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$ECCO_2R$: What criteria for a future Trial

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Conflict of Interest

Dräger
Hamilton
Medtronic
Baxter
Fisher Paykel

The dilemma

Dead Space
Shunt

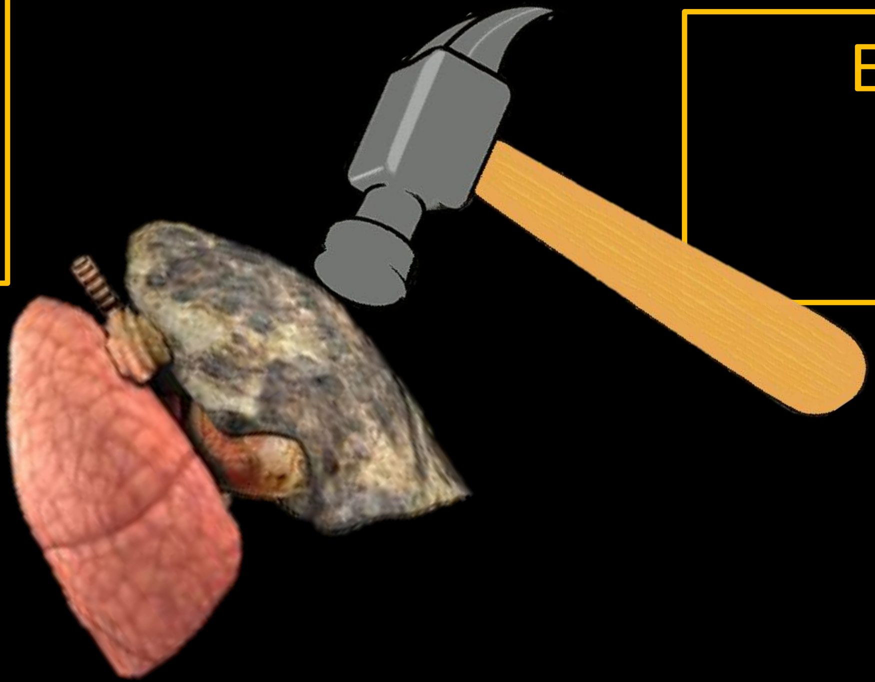
Increased
'CO_2' Load

Increase
MP

Barotrauma
Volutrauma
Biotrauma

Maintain
'normal/Low' MP

Enhance CO_2
Removal
ECLS/ECOS

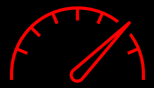


Effect of Ventilation on $PaCO_2$

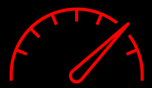
$$P_aCO_2 = k \cdot \frac{VCO_2}{V_E \cdot (1 - \frac{V_D}{V_T})}$$

CO_2 produced

Alveolar Ventilation Fraction



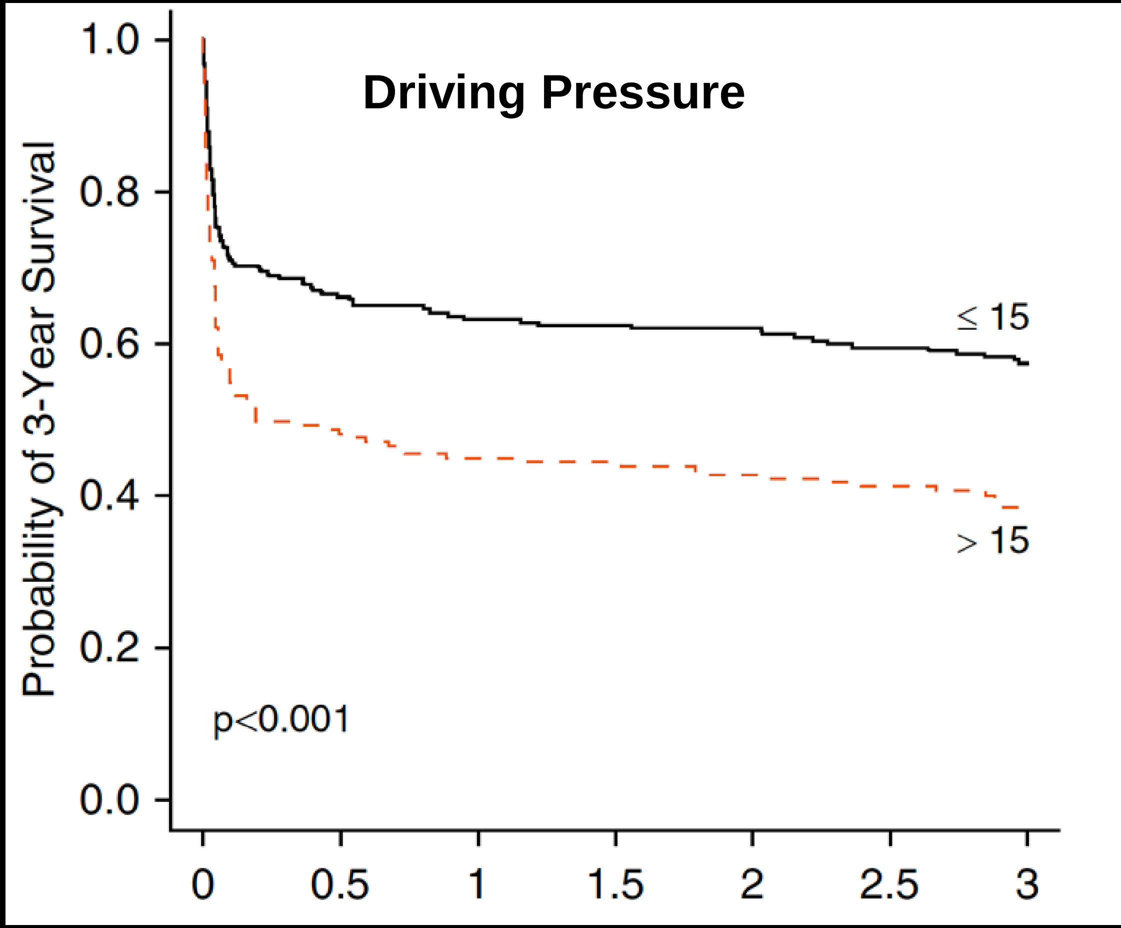
V_E

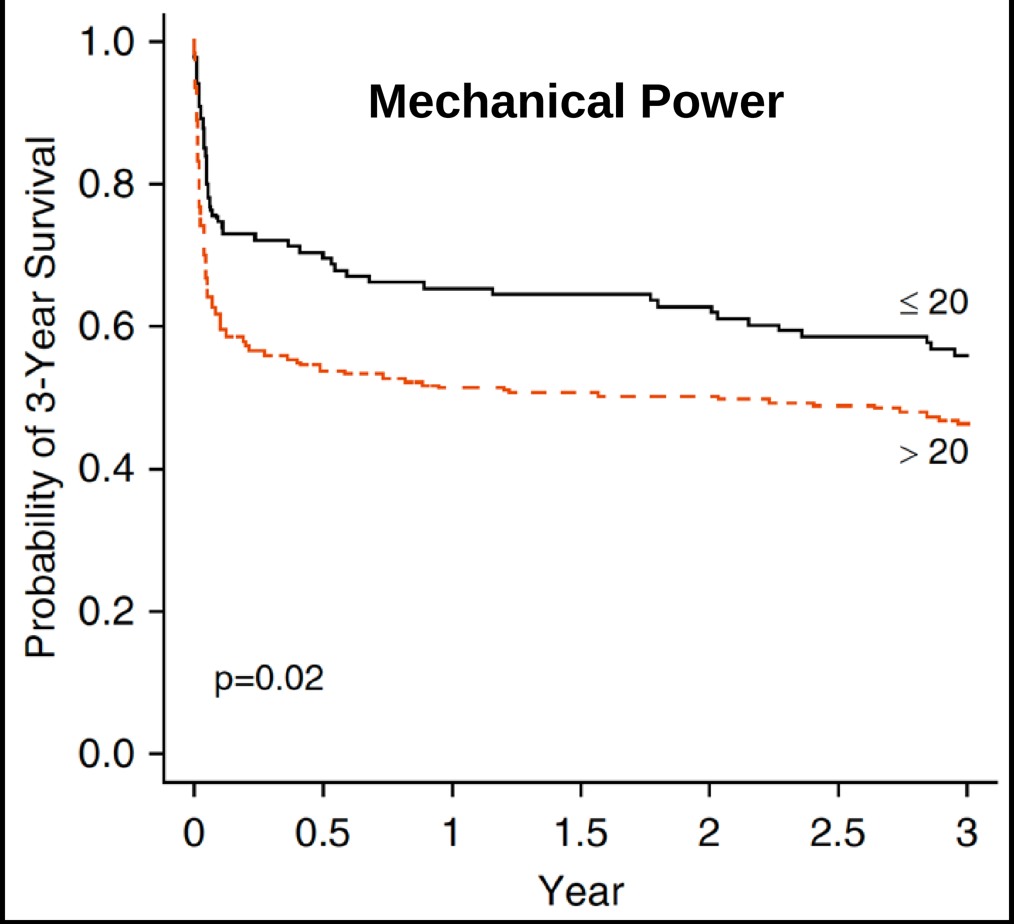


MP

High Dead-space

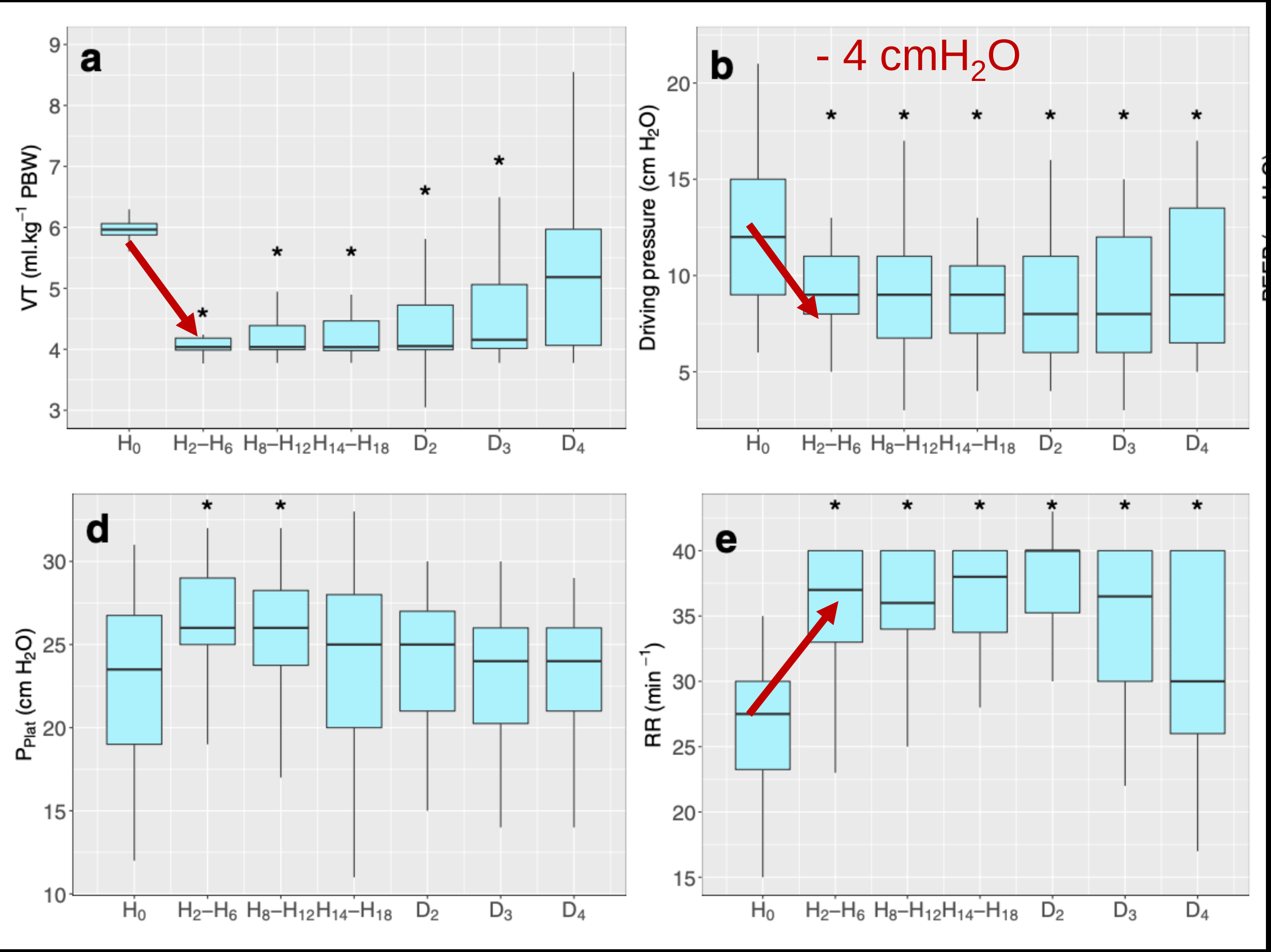
Driving Pressure & Mechanical Power and 3-Year Outcomes in ARDS (n= 7,944)

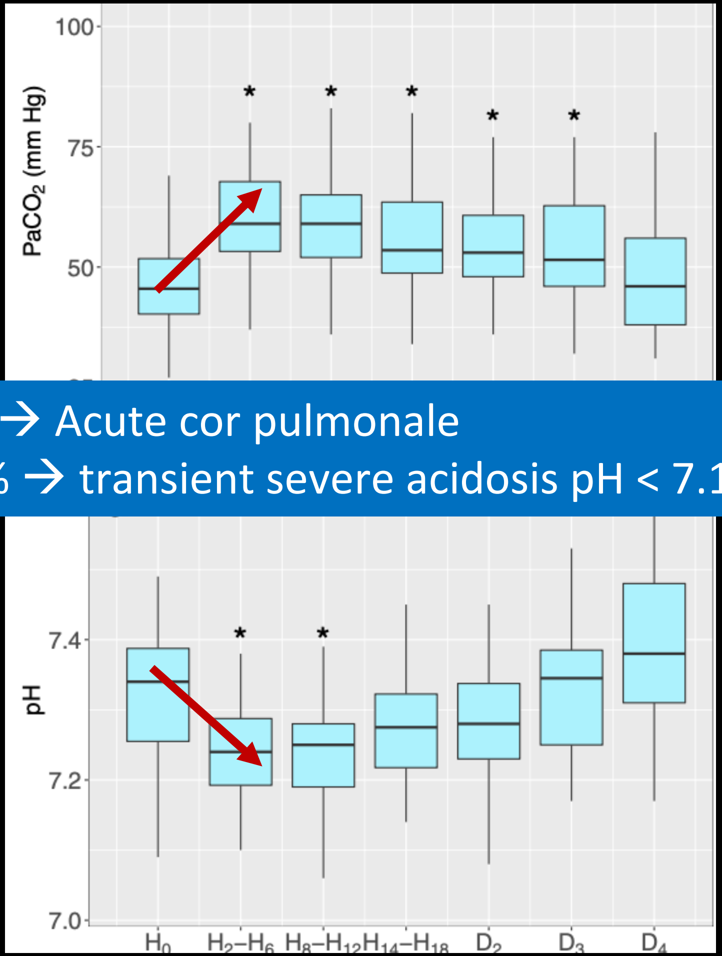




Parhar, et al Ann Am Thorac Soc Vol 16, No 10, pp 1263–1272, Oct 2019

Ultra-Low Ventilation without $ECCO_2R$ in moderate-severe ARDS





6% → Acute cor pulmonale
32% → transient severe acidosis pH < 7.15.

Richard JC, et al *Intensive Care Med* 2019, **45**(11):1590-1598.

$ECCO_2R$

Does it change outcome?

Effect of $ECCO_2R$ on $PaCO_2$

$$P_aCO_2 = k \cdot \frac{VCO_2}{V_E \cdot (1 - \frac{V_D}{V_T})}$$

V_E

MP

High Dead-space

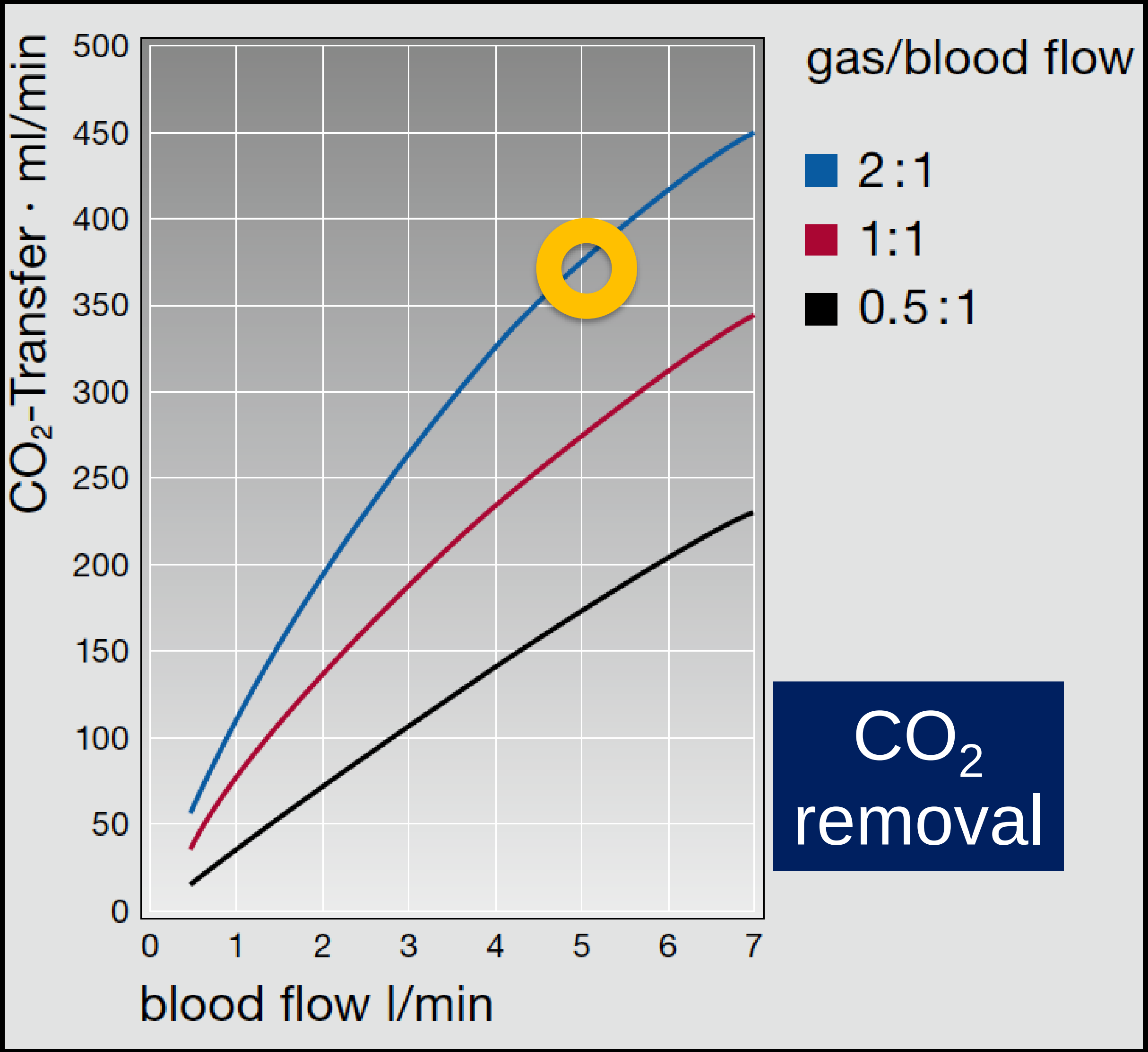
$$P_aCO_2 = k \cdot \frac{VCO_2}{V_E \cdot \left(1 - \frac{V_D}{V_T}\right) + V_{Sweep}}$$

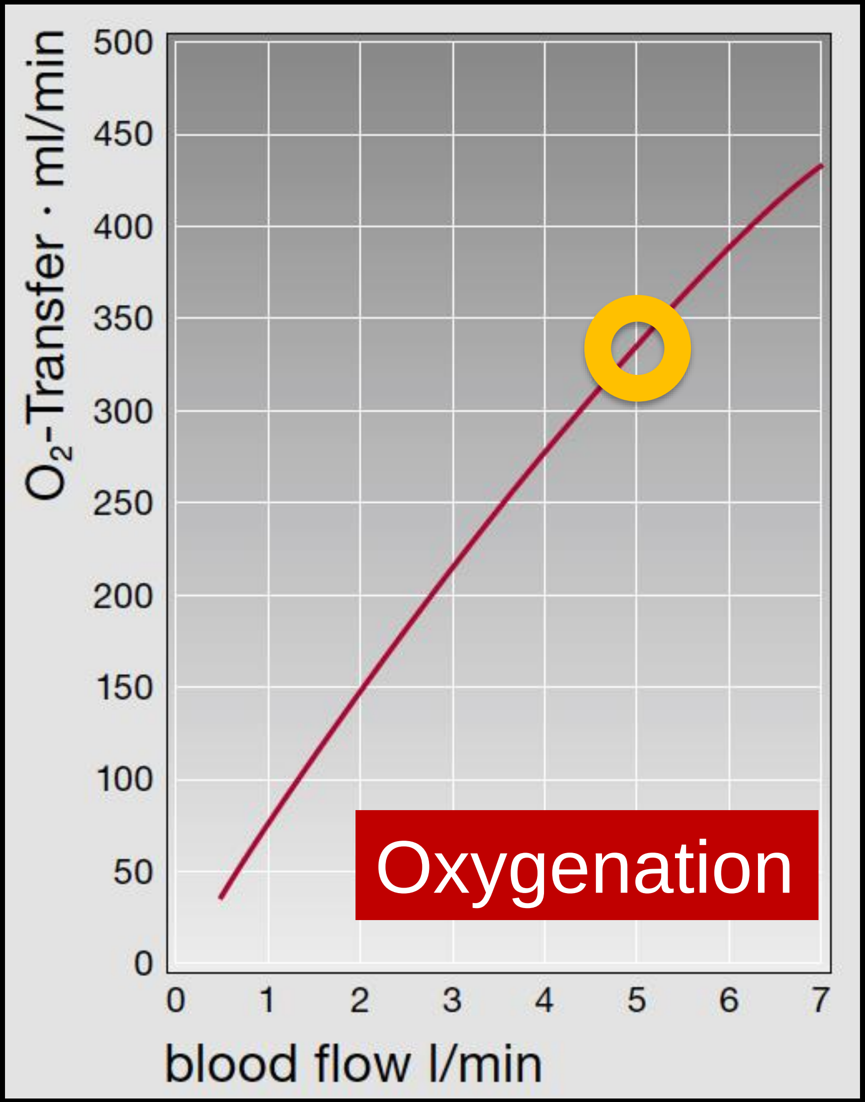
V_E

MP

Extracorporeal Ventilation

ECBF and Gas transfer : ECMO vs $ECCO_2R$





7071

9% ARR
90d Mortality

412

1120/ 412

- Moderate-Severe AHRF

N=200

VLTVV
≤ 3 mL/Kg PBW
+ $ECCO_2R$ max 7

REST

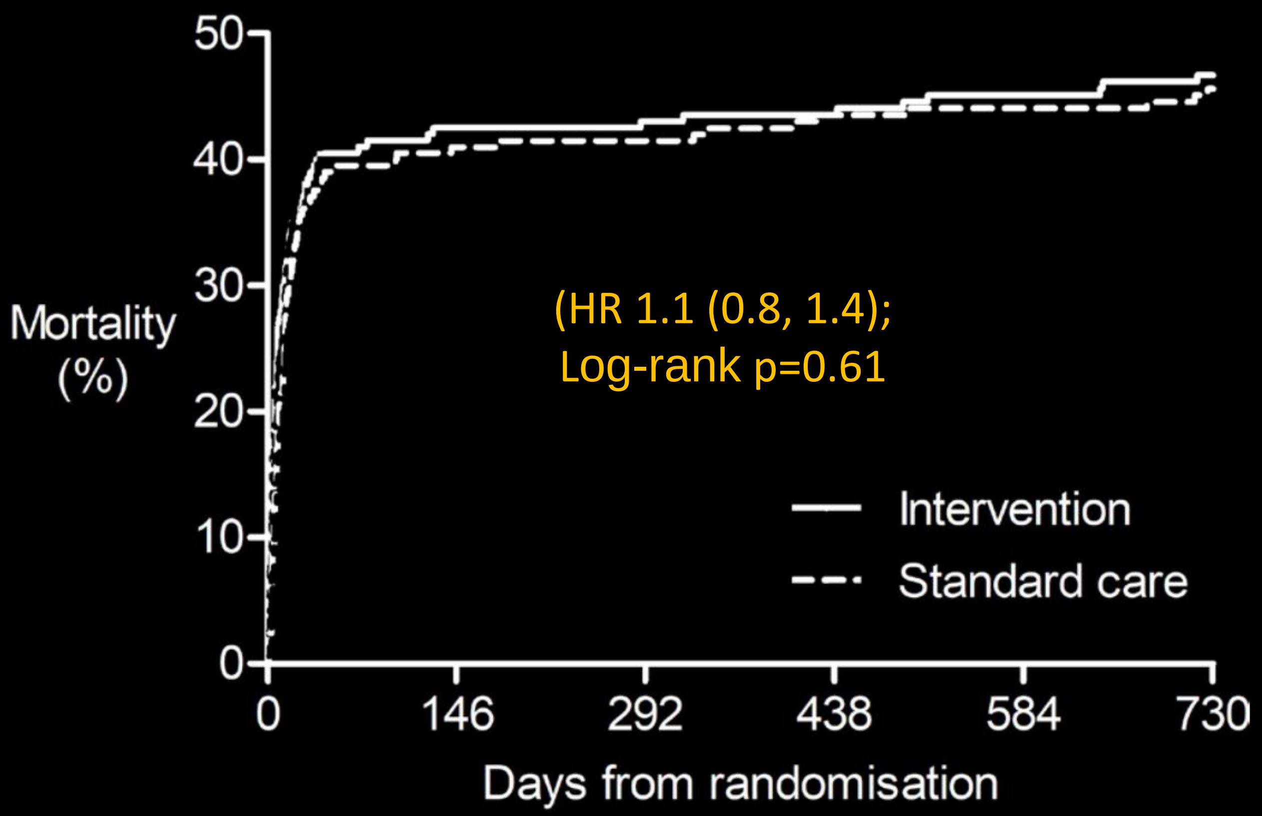
N=205

LTVV
6 mL/Kg PBW
$PEEP/FiO_2$

	VLTVV		LTVV
Mortality (90 d)	41.5%	**2% d** (95%CI -7.6% to 11.5%)	39.5%
VFD (d28)	7.1	**-2.1 d** (95%CI -3.8 to 0.3) P=0.03)	9.2
SAE (d28)	31%		9%
ICH	3%		0.5%

McNamee JJ, et al : The REST RCT. *JAMA* 2021; 326: 1013-1023.

Long Term Outcome : REST Trial

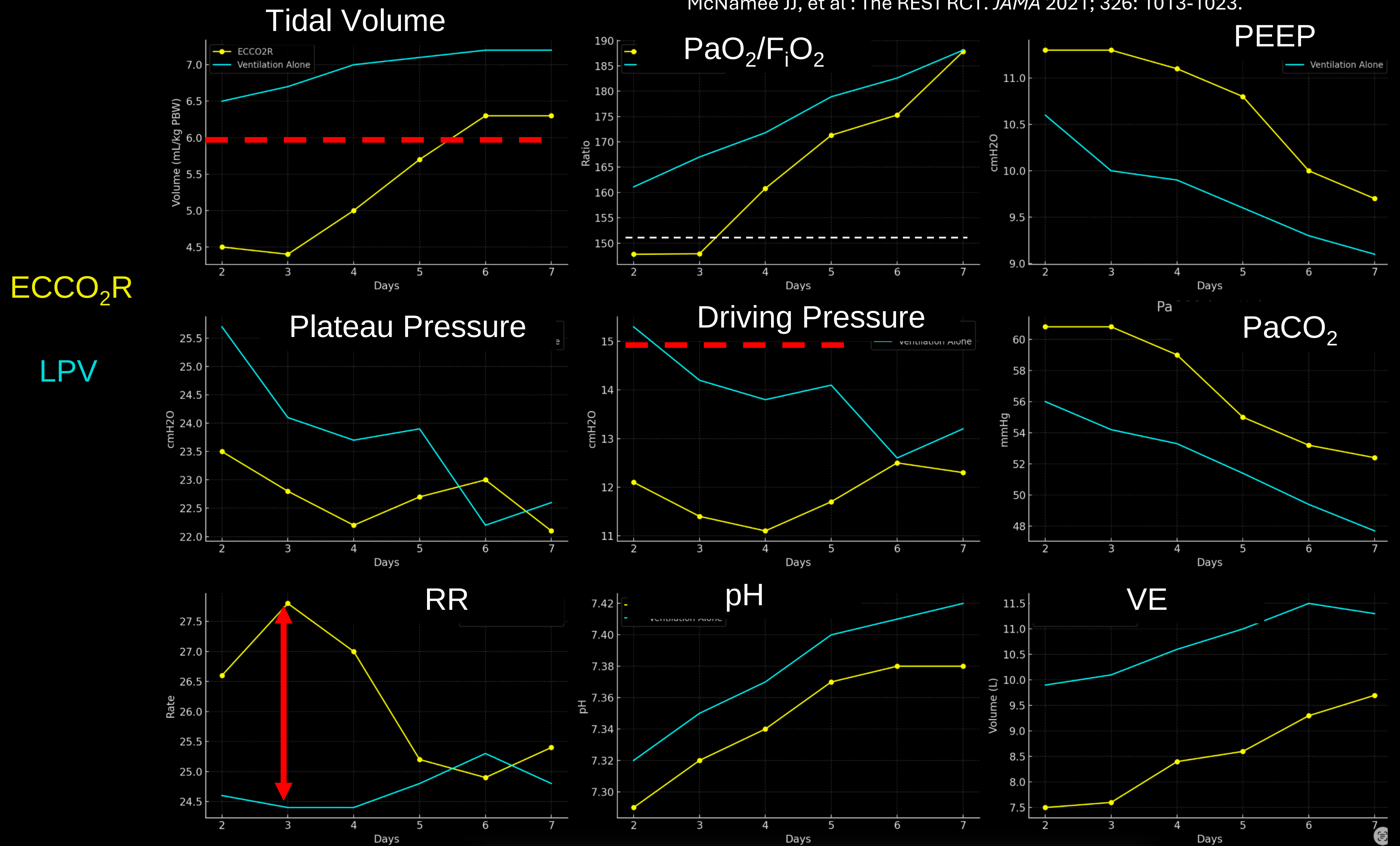


	Intervention, N (%)	Standard care, N (%)	% point difference (95% CI)	Risk ratio (95% CI)	P value
6-month mortality	85 (42.9%)	85 (41.9%)	1.1% (–8.6% to 10.7%)	1.0 (0.8 to 1.3)	0.83
1-year mortality	87 (43.9%)	87 (42.9%)	1.1% (–8.6% to 10.8%)	1.0 (0.8 to 1.3)	0.83
2-year mortality	93 (47.2%)	93 (47.9%)	0.7% (–9.2% to 10.6%)	1.0 (0.8 to 1.3)	0.89

Boyle AJ, McDowell C, Agus A, *et al*. *Thorax* 2023;**78**:767–774.

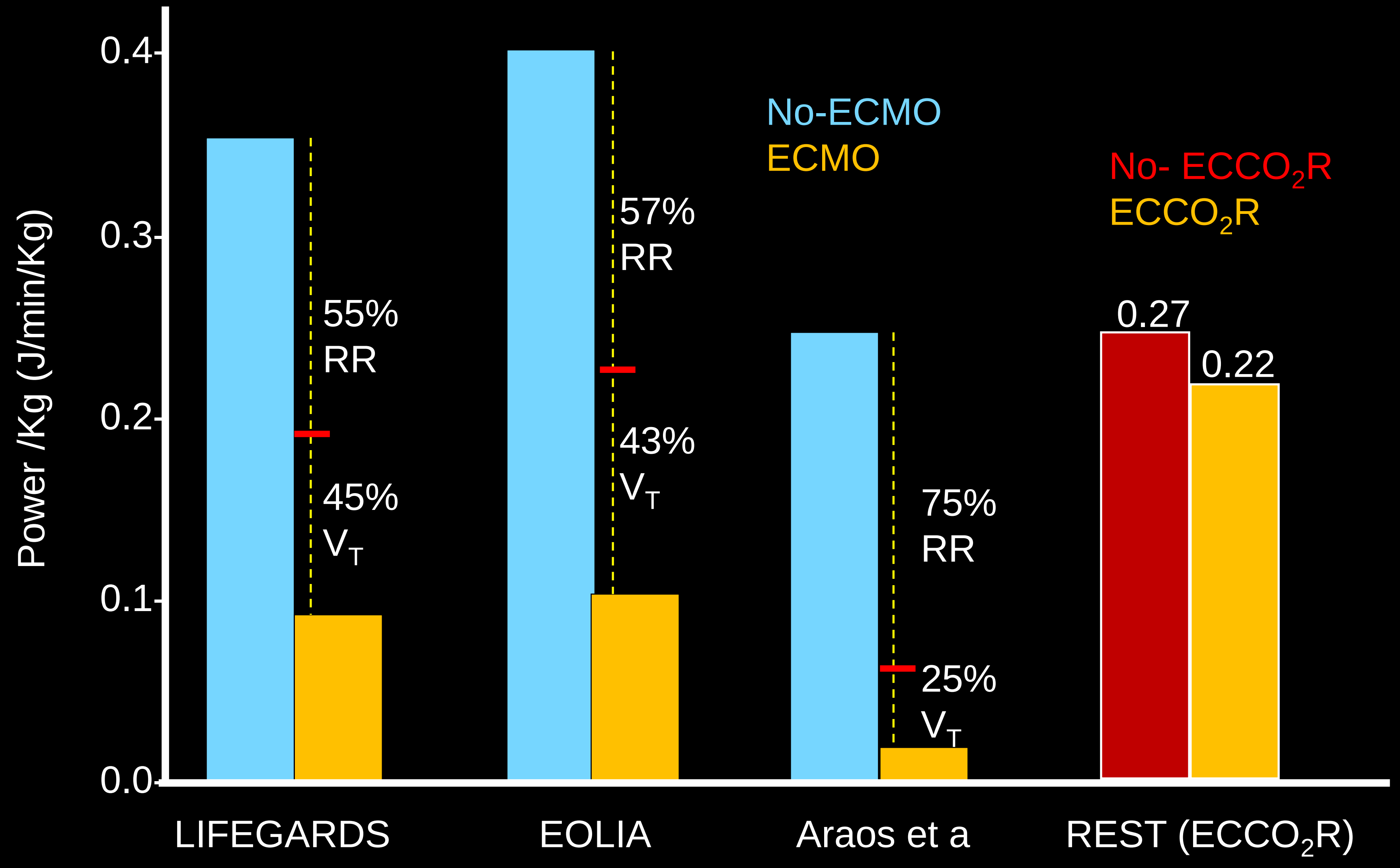
Effect of $ECCO_2R$ on physiological variables

McNamee JJ, et al : The REST RCT. *JAMA* 2021; 326: 1013-1023.

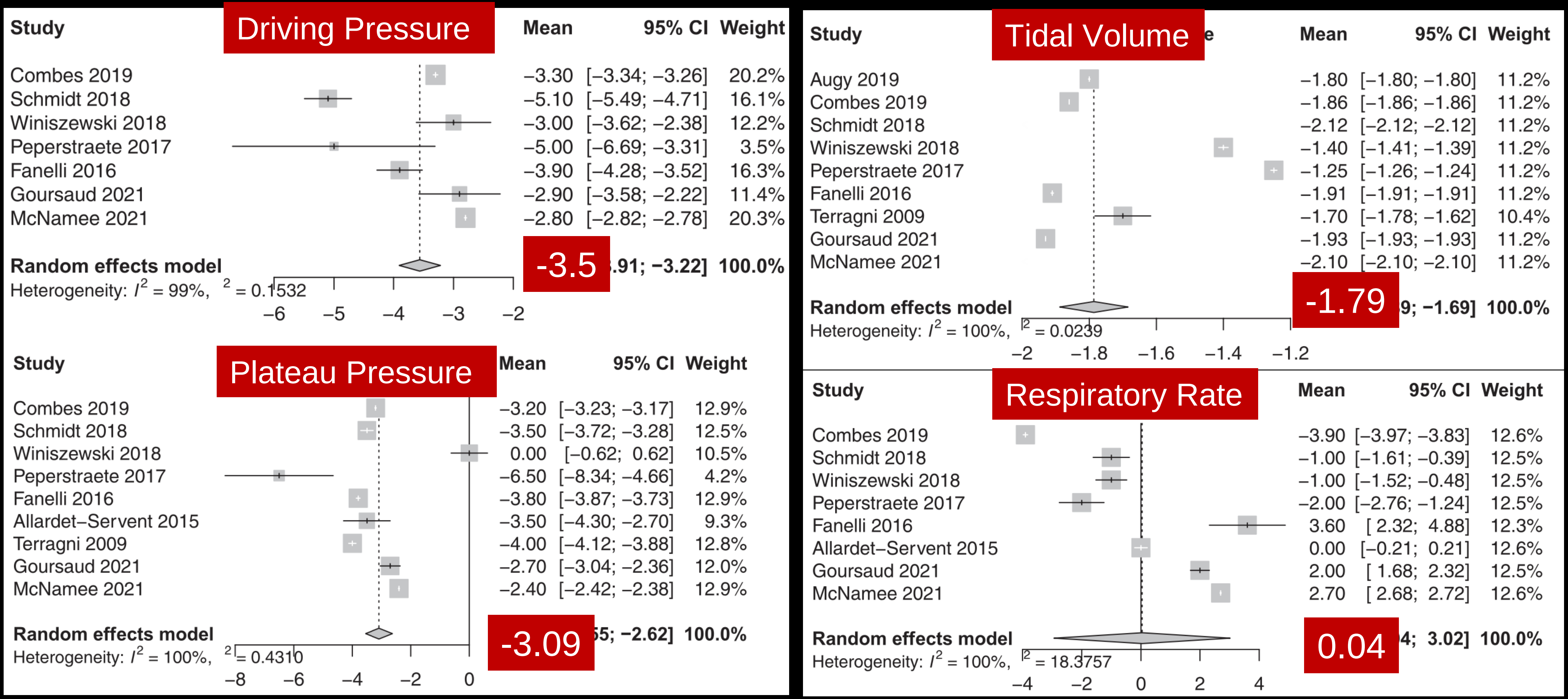


Reduction in intensity of mechanical ventilation

Modified from Quintel, Busana, Gattinoni AJRCCM 2019



Changes in ΔP, VT, P_{plat} and RR with $ECCO_2R$

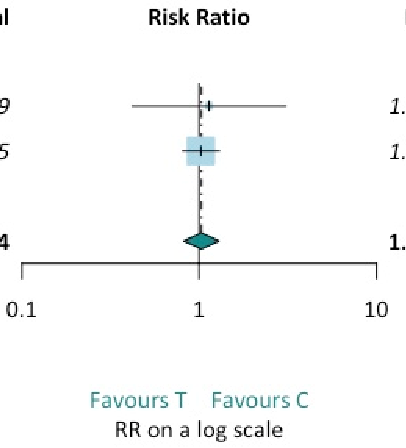


Worku E, et al *Perfusion* 2022:2676591221096225.

Does $ECCO_2R$ reduce mortality in ARDS?

We recommend against the use of $ECCO_2R$ to reduce mortality in ARDS outside of RCT

Study	ECMO Events	ECMO Total	Control Events	Control Total	RR	95%-CI	Weight
Bein-2013	*7*	*40*	*6*	*39*	*1.14*	*[0.42; 3.08]*	*5.4%*
McNamee-2021	*81*	*200*	*81*	*205*	*1.02*	*[0.81; 1.30]*	*94.6%*
Total	**88**	**240**	**87**	**244**	**1.03**	**[0.82; 1.30]**	**100.0%**

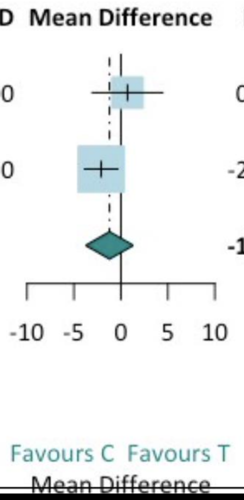


Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.84$

Test for overall effect: $z = 0.26$ ($p = 0.798$)

Mortality at hospital discharge or day 90

Study	Intervention Total	Intervention Mean	Intervention SD	Control Total	Control Mean	Control SD	MD	95%-CI	Weight
Bein-2013	40	10.00	8.00	39	9.30	9.00	0.70	[-3.06; 4.46]	31.7%
McNamee-2021	199	7.10	8.80	206	9.20	9.30	-2.10	[-3.86; -0.34]	68.3%
Total	**239**			**245**			**-1.21**	**[-3.77; 1.34]**	**100.0%**



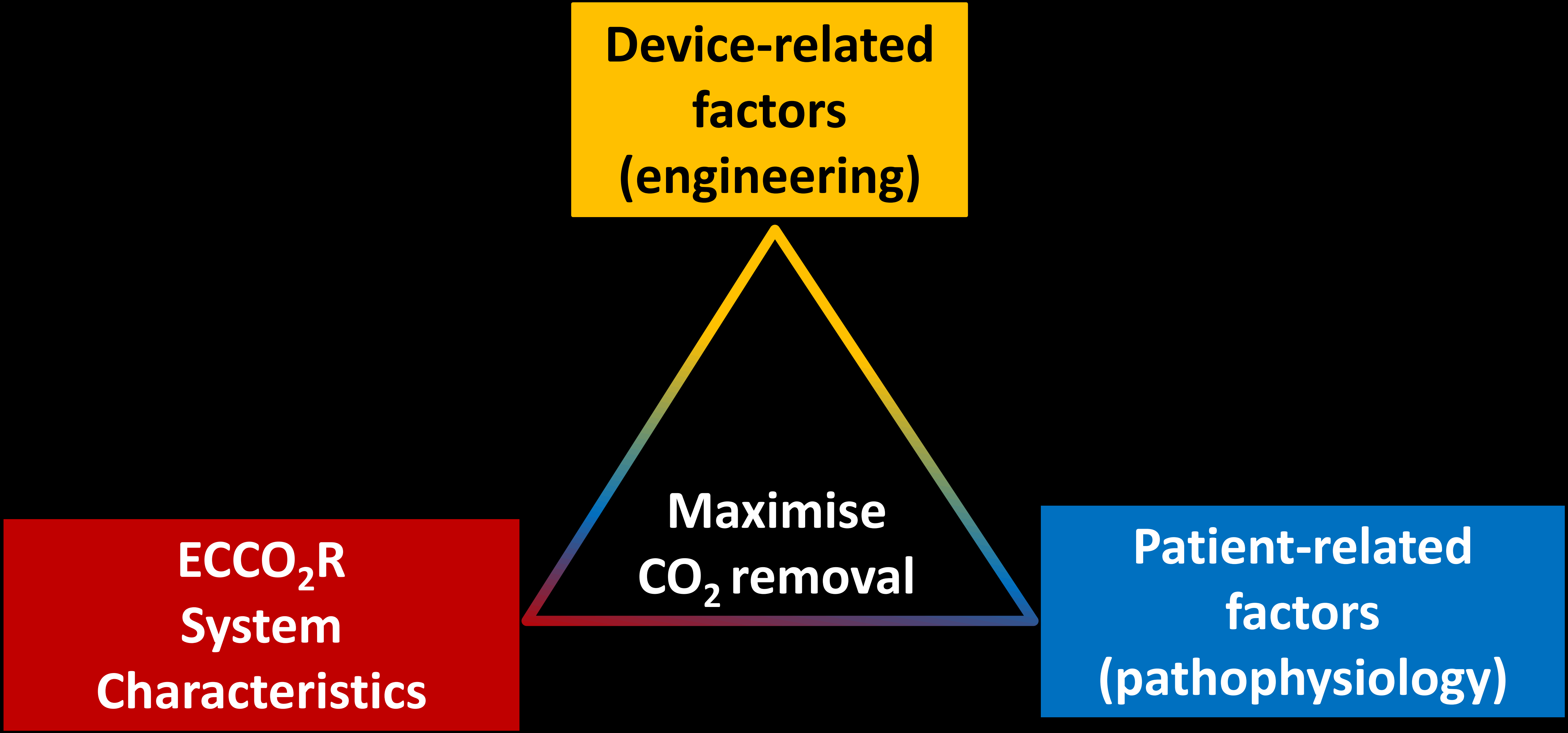
Heterogeneity: $I^2 = 43\%$, $\tau^2 = 1.6770$, $p = 0.19$

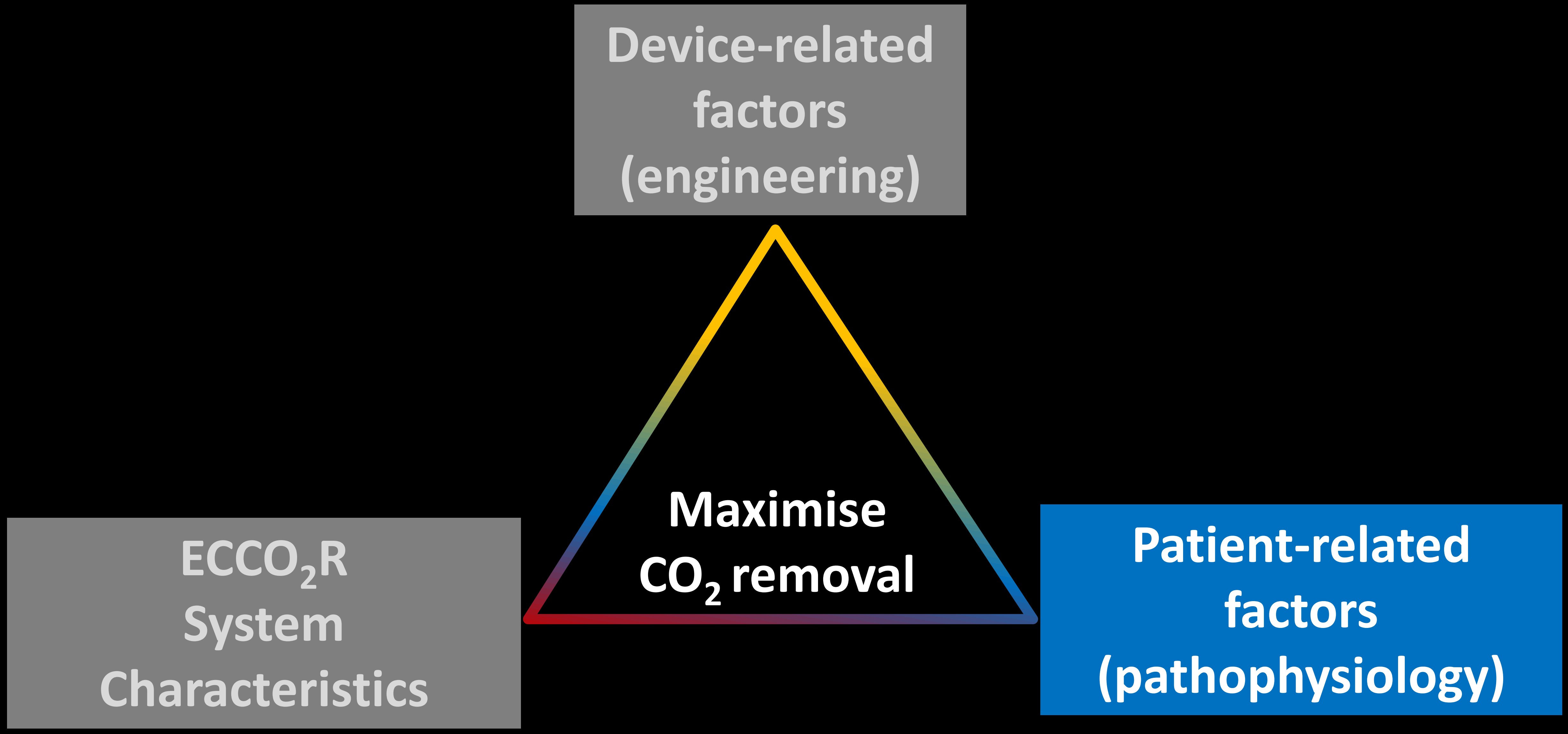
Test for overall effect: $z = -0.93$ ($p = 0.352$)

Ventilator-Free days at 28 days

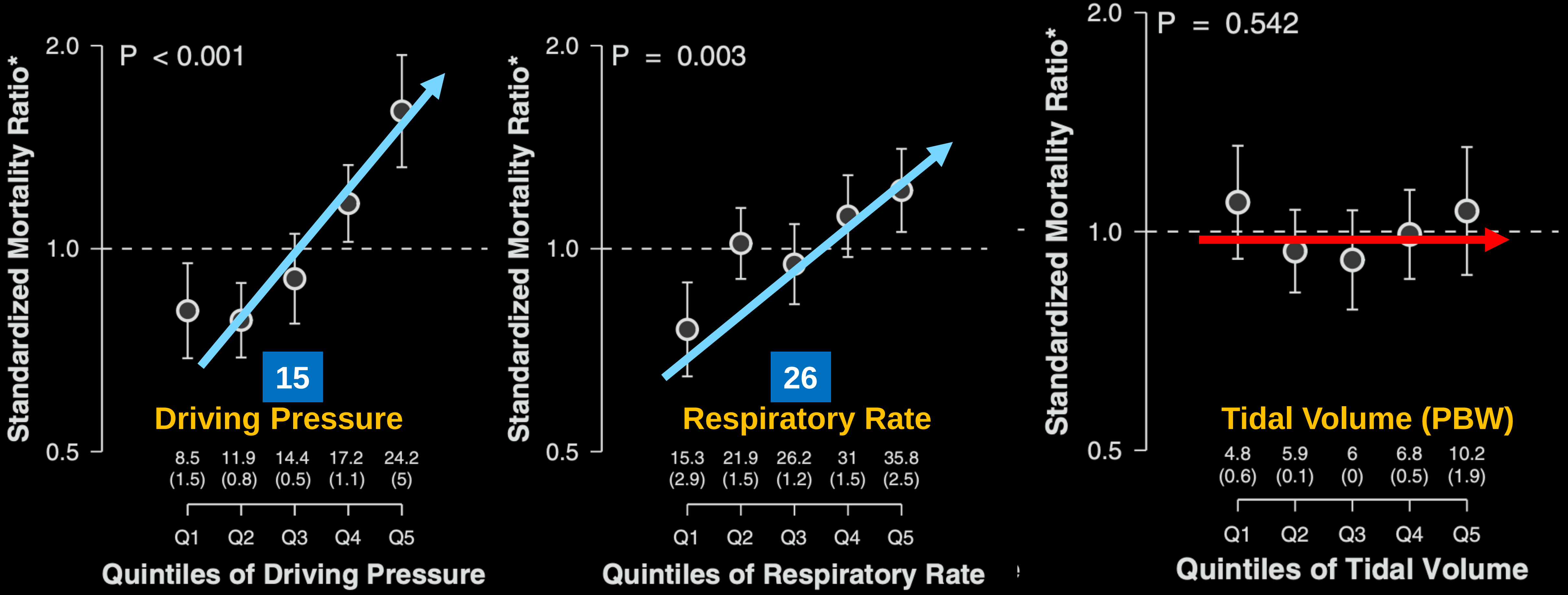
$ECCO_2R$

What Next?


Device-related factors (engineering)
Maximise CO_2 removal
$ECCO_2R$ System Characteristics
Patient-related factors (pathophysiology)


Device-related factors (engineering)
$ECCO_2R$ System Characteristics
Maximise CO_2 removal
Patient-related factors (pathophysiology)

Driving Pressure , Respiratory rate, Tidal volume:
Effect on Outcome



Costa et al; AJRCCM 2021

Factors influencing the effect of $ECCO_2R$ on DP

$$\Delta DP = -k \cdot \frac{VCO_{2-ML}}{C_{RS} \cdot \left(1 - \frac{V_D}{V_T}\right) \cdot RR \cdot P_aCO_2}$$

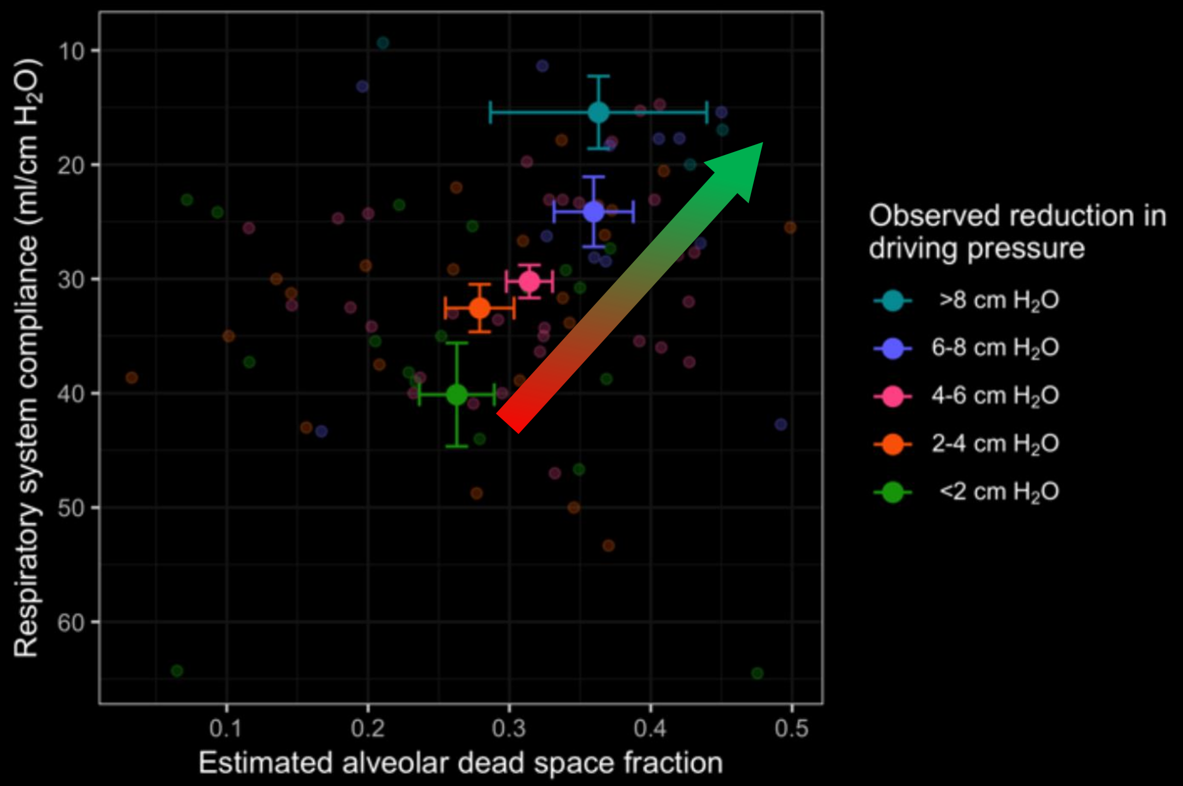
CO_2 Eliminated by $ECCO_2R$

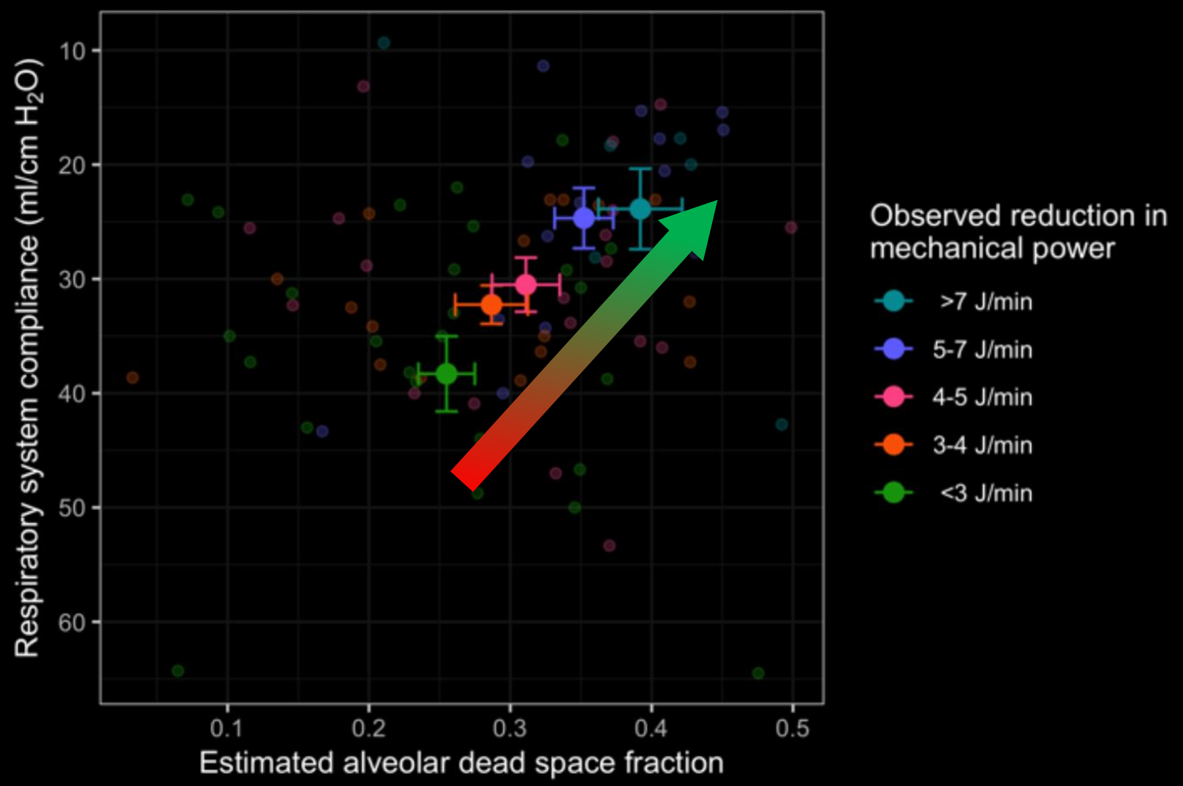
Alveolar Ventilation Fraction

Device factors

Patient factors

Change in Driving Pressure and MP





E. Goligher et al *Intensive Care Med (2019) 45:1219–1230*

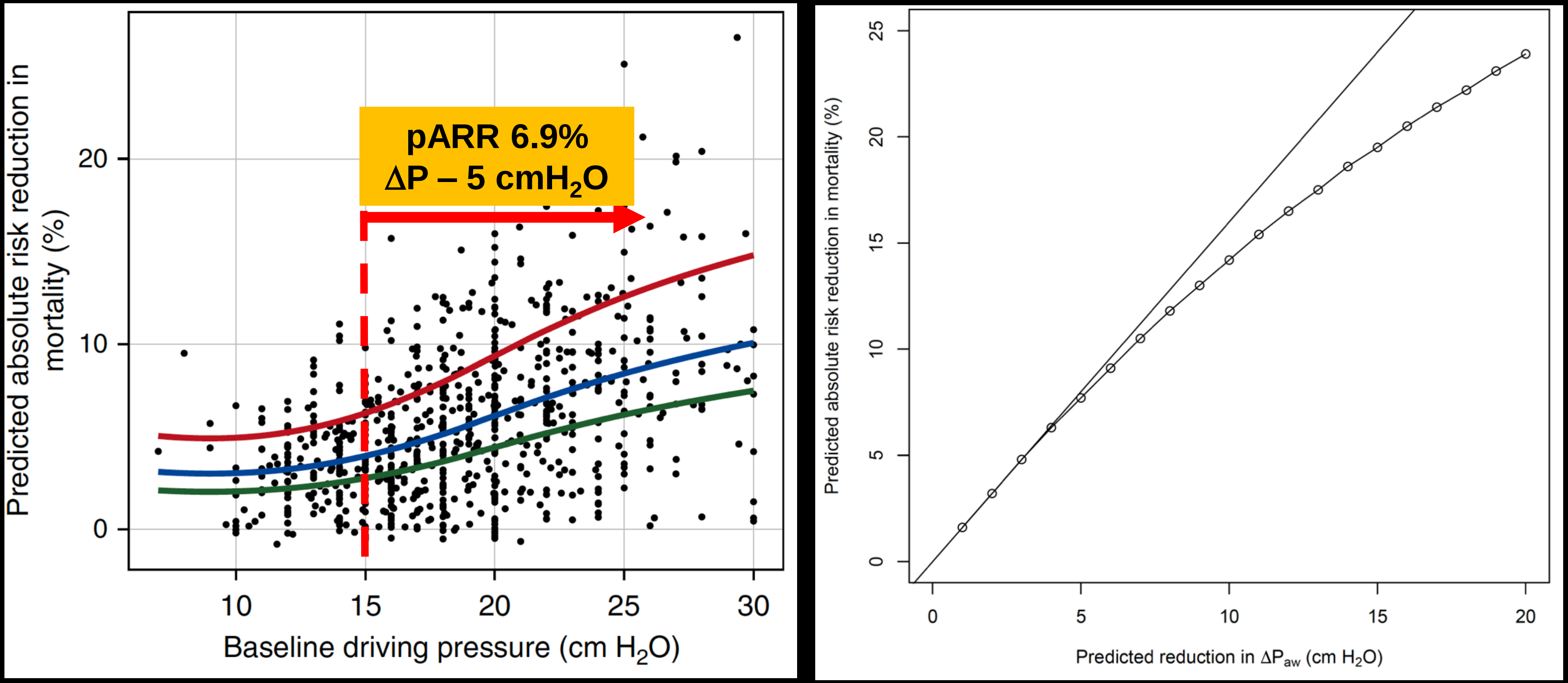
SUPERNOVA

VT (mL/Kg PBW)	6	→	4	- 2
RR/min			28	
ΔP (cmH_2O)	13	→	9	- 4

REST

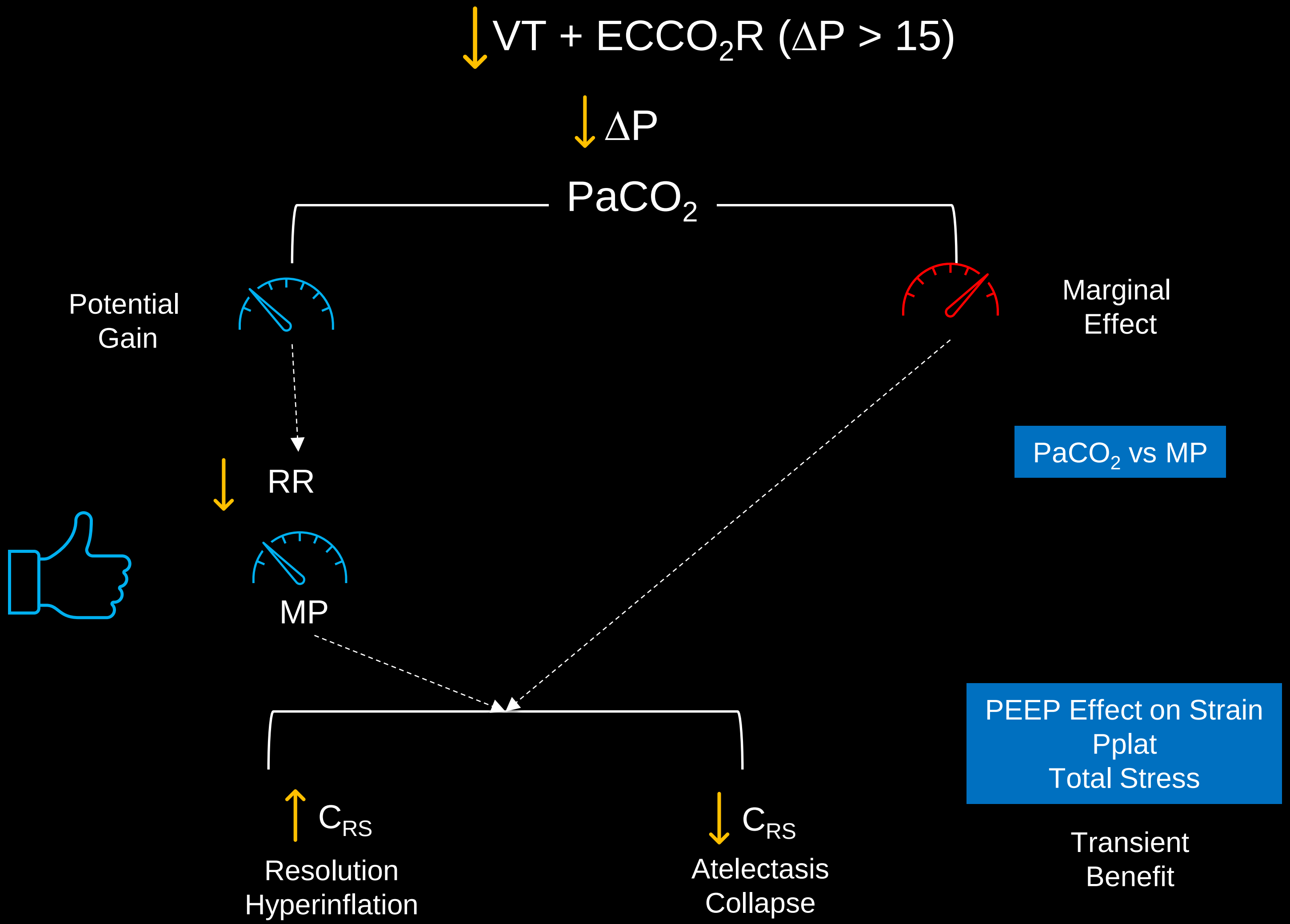
VT (mL/Kg PBW)	6
RR/min	24
ΔP (cmH_2O)	15
	50% < 15 cmH_2O

The lung protective effects of CO_2 removal depends on (changing) lung physiology



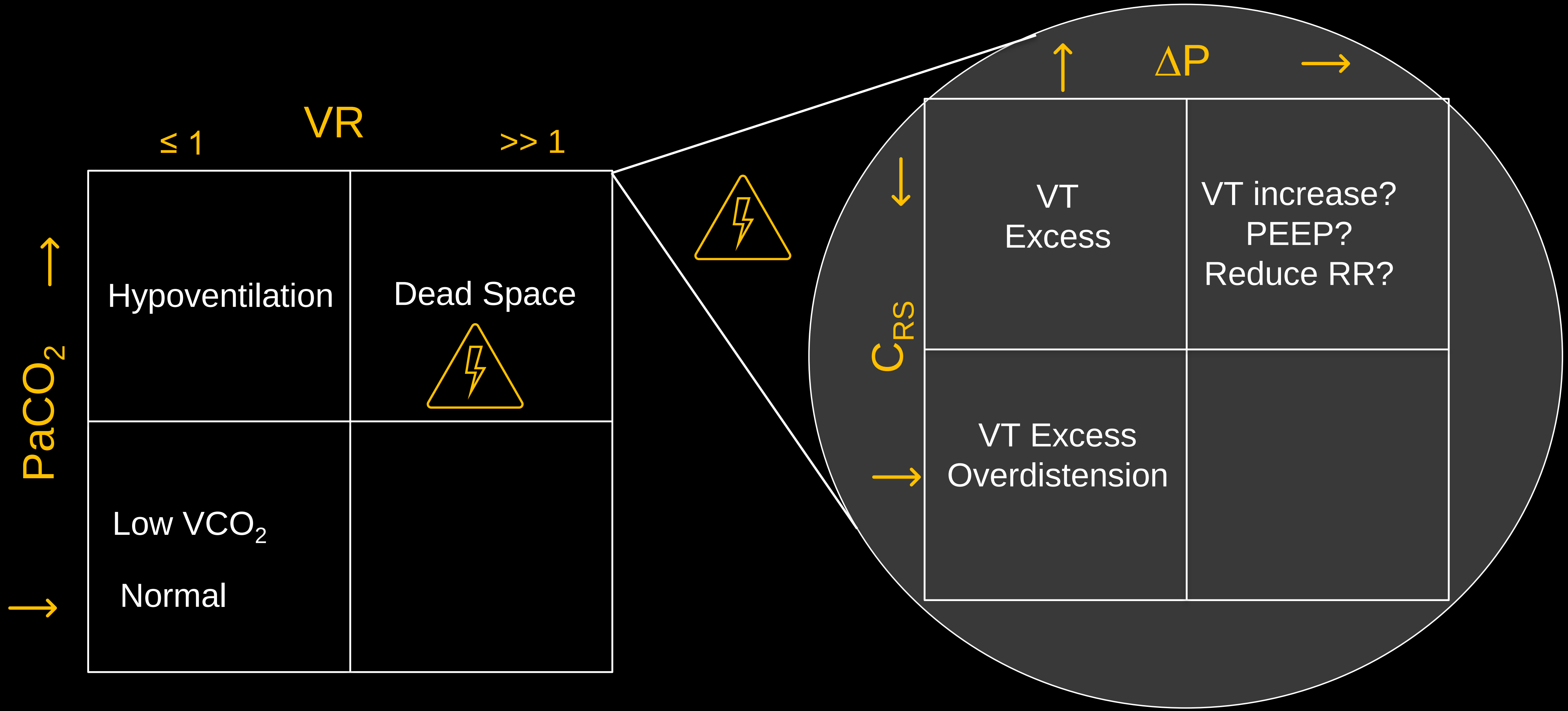
Goligher et al Intensive Care Med (2019) 45:1219–1230
E. Goligher et al AJRCCM, 2017

Response to tidal volume reduction and $ECCO_2R$



$VCO_{2\text{-}ML}$ =
2-3 mL/min/mmHg
90-135 mL/min

Ventilatory changes in ARDS on $ECCO_2R$



Approach to reduce rate

MP = 16.9

MP = 7.3

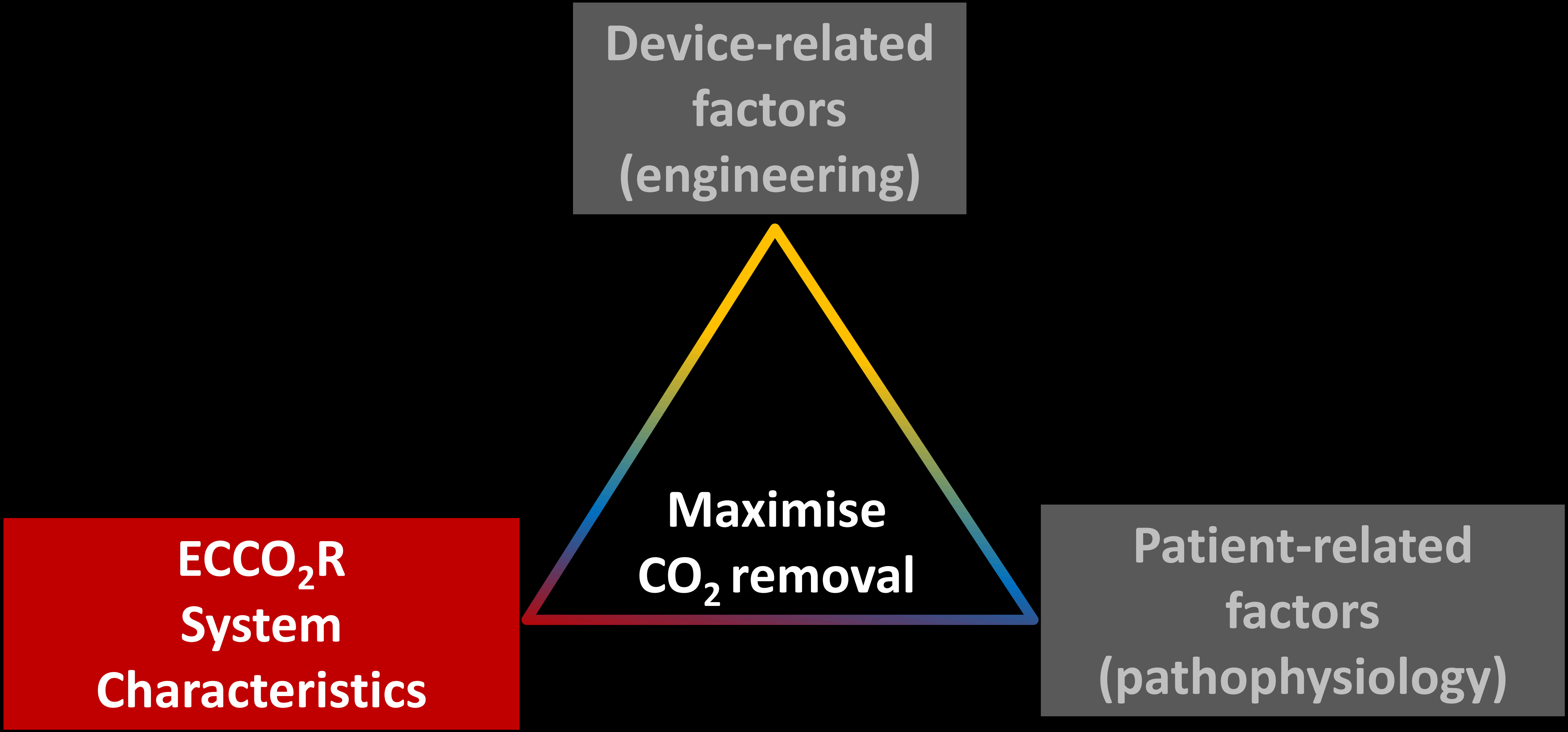
	6–7 ml/kg	Vt 4–5 ml/kg		p
Tidal Volume, *ml*	450 [431–450]	325 [300–358]*	335 [305–375]*	***<0.001***
Vt/PBW, *mlL/kg*	6.5 [6.0–7.1]	5.0 [4.7–5.6]*	5.0 [4.6–5.8]*	***<0.001***
...essure, *cmH_2O*	...–28]	24 [22–26]	...–28]	*0.101*
...essure, *cmH_2O*	...–15]	10 [8–13]*	...13]*	***0.002***
MAP, *cmH_2O*	17[15–17]	15 [12–17]	16 [14–17]	*0.290*
...y rate, *bpm*	...–24]	25 [24–30]*	...14]*°	***<0.001***
...ntilation, l/min	...10.3]	7.7 [6.4–9.8]	...4.9]*°	***<0.001***
PEEP, *cmH_2O*	13 [12–15]	14 [12–15]	14 [13–15]	*0.058*
$Elastance_{RS}$, *cmH_2O/l*	26 [24–34]	33 [28–41]	34 [26–40]	*0.909*
$Elastance_L$, *cmH_2O/l*	20 [19–28]	27 [18–29]	24 [18–33]	*0.289*
$Elastance_{CW}$, *cmH_2O/l*	7 [5–10]	8 [6–13]	8 [5–10]	*0.638*
Mechanical power, *J/min*	20 [16–26]	18 [13–23]	8 [7–11]*°	***<0.001***
Arterial pH	7.35 [7.32–7.39]	7.31 [7.25–7.35]	7.31 [7.25–7.36]	*0.084*
PaO_2, *mmHg*	73.4 [78.0–98.3]	76.2 [68.7–86.6]	71.0 [59.4–89.6]	*0.187*
PaO_2/FiO_2, *mmHg*	115 [97–174]	112 [91–153]	110 [90–146]	*0.197*
$\Delta_{av}CO_2$, *ml/dl*	3.7 [3.1–4.0]	2.6 [2.2–3.5]	2.7 [2.0–3.3]*	***0.016***
Right-to-left shunt, *%*	35 [32–42]	37 [32–46]	43 [36–61]	*0.060*
$ScvO_2$, *%*	63 [61–68]	66 [61–74]	71 [64–78]	*0.193*
$PaCO_2$, *mmHg*	49.7 [40.3–50.9]	55.2 [43.8–61.9]	55.6 [52.6–58.7]	*0.141*
	...0.80]	0.77 [0.68–0.89]	...4–0.84]	*0.727*
...n	...184]	140 [103–161]	...87]*°	***<0.001***

DP: 11 → 11

RR: 20 → 11

VCO_2 -p: 140 → 76

Chiumello D, et al. *J Crit Care* 2022, **71**:154092.


Device-related factors (engineering)
Maximise CO_2 removal
$ECCO_2R$ System Characteristics
Patient-related factors (pathophysiology)

$ECCO_2R$ in moderate ARDS: SUPERNOVA

(n=95)

- <u>End points:</u>
- Vt < 4 mL/kg PBW
- Increase in $PaCO_2$ < 20%
- pH > 7.3

- HemoLung = 33
- iLA ACTIVVE = 34
- CardioHelp ® = 28

Lower- Extraction $ECCO_2R$

- Proportion achieved endpoint <u>55%</u>
- ECBF = 0.44 L/min
- SGF 10 L/min

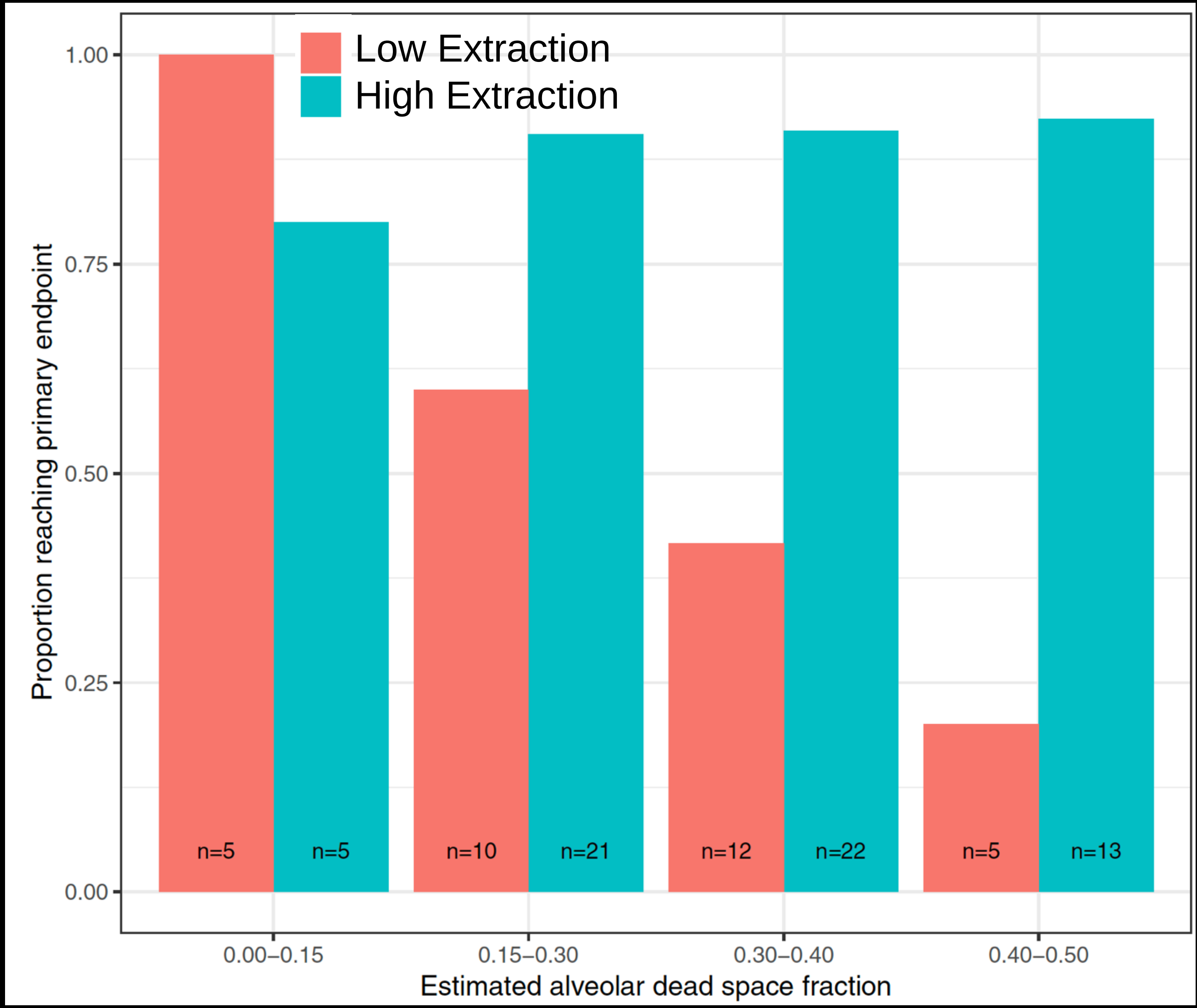
Higher- Extraction $ECCO_2R$

- Proportion achieved endpoint <u>90%</u>
- ECBF = 0.97 L/min
- SGF 8 L/min

Combes et al Intensive Care Med (2019) 45:592–600

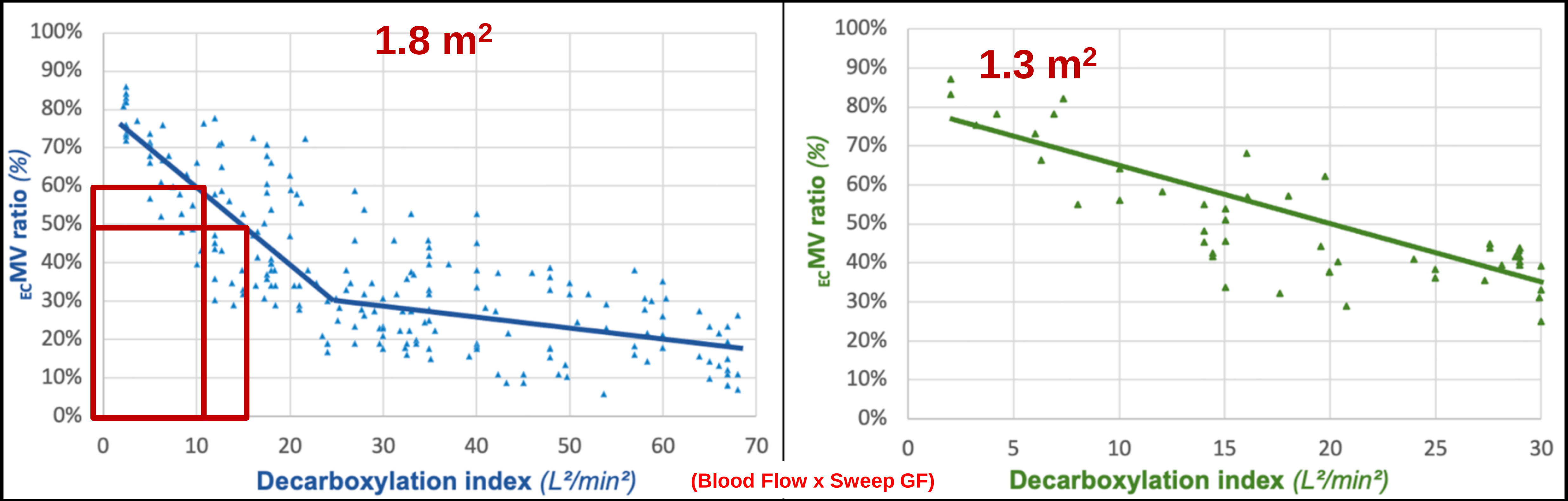
Goligher et al Intensive Care Med (2019) 45:1219–1230

Low flow $ECCO_2R$ inefficient in patients with high alveolar dead space fraction



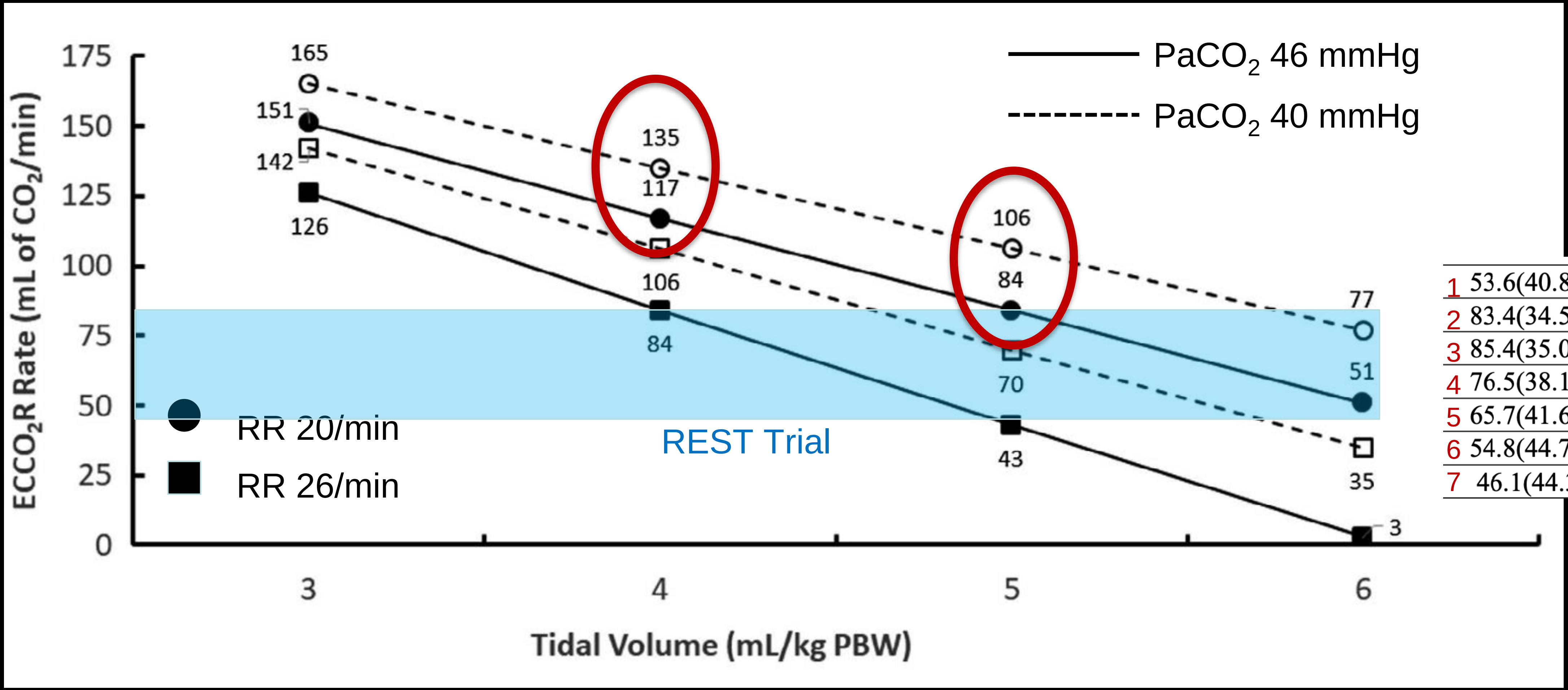
Goligher et al Intensive Care Med (2019) 45:1219–1230

ECBF-Gas flow requirements $ECCO_2R$



Laumon T et al . *Artif Organs* 2022.

Calculated $ECCO_2R$ rate required to achieve a set $PaCO_2$



1	53.6(40.8) n=158
2	83.4(34.5) n=173
3	85.4(35.0) n=171
4	76.5(38.1) n=158
5	65.7(41.6) n=139
6	54.8(44.7) n=112
7	46.1(44.3) n=95

Leypoldt JK, et *Artif Organs* 2020, **44**(5):488-496.

Conclusions

- Mechanical power reduction is limited with 'low flow’ systems
- Mid-flow systems or tech advancements might be necessary
- Optimal ventilation for $ECCO_2R$ patients is essential
- Selection of patients based on physiology and thresholds of ventilation

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