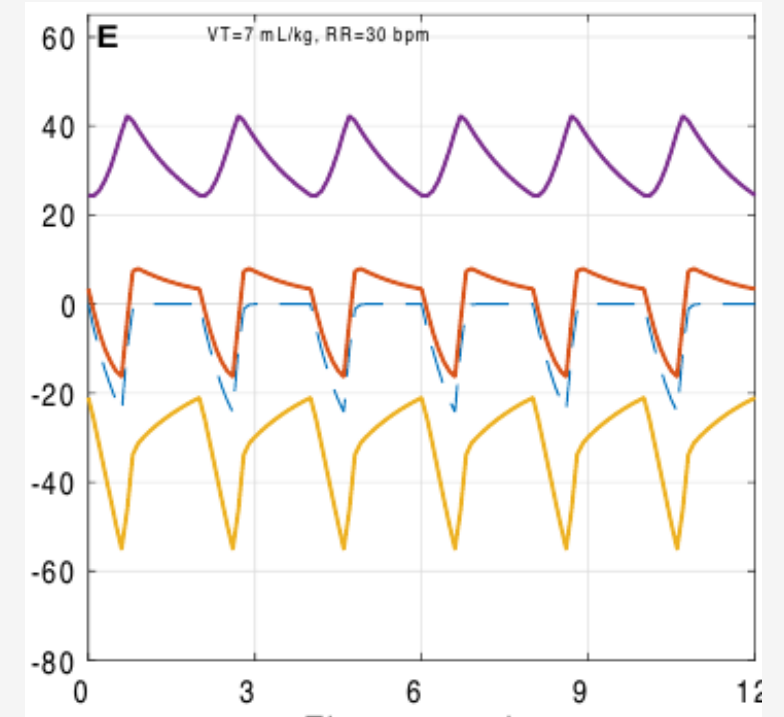
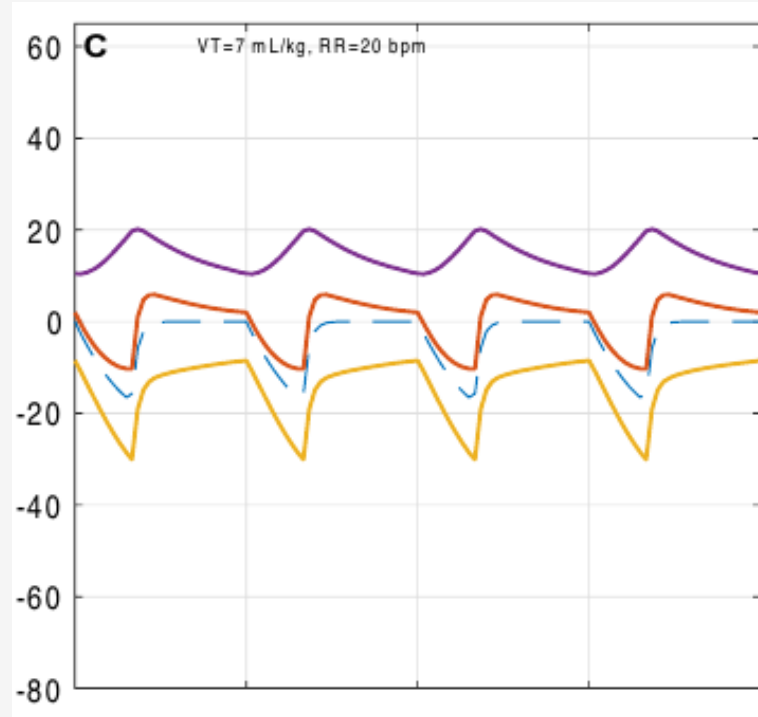
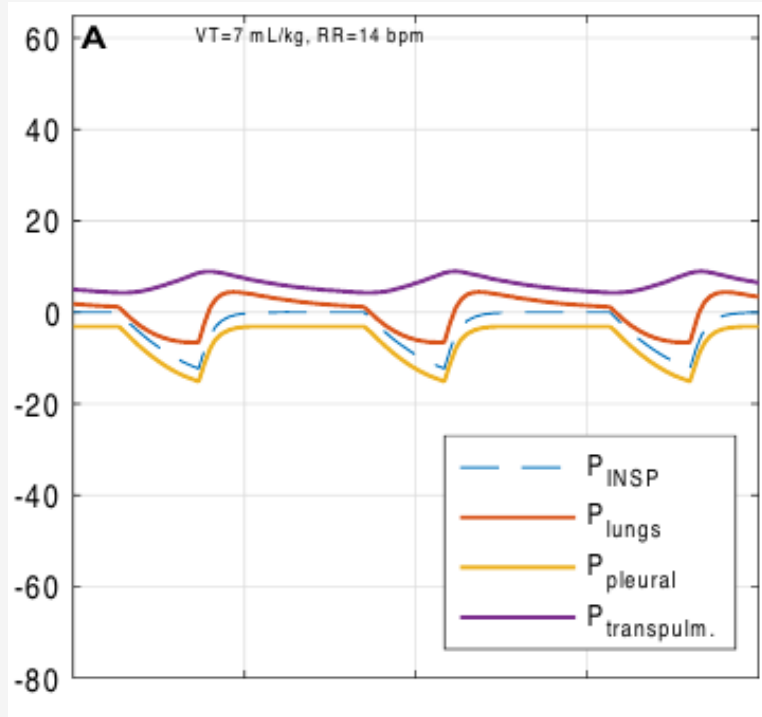
Spontaneous breathing could worsen lung injury in severe lung injury

SB (-)

SB (+)



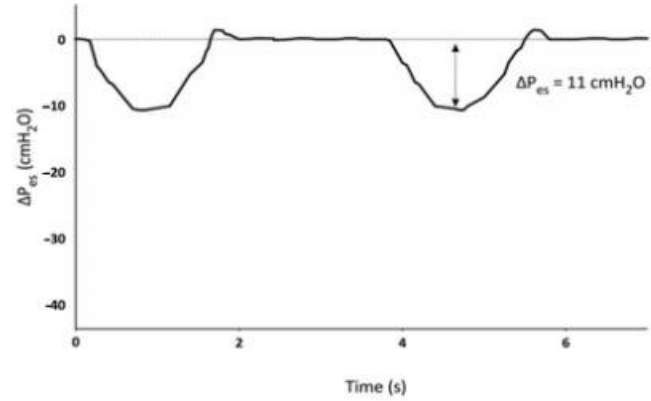
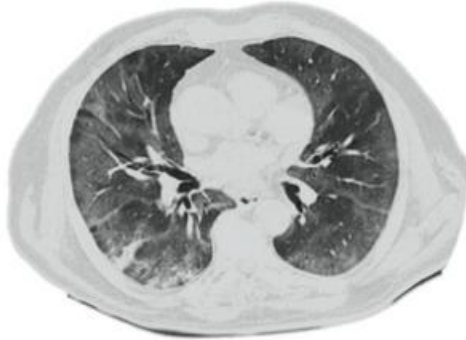
Inspiratory effort & Transpulmonary Pressure



VT (ml)	487.7 ± 2.1	487.9 ± 2.2	489.6 ± 0.7	695.9 ± 1.9	695 ± 2.8	697.5 ± 1.3
Compliance (ml/cmH ₂ O)	63 ± 1.4	39.6 ± 0.9	25 ± 0.3	64.7 ± 1.4	41.3 ± 0.7	26 ± 0.3
DP (cmH ₂ O)	7.7 ± 0.2	12.2 ± 0.2	12.1 ± 0.2	12.2 ± 0.2	11.2 ± 0.2	21.2 ± 0.2
Power (J/min)	1.6 ± 0.1	4.7 ± 0.1	12.9 ± 0.2	3.0 ± 0.1	8.9 ± 0.2	24.9 ± 0.3
Total Strain	0.29 ± 0.006	0.35 ± 0.005	0.44 ± 0.008	0.44 ± 0.008	0.51 ± 0.011	0.65 ± 0.016

Influence of inspiratory effort in SB

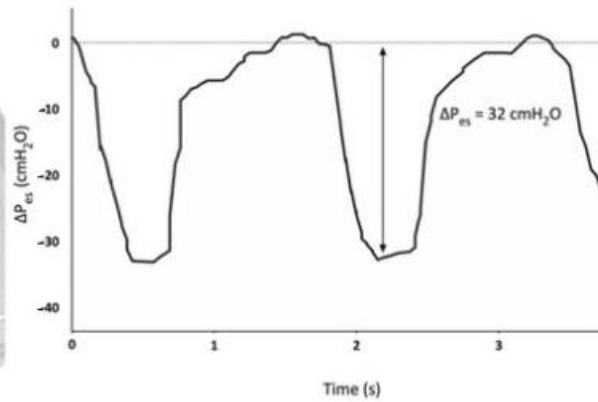
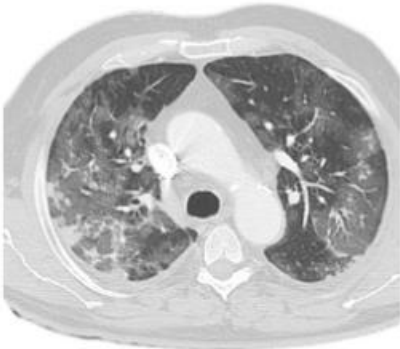
L type – Low distress



Recovery



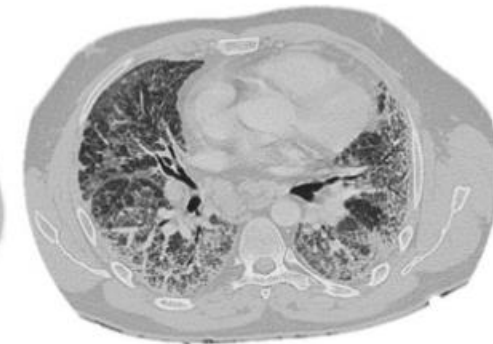
L type – High distress



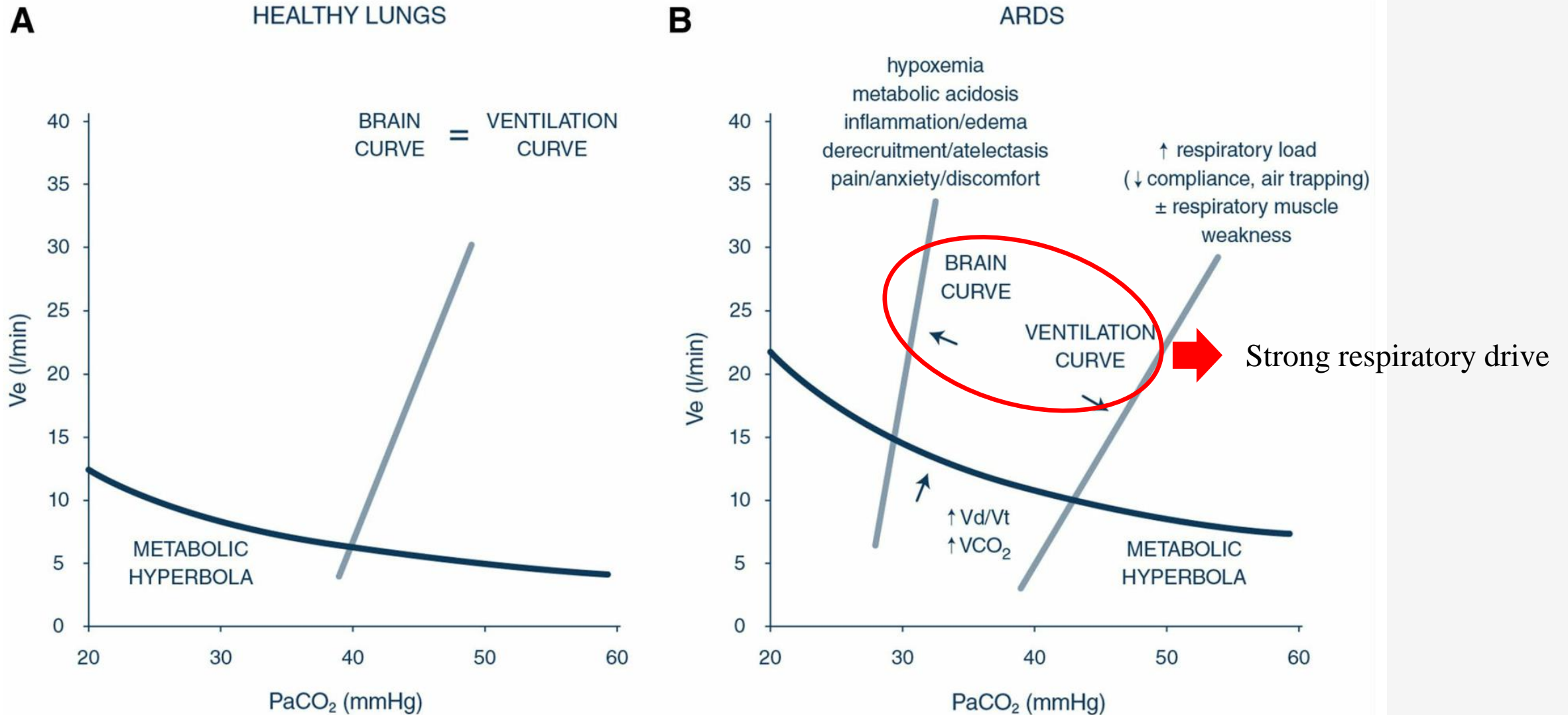
H type



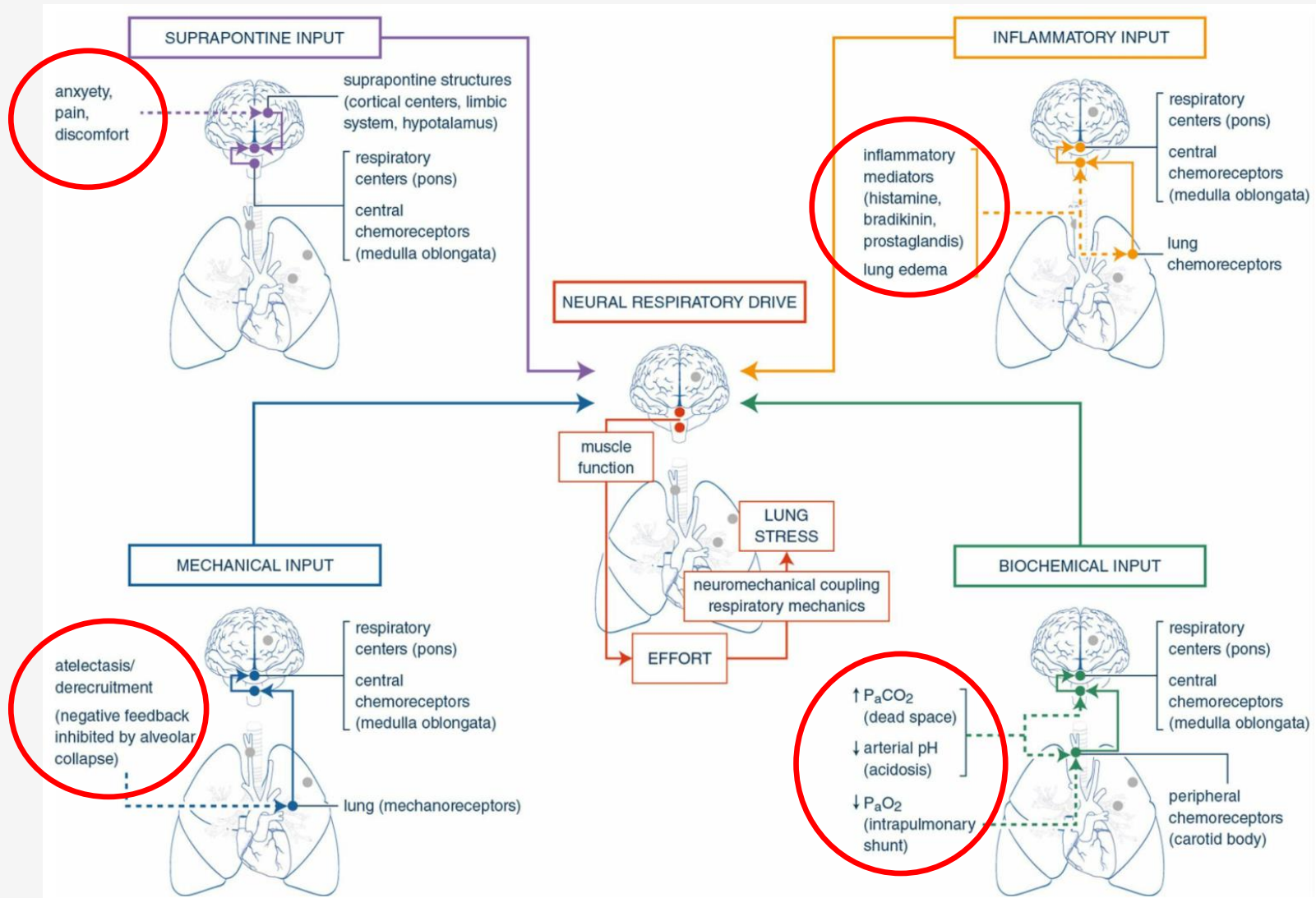
F type



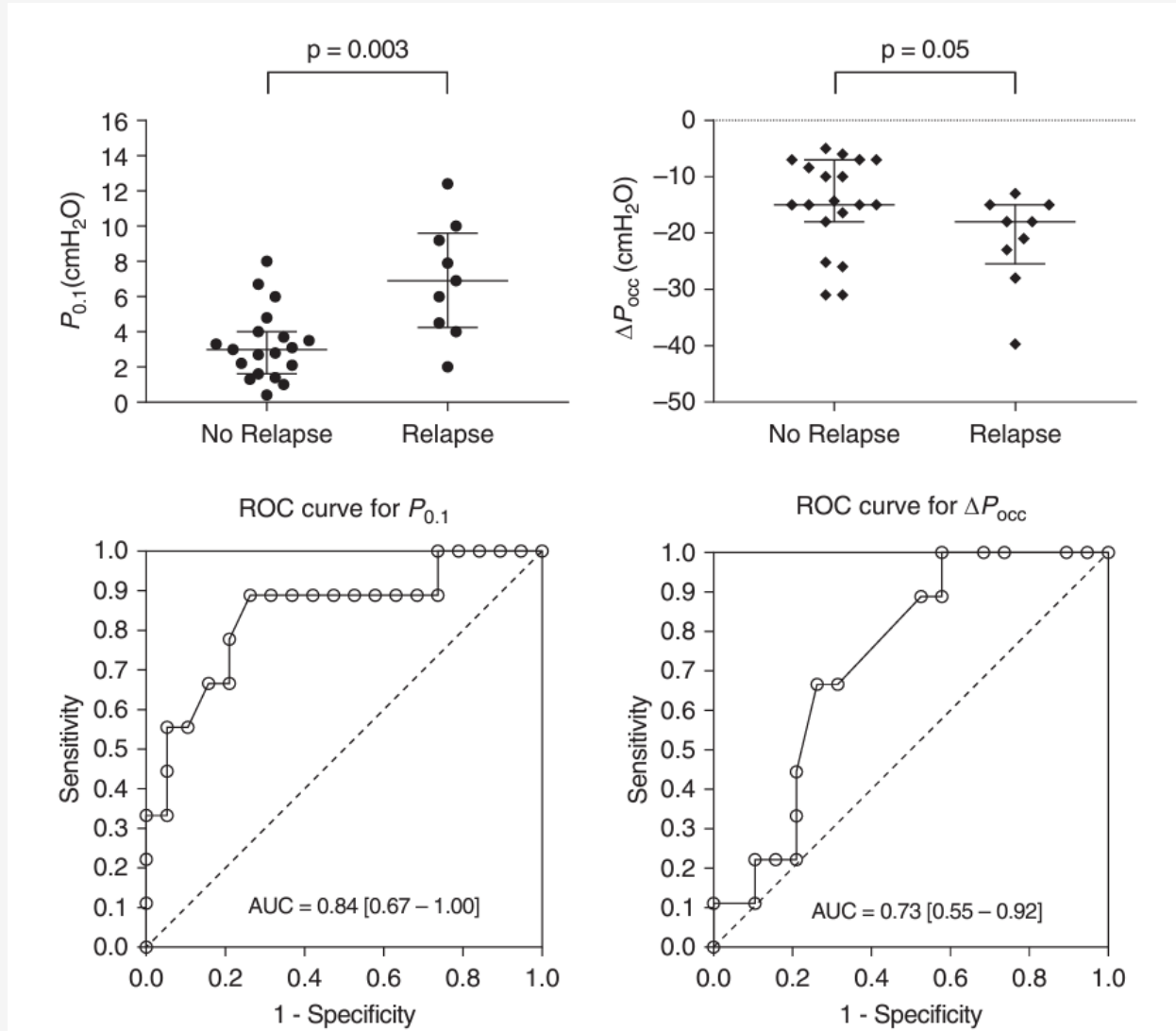
Respiratory drive in ARDS



Control of respiratory drive in ARDS



High respiratory drive and excessive respiratory efforts predict relapse of respiratory failure in Critically Ill Patients with COVID-19

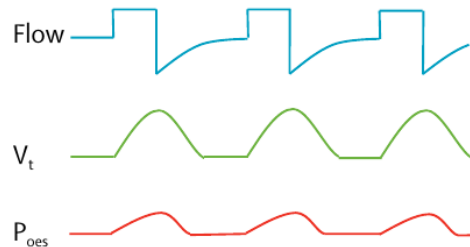


SB induced diaphragm injury



Diaphragmatic myotrauma mechanisms

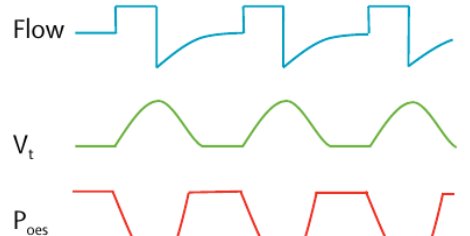
A Over-assistance myotrauma



Insufficient muscle loading

Disuse atrophy and myofibril damage

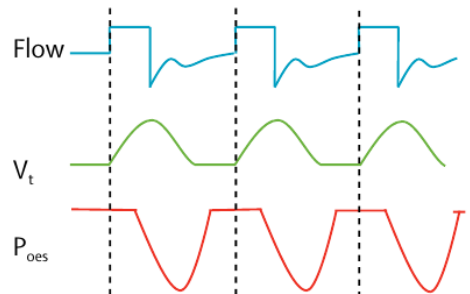
B Under-assistance myotrauma



Excess muscle loading

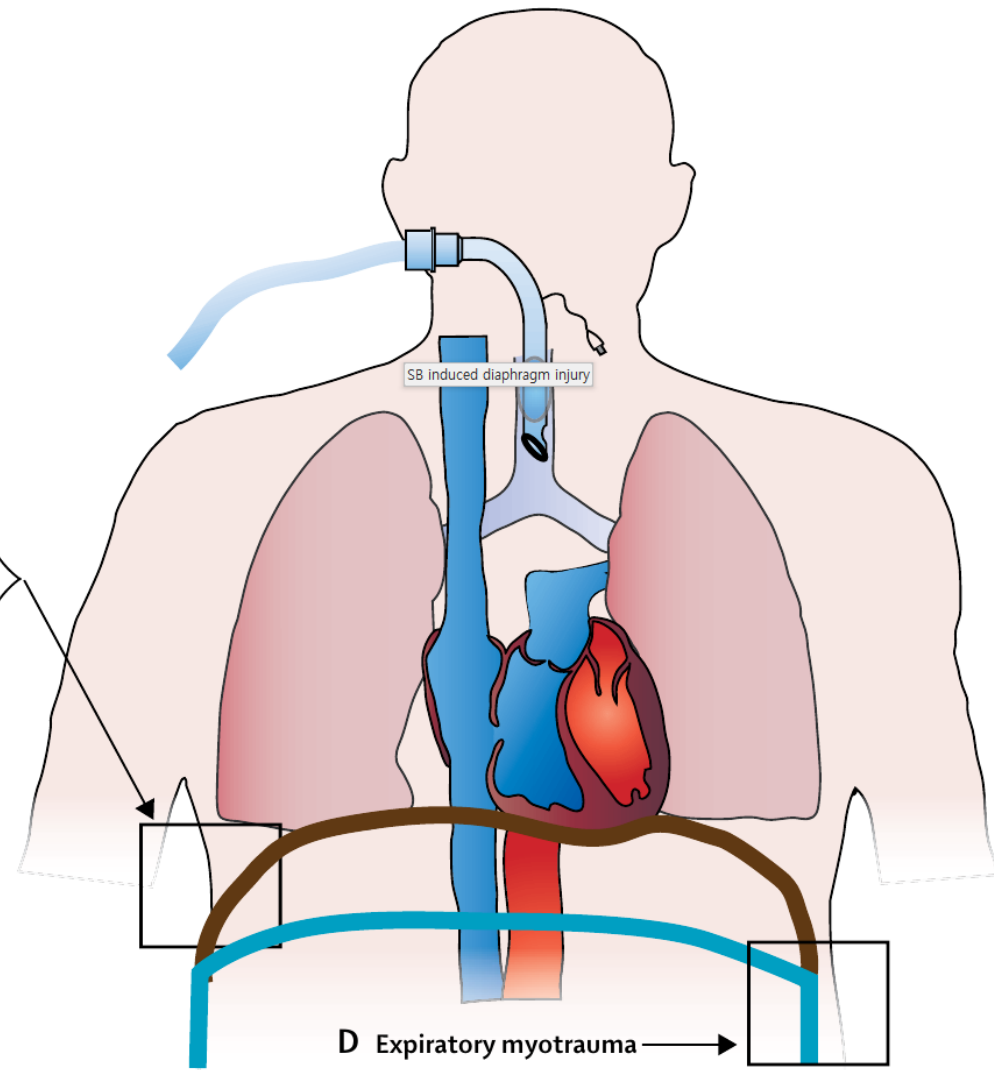
Sarcomeric disruption and contractile fatigue

C Eccentric myotrauma

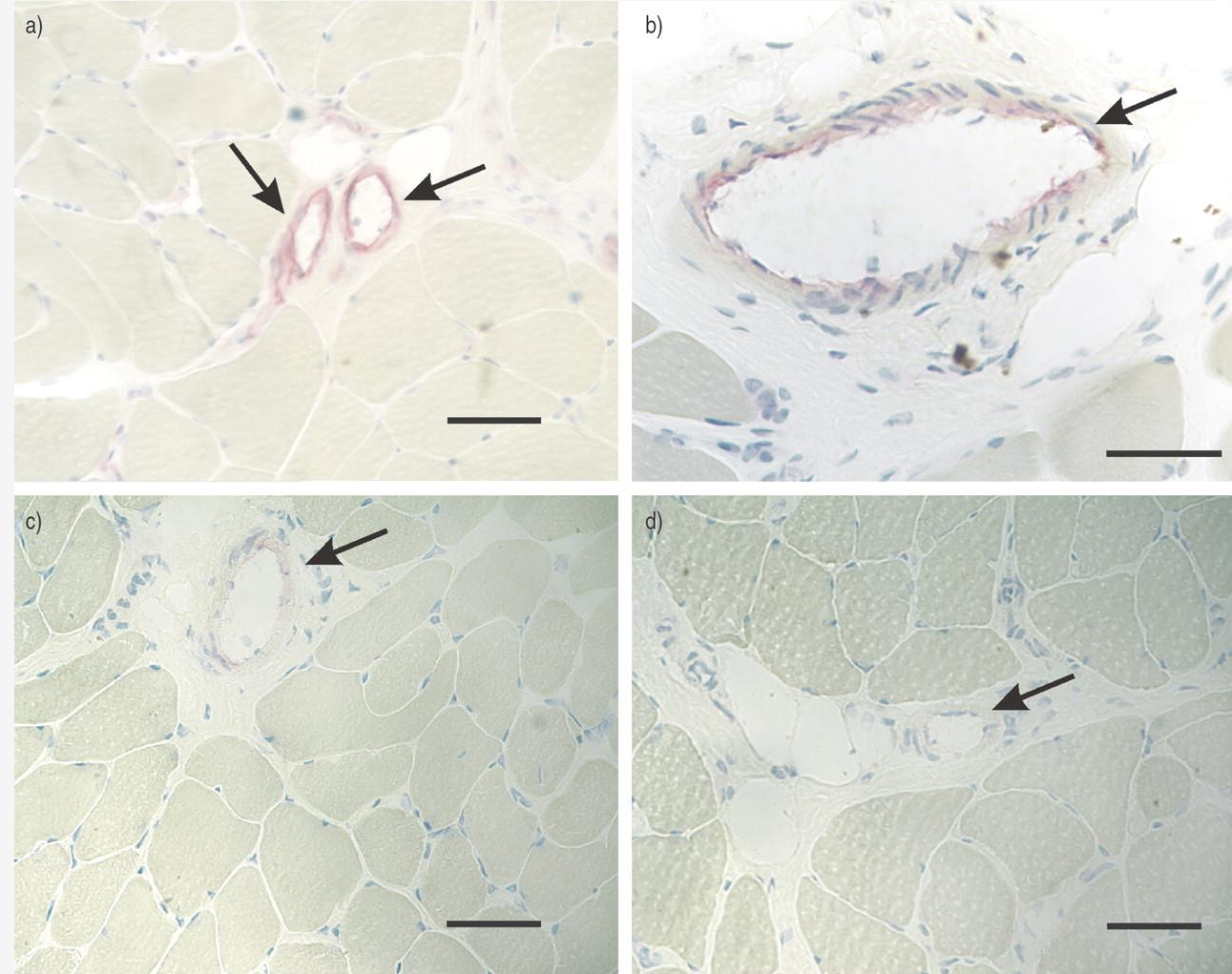
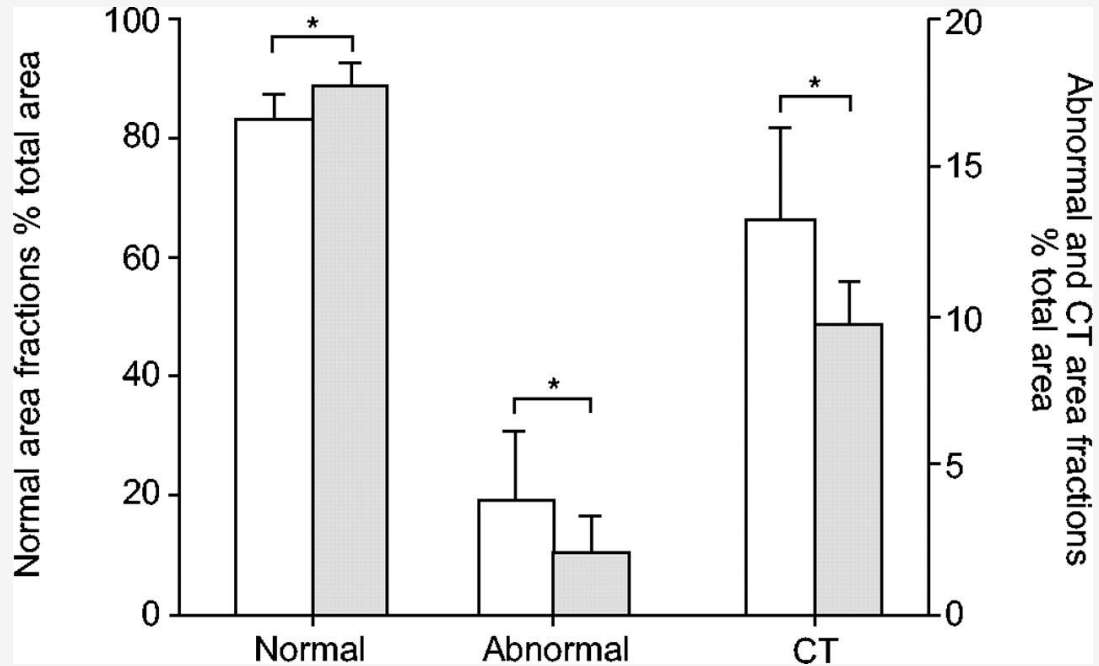


Patient-ventilator dyssynchrony

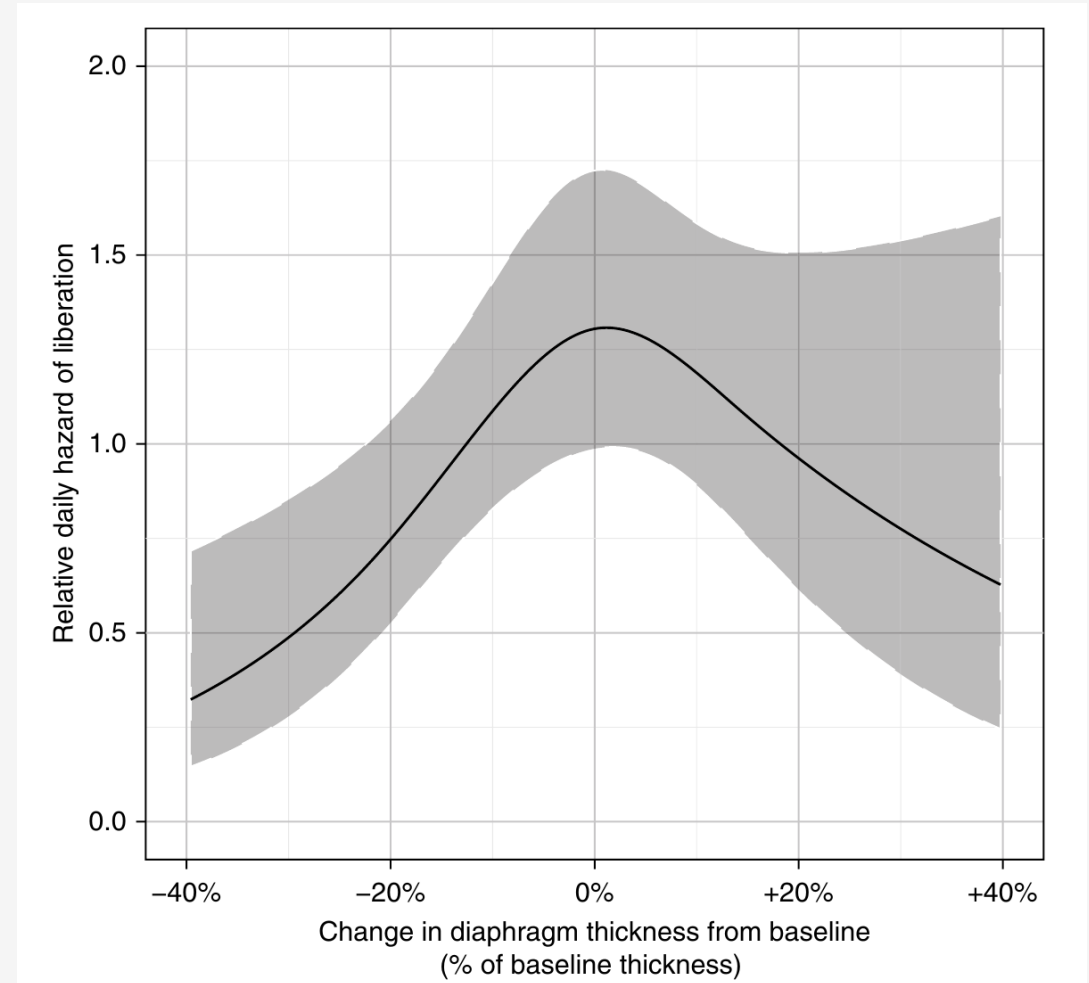
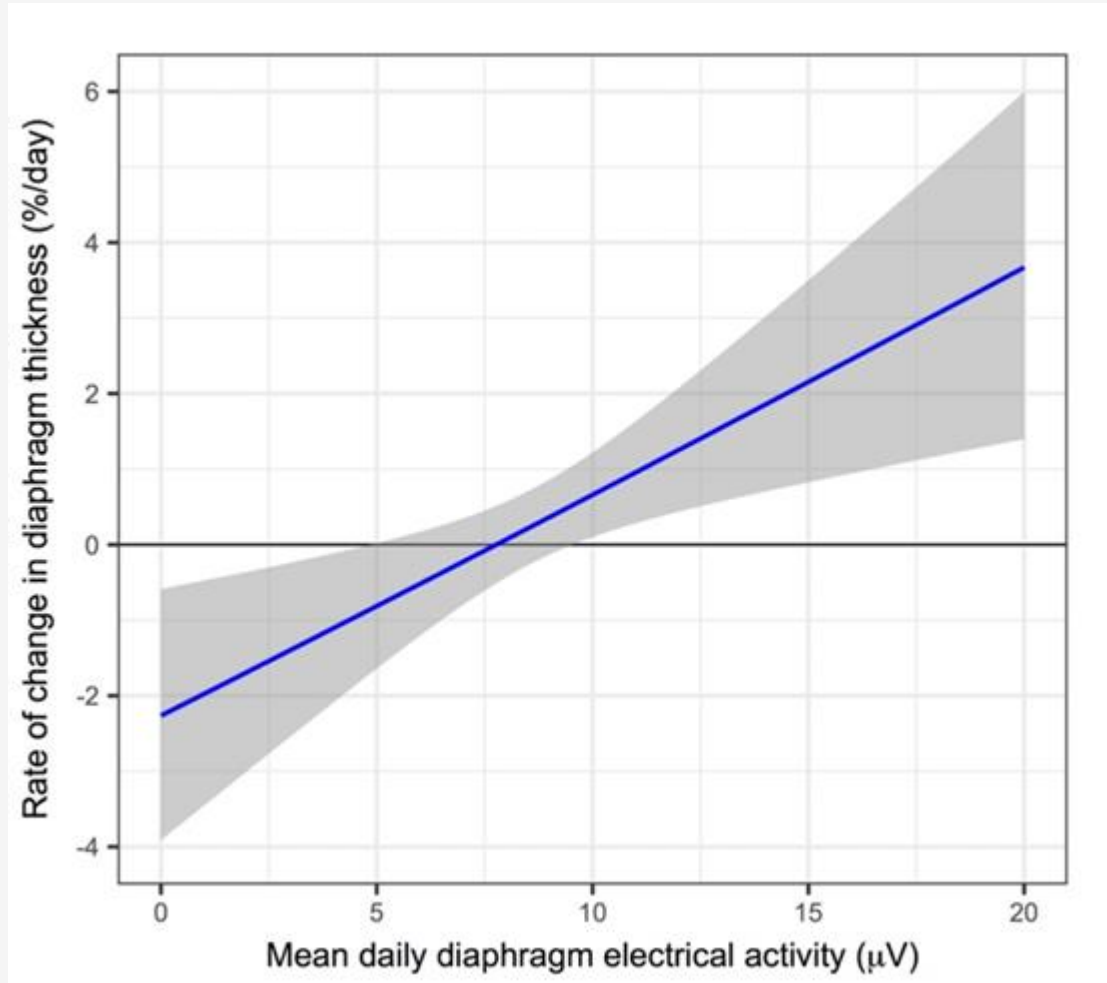
Eccentric muscle loading and injury



Excessive loading of diaphragm increase inflammation and injury



MV weaning is related to the magnitude of change in diaphragm thickness from baseline

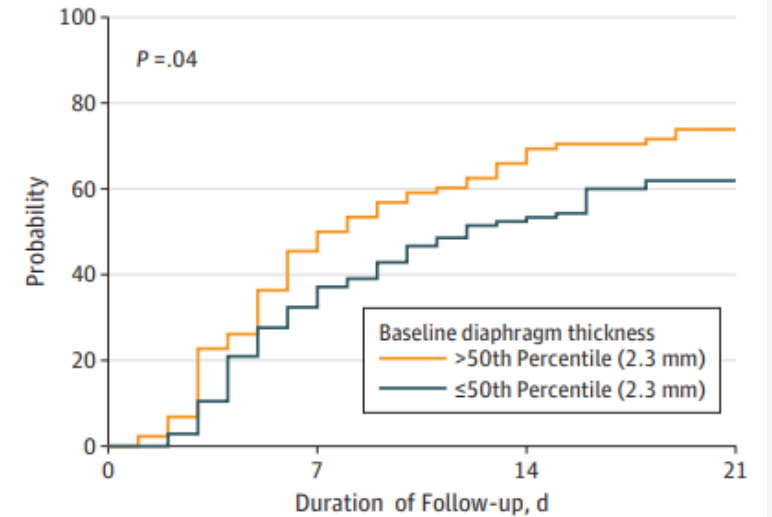


Association of Low Baseline Diaphragm Muscle Mass With Prolonged Mechanical Ventilation and Mortality Among Critically Ill Adults

Table. Baseline Tdi and Clinical Outcomes

Outcome	No. (%)			Unadjusted P Value	Adjusted Association per 0.5-mm Decrement in Tdi (95% CI) ^b
	Total (N = 193)	Tdi ≤2.3 mm (n = 105) ^a	Tdi >2.3 mm (n = 88)		
Competing risk analysis to day 21					
Liberation from ventilation	130 (67)	65 (62)	65 (74)	.04	Hazard ratio, 0.84 (0.70-1.00)
Death while receiving ventilation	30 (16)	15 (14)	15 (17)	.52	Hazard ratio, 0.62 (0.34-1.13)
Hospital mortality	65 (34)	44 (43)	21 (24)	.01	Odds ratio, 1.47 (1.00-2.16)
Death in ICU	44 (23)	27 (26)	17 (19)	.38	Odds ratio, 1.03 (0.67-1.57)
Death in hospital in ICU survivors	21 (14)	17 (22)	4 (6)	.01	Odds ratio, 2.68 (1.35-5.32)
Ventilator-free days to day 60, median (IQR)	48 (0-55)	42 (0-54)	53 (36-56)	.001	Duration ratio, 0.89 (0.80-0.99)
Duration of mechanical ventilation in ICU survivors, median (IQR), d	7 (4-13)	8 (4-16)	6 (3-12)	.06	Duration ratio, 1.29 (1.13-1.47)
Duration of ICU admission in ICU survivors, median (IQR), d	9 (5-16)	10 (5-18)	8 (5-14)	.12	Duration ratio, 1.30 (1.14-1.48)
Duration of hospitalization in hospital survivors, median (IQR), d	24 (14-58)	28 (16-62)	22 (13-51)	.47	Duration ratio, 1.23 (1.04-1.46)
Complications of acute respiratory failure					
Reintubation	33 (17)	22 (21)	11 (12)	.17	Odds ratio, 1.91 (1.18-3.11)
Tracheostomy	34 (18)	22 (21)	12 (14)	.26	Odds ratio, 1.60 (1.01-2.53)
Mechanical ventilation >14 d	57 (30)	41 (39)	16 (18)	.003	Odds ratio, 1.80 (1.23-2.64)
Rate of ≥1 complication of mechanical ventilation ^c	105 (55)	67 (65)	38 (43)	.004	Odds ratio, 1.77 (1.20-2.61)
Readmission to ICU after ICU discharge	20 (11)	13 (13)	7 (9)	.45	Odds ratio, 1.37 (0.79-2.39)
Weaning classification ^d					
No attempt	32 (17)	18 (17)	14 (16)	.007	Odds ratio, 2.30 (1.42-3.74) ^e
Simple	75 (39)	34 (33)	41 (47)		
Difficult	45 (23)	21 (20)	24 (27)		
Prolonged	40 (21)	31 (30)	9 (10)		

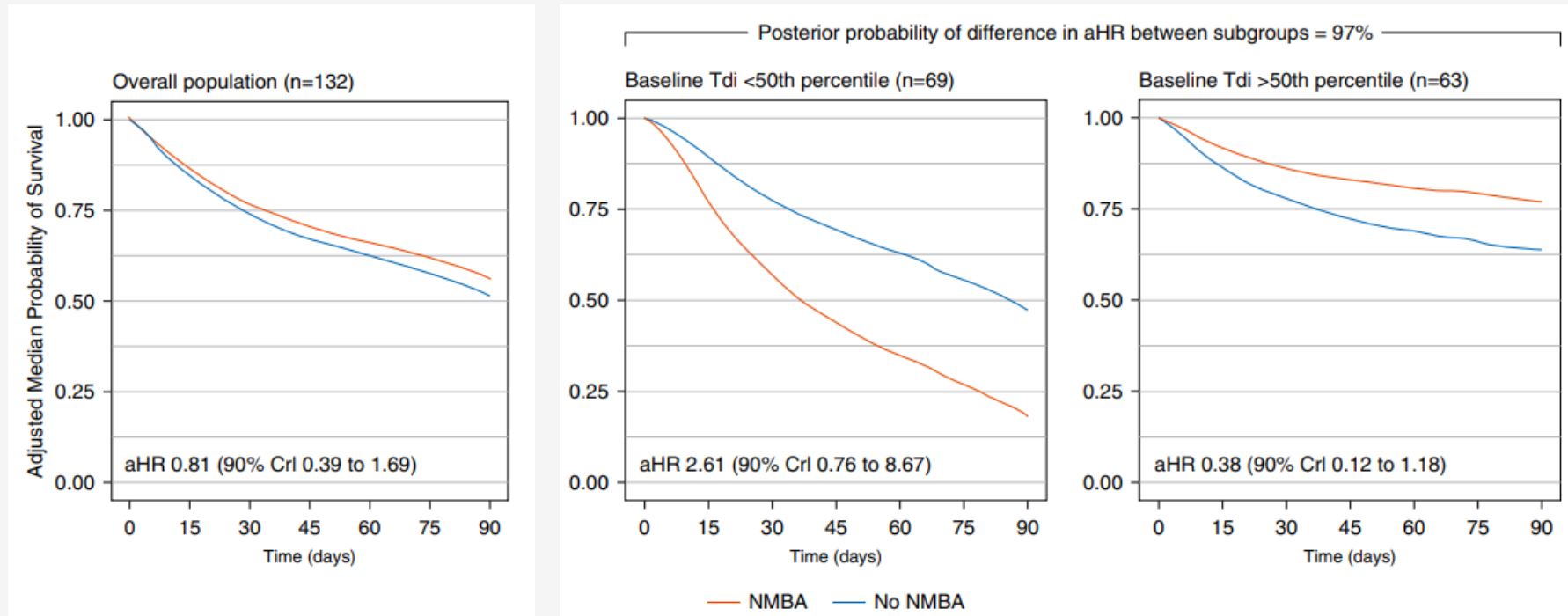
A All patients



No. at risk	0	7	14	21
>2.3 mm	88	34	13	8
≤2.3 mm	105	62	39	25

Association of Mortality with Neuromuscular Blockade Differs according to Baseline Diaphragm Thickness

Second analysis of patients with PF ratio < 200 (N=132)



- ✓ **Thinner diaphragm** → Less transpulmonary pressure swings → **Lower injurious lung stress** from respiratory effort → **Increased ICU acquired weakness after NBMs**
- ✓ **Thicker diaphragm** → higher risk of injurious breath → More benefit from abolishing spontaneous breathing

Short-term NMB did not increase ICU-acquired weakness

Table 3. Secondary Outcomes, According to Study Group.*

Outcome	Cisatracurium (N=177)	Placebo (N=162)	Relative Risk with Cisatracurium (95% CI)	P Value
Death — no. (% [95% CI])				
At 28 days	42 (23.7 [18.1–30.5])	54 (33.3 [26.5–40.9])	0.71 (0.51–1.00)	0.05
In the ICU	52 (29.4 [23.2–36.5])	63 (38.9 [31.7–46.6])	0.76 (0.56–1.02)	0.06
In the hospital	57 (32.2 [25.8–39.4])	67 (41.4 [34.1–49.1])	0.78 (0.59–1.03)	0.08
No. of ventilator-free days†				
From day 1 to day 28	10.6±9.7	8.5±9.4		0.04
From day 1 to day 90	53.1±35.8	44.6±37.5		0.03
No. of days without organ failure, from day 1 to day 28				
No cardiovascular failure	18.3±9.4	16.6±10.4		0.12
No coagulation abnormalities	22.6±8.9	20.5±9.9		0.05
No hepatic failure	21.3±9.6	19.1±10.6		0.05
No renal failure	20.5±10.1	18.1±11.6		0.05
None of the four	15.8±9.9	12.2±11.1		0.01
No. of days outside the ICU				
From day 1 to day 28	6.9±8.2	5.7±7.8		0.16
From day 1 to day 90	47.7±33.5	39.5±35.6		0.03
Hospital survivors admitted to other health care facilities from day 1 to day 90 — % (95% CI)	22.3 (15.8–30.5)	18.8 (12.2–27.8)		0.52
Barotrauma — no. (% [95% CI])‡	9 (5.1 [2.7–9.4])	19 (11.7 [7.6–17.6])	0.43 (0.20–0.93)	0.03
Pneumothorax — no. (% [95% CI])	7 (4.0 [2.0–8.0])	19 (11.7 [7.6–17.6])	0.34 (0.15–0.78)	0.01
MRC score — median (IQR)§				
At day 28	55 (46–60)	55 (39–60)	1.07 (0.80–1.45)	0.49
At ICU discharge	55 (43–60)	55 (44–60)	0.92 (0.71–1.19)	0.94
Patients without ICU-acquired paresis¶				
By day 28 — no./total no. (% [95% CI])	68/96 (70.8 [61.1–79.0])	52/77 (67.5 [56.5–77.0])		0.64
By ICU discharge — no./total no. (% [95% CI])	72/112 (64.3 [55.1–72.6])	61/89 (68.5 [58.3–77.3])		0.51

Table 2. End Points.*

Variable	Intervention Group (N=501)	Control Group (N=505)	Between-Group Difference (95% CI)	P Value
<i>percentage points</i>				
Primary end point: in-hospital death by day 90 — no. (%)†				
	213 (42.5±2.2)	216 (42.8±2.2)	-0.3 (-6.4 to 5.9)	0.93
Secondary end points				
In-hospital death by day 28 — no. (%)				
	184 (36.7)	187 (37.0)	-0.3 (-6.3 to 5.7)	
Days free of ventilation at day 28‡				
	9.6±10.4	9.9±10.9	-0.3 (-1.7 to 1.0)	
Days not in ICU at day 28				
	9.0±9.4	9.4±9.8	-0.4 (-1.6 to 0.8)	
Days not in hospital at day 28‡				
	5.7±7.8	5.9±8.1	-0.2 (-1.1 to 0.8)	
Safety end points				
In-hospital recall of paralysis				
Total no. of patients (%)				
	9 (1.8)	10 (2.0)	-0.2 (-1.9 to 1.5)	
Among patients who received neuromuscular blockade — no./total no. (%)				
	9/487 (1.8)	2/129 (1.6)	0.3 (-2.1 to 2.7)	
MRC score§				
Day 7				
	46.7±14.4	49.5±12.3	-2.8 (-6.1 to 0.6)¶	
Day 28				
	45.7±13.9	49.8±10.6	-4.1 (-9.0 to 0.9)¶	
ICU-acquired weakness — no./total no. (%)				
Day 7				
	50/122 (41.0)	41/131 (31.3)	-9.7 (-21.5 to 2.1)	
Day 28				
	22/47 (46.8)	14/51 (27.5)	-19.4 (-38.2 to -0.6)	
Any time through day 28				
	107/226 (47.3)	89/228 (39.0)	-7.3 (-15.7 to 1.1)	
Serious adverse events — no. of events**				
	35	22		0.09
Serious cardiovascular adverse events — no. of events**				
	14	4		0.02
Atrial fibrillation or SVT during ICU stay — no. (%)				
	101 (20.2)	99 (19.6)		0.88
Barotrauma — no. (%)				
	20 (4.0)	32 (6.3)		0.12
Pneumothorax on days 0 through 2 — no. (%)				
	8 (1.6)	10 (2.0)		0.81
Pneumothorax on days 0 through 7 — no. (%)				
	14 (2.8)	25 (5.0)		0.10

Feasibility of Clinical application



Spontaneous breathing is not easy in clinical setting

Table 1. Characteristics of the Patients at Randomization.*

Characteristic	ECMO Group (N=124)	Control Group (N=125)
Age — yr	51.9±14.2	54.4±12.7
Male sex — no. (%)	87 (70)	90 (72)
Immunocompromised condition — no. (%)	27 (22)	27 (22)
SOFA score†	10.8±3.9	10.6±3.5
Median time since intubation (interquartile range) — hr	34 (15–89)	34 (17–100)
Cause of ARDS — no. (%)		
Pneumonia		
Bacterial	54 (44)	58 (46)
Viral	26 (21)	20 (16)
Other	44 (35)	47 (38)
PaO ₂ :FIO ₂ — mm Hg	73±30	72±24
PEEP — cm of water	11.7±3.9	11.8±3.7
Tidal volume — ml/kg of predicted body weight	6.0±1.3	6.1±0.9
Respiratory rate — breaths/min	30.4±4.7	31.2±4.5
Plateau pressure — cm of water	29.8±5.5	29.5±4.8
Driving pressure — cm of water	17.8±7.0	17.7±5.8
Respiratory-system compliance — ml/cm of water	25.0±11.5	25.4±10.8
Arterial blood pH	7.24±0.13	7.24±0.12
PaO ₂ — mm Hg‡	69±25	68±22
Paco ₂ — mm Hg	57±15	57±16
Prone positioning — no. (%)§	70 (56)	78 (62)
Inhaled nitric oxide or prostacyclin — no. (%)§	64 (52)	68 (54)
Recruitment maneuvers — no. (%)§	22 (18)	34 (27)
Neuromuscular blockade — no. (%)§	114 (92)	120 (96)

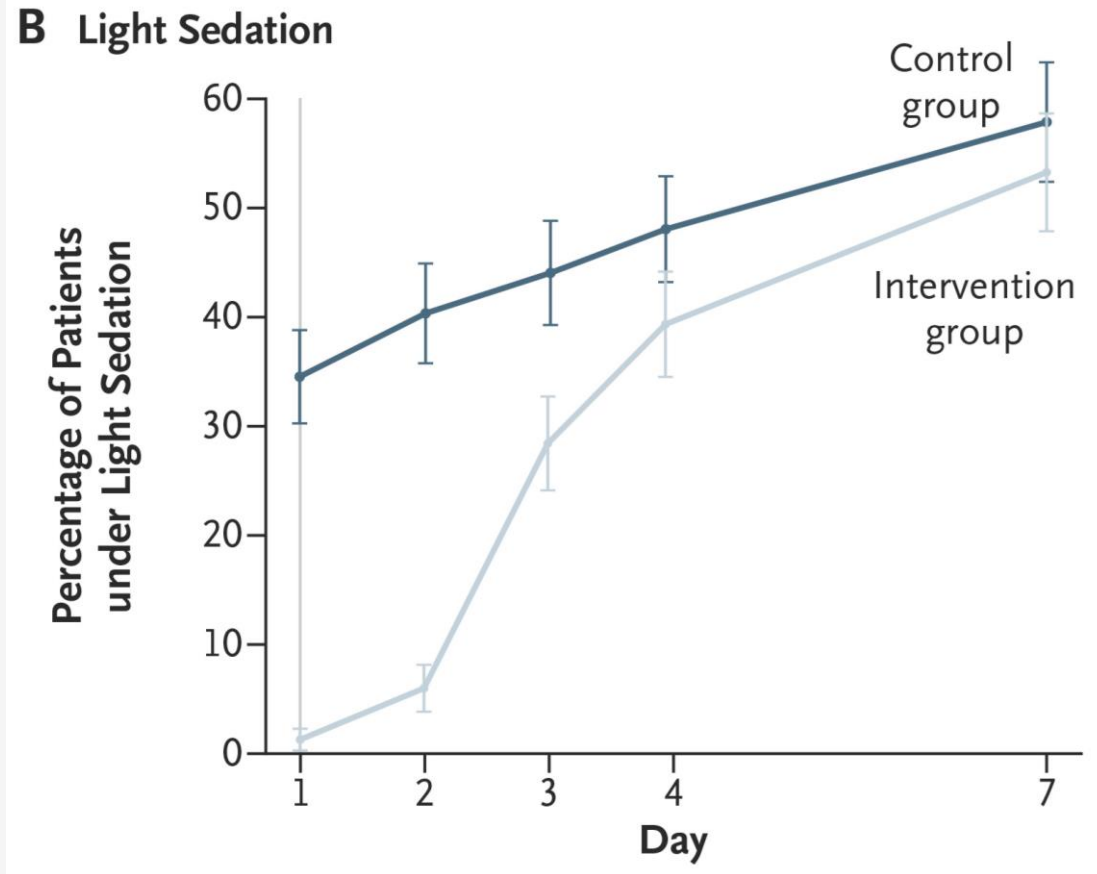
➤ EOLIA trial

✓ Indication

- PaO₂:FIO₂ ratio < 50 mmHg for > 3 hours
- PaO₂:FIO₂ < 80 mmHg for > 6 hours
- Arterial blood pH < 7.25 with a partial pressure of arterial carbon dioxide (PaCO₂) > 60 mmHg for >6 hours

→ NMB 94%

Spontaneous breathing is not easy in clinical setting



- 65% of patients in control group needed deep sedation to achieve lung protective ventilation
- 17% of patients needed NMB

- 35% of patient in control group did not need deep sedation to achieve lung protective ventilation

Management of ARDS

Tidal volume				In agreement with the use of low tidal volume strategies. 2023 guidelines extend this recommendation to patients with COVID-19.
Positive end-expiratory pressure				2017: suggest that adult patients with moderate or severe ARDS receive higher rather than lower levels of PEEP. 2023: analysis of data does not allow to make a recommendation for or against higher PEEP strategy.
Recruitment maneuvers				2017: suggest that adult patients with ARDS receive RMs. 2023: recommend against RMs due to increased mortality and risks.
Oscillatory ventilation				2017: recommend that HFOV not be used routinely in patients with moderate or severe ARDS. 2023: not examined given the absence of studies since 2017 and the lack of use of HFVO in adults.
Prone position				Agreement with the use of prone position in ARDS. Additions in 2023 are the use of awake proning and the use in COVID-19.
Neuromuscular blockade				No comparison available as the 2017 guidelines did not include recommendations on neuromuscular blockade.
Extracorporeal membrane oxygenation				2017: additional evidence is necessary to make a definitive recommendation. 2023: recommend ECMO in patients with severe ARDS.
Extracorporeal CO₂ removal				No comparison available as the 2017 guidelines did not include recommendations on extracorporeal CO ₂ removal. 2023 guidelines recommend against ECCO ₂ R in ARDS.

Prone position ventilation

➤ PROSEVA trial

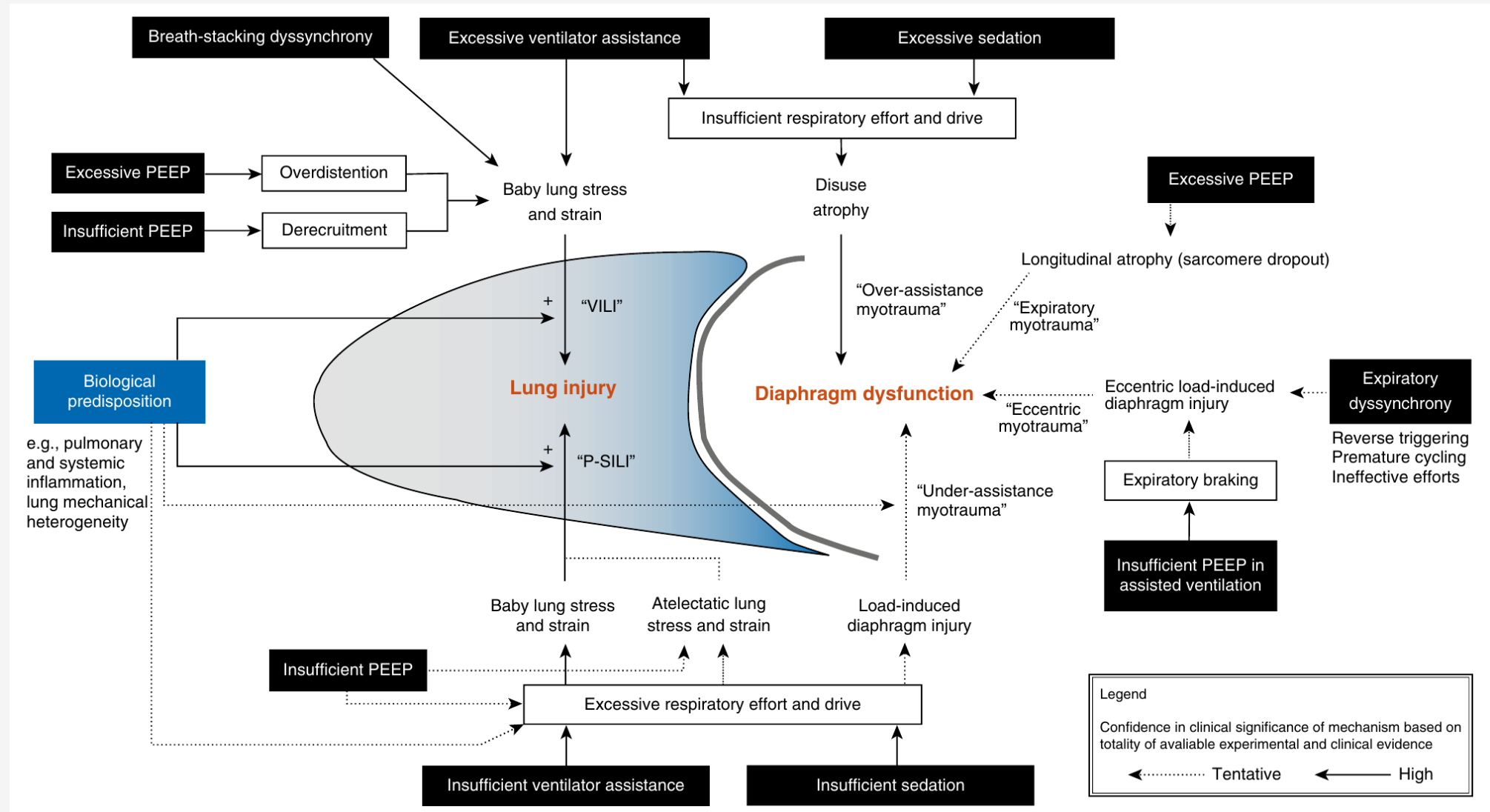
- Moderate to severe ARDS (PaO₂/FiO₂ < 150mmHg, FiO₂ ≥ 0.6 PEEP ≥ 5cmH₂O)
- Prone position ventilation vs. no intervention

The protocol strongly recommended the use of a NB during the first 48 hours using cisatracurium besilate administered intravenously with an initial 0.15 mg.kg⁻¹ bolus then 0.06

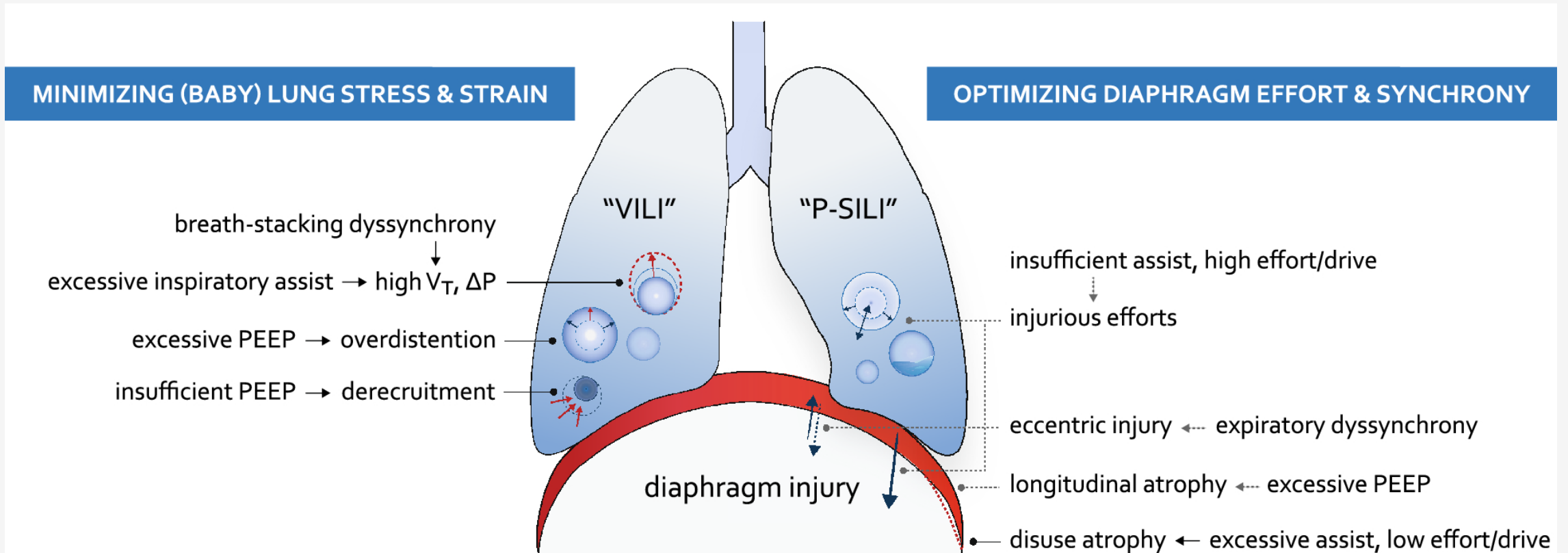
Co-interventions		
Vasopressors, n (%)	190 (83.0)*	172 (72.6)
Neuromuscular blockers, n (%)	186 (82.3)*	212 (91.0)
Renal replacement therapy, n (%)	39 (17.1)	27 (11.4)
Glucocorticoids, n (%)	101 (44.9)	91 (39.6)

No. at Risk	Days				
	237	202	191	186	182
Prone group	237	202	191	186	182
Supine group	229	163	150	139	136

Mechanisms of injury to the lung and diaphragm during MV



Lung and Diaphragm protective ventilation



Lung protective ventilation should be prioritized

Topic	Statement	Distribution of Ratings (1–9)* [Median (IQR)]	Range of Ratings (Min–Max)	Number of Panelists Expressing Support (N = 31) [n (%)]
Lung protection versus diaphragm protection	Given currently available evidence, protecting the lung should be prioritized over protecting the diaphragm when necessary, although every effort should be made to protect both organs simultaneously.	8 (7–9)	5–9	28 (90)
	Even when V_T is acceptably low, respiratory efforts may induce regional lung overdistension.	8 (7–9)	3–9	27 (87)
	When considering the application of a higher PEEP strategy, the integrated physiological response to an increase in PEEP (oxygenation, respiratory mechanics, and hemodynamics) should be carefully assessed to determine evidence of lung recruitability.	8 (7–9)	5–9	27 (87)
	Targeting a V_T of 6 ml/kg of predicted body weight is not universally protective against VILI. In some patients with severe ARDS, lower V_T may be necessary to prevent clinically significant lung injury.	8 (8–9)	5–9	26 (84)
	The dominant mechanism of ventilation-induced lung injury is excessive lung stress and strain during tidal ventilation (volutrauma), either from excessive ventilator-delivered volume and pressure or from excessive patient respiratory effort.	8 (7–9)	3–9	26 (84)

Summary

- SB worsens the lung injury (P-SILI)
 - ✓ Patient-ventilator asynchrony
 - ✓ Pendelluft phenomenon
 - ✓ Regional high transpulmonary pressure
 - ✓ Increased lung edema
- High respiratory drive and efforts enhanced P-SILI
- SB during MV can also induce diaphragm injury
- Suppressing SB is advantageous for ARDS management.