Geoff Shaw
Professor, Dept of Surgery and Critical Care, University of Otago, Christchurch, NZ
Honorary /Adjunct Professor, College of Engineering, University of Canterbury, NZ
Intensive Care Specialist, Te Whatu Ora, Waitaha Canterbury, Christchurch, NZ
Editor-in-Chief, Journal of Mechanical Ventilation

1

Declaration

Shareholder in **TIRO MEDICAL LIMITED** (5024040) https://app.companiesoffice.govt.nz/co/5024040
Med tech company registered in Christchurch , NZ

absolutelymaybe.plos.org/2018/09/24/scientific-advocacy-and-biases-of-the-ideological-and-industry-kinds/

2

The story starts here:

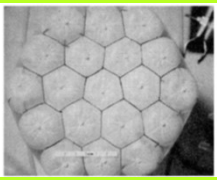
The Lancet · Saturday 12 August 1967 **ACUTE RESPIRATORY DISTRESS IN ADULTS** David G. Ashbaugh, D. Boyd Bigelow, Thomas L. Petty, Bernard E. Levine

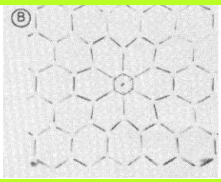
"…severe dyspnoea, tachypnoea, cyanosis that is refractory to oxygen therapy, loss of lung compliance, and diffuse alveolar infiltration seen on chest X-ray." "…[PEEP] was most helpful in combating atelectasis and hypoxaemia."

Stress distribution in lungs: a model of pulmonary elasticity

JERE MEAD, TAMOTSU TAKISHIMA, AND DAVID LEITH

Department of Physiology, Harvard University School of Public Health, Boston, Massachusetts 02115





If transpulmonary pressure = 30 cmH_2O, the effective pressure (P_{eff}) tending to expand an atelectatic region (V_0), surrounded by a fully expanded lung(V), is: $(V/V_0)^{2/3}$ x 30 = **139.2 cmH_2O**, (where V/V_0 = 10)

Intensive Care Medicine © Springer-Verlag 1992

Editorial

Open up the lung and keep the lung open

B. Lachmann

"Keeping the lung open by the appropriate ventilatory modes not only prevents lung damage due to high shear forces, but may also prevent alveolar flooding"

Ashbaugh D, Bigelow DB, Petty T, Levine B. Acute respiratory distress in adults. ***The Lancet. 1967 Aug 12;290(7511):319-23*** **(Cited 5646 times)**

Mead J, et.al. Stress distribution in lungs: a model of pulmonary elasticity. ***Journal of Applied Physiology. 1970 May;28(5):596-608.***

Lachmann B. Open up the lung and keep the lung open. ***Intensive Care Medicine. 1992 Jun 1;18(6):319-21***.

3

The story starts here:

Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome

The NEW ENGLAND JOURNAL of MEDICINE

No difference in hospital mortality or duration of unassisted breathing using PEEP of 13.2 vs. 8.3 cmH_2O

Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

CARING FOR THE CRITICALLY ILL PATIENT

Better lung function, shorter MV and less organ failure using PEEP of 14.6 vs. 7.1 cmH_2O

Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

The NEW ENGLAND JOURNAL of MEDICINE

Patients with more recruitable lung had worse oxygenation and compliance, higher dead space, and higher mortality. Percentage of recruitable lung is extremely variable, and PEEP responsive

National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. ***New England Journal of Medicine. 2004 Jul 22;351(4):327-36.***

Mercat A, Richard JC, Vielle B, et. al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. ***JAMA. 2008 Feb 13;299(6):646-55.***

Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G. Lung recruitment in patients with the acute respiratory distress syndrome. ***New England Journal of Medicine. 2006 Apr 27;354(17):1775-86.***

4

3 RCTs showed promise:

A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome

CRITICAL CARE

(RCT, n=20) Open lung strategy associated with amelioration in some cytokines, better oxygenation and lung compliance

Open Lung Approach for the Acute Respiratory Distress Syndrome: A Pilot, Randomized Controlled Trial*

Critical Care Medicine

(RCT, n=200) Improved oxygenation and driving pressure; no impact on mortality, ventilator- free days, or barotrauma

Maximal Recruitment Open Lung Ventilation in Acute Respiratory Distress Syndrome (PHARLAP)

A Phase II, Multicenter Randomized Controlled Clinical Trial

(RCT, n=115*) No reduction in VFDs or mortality; more arrhythmias, but reduced use of nitric oxide, ECMO, and prone positioning. However, significantly increased VFDs and reduced ICU and hospital LoS, if compliance improved in the first 48 hours (responders) of the intervention group.

*planned 340, but enrolment stopped after publication the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial

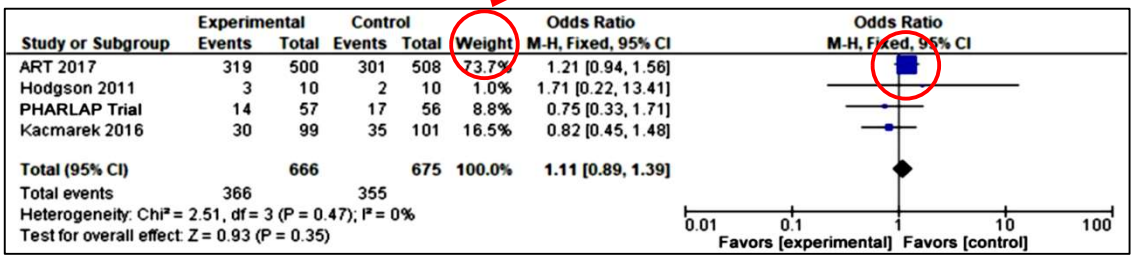
Hodgson CL, Tuxen DV, Davies AR, et.al. A randomised controlled trial of an open lung strategy with staircase recruitment, titrated PEEP and targeted low airway pressures in patients with acute respiratory distress syndrome. ***Critical care. 2011 Jun;15:1-9***.

Kacmarek RM, Villar J, Sulemanji D, Montiel R, Ferrando C, Blanco J, Koh Y, Soler JA, Martínez D, Hernández M, Tucci M. Open lung approach for the acute respiratory distress syndrome: a pilot, randomized controlled trial. ***Critical Care Medicine. 2016 Jan 1;44(1):32-42.***

Hodgson CL, Cooper DJ, Arabi Y, et.al. Maximal recruitment open lung ventilation in acute respiratory distress syndrome (PHARLAP). A phase II, multicenter randomized controlled clinical trial. ***American Journal of Respiratory and Critical Care Medicine. 2019 Dec 1;200(11):1363-72.***

5

But then we got the ART study, which accounts for 73.7% of data from RCTs using SRMs



Forest plot of hospital mortality of 4 RCTs of a staircase recruitment manoeuvre (SRM) and PEEP titration*

*Online data supplement

We need to take a closer look at what went wrong…

Hodgson CL, Cooper DJ, Arabi Y, et.al. Maximal recruitment open lung ventilation in acute respiratory distress syndrome (PHARLAP). A phase II, multicenter randomized controlled clinical trial. ***American Journal of Respiratory and Critical Care Medicine. 2019 Dec 1;200(11):1363-72.***

6

ART- a well-intended study….but….

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome

A Randomized Clinical Trial

OBJECTIVE

Does lung recruitment using PEEP titration to the best respiratory-system compliance decrease 28-day mortality in patients with moderate to severe ARDS compared with a conventional low-PEEP strategy?

DESIGN, SETTING, AND PARTICIPANTS

Multicenter, RCT in 120 ICUs from 9 countries over 5y. 5 mo., in adults with moderate to severe ARDS.

INTERVENTIONS

Lung recruitment maneuver and PEEP titration to best compliance (n = 501) vs. low PEEP ARDSnet protocol (n = 509) using volume-assist control mode until weaning

RESULTS

Higher 28 day mortality. 277 /501 pts. **(55.3%)** in recruitment group vs. 251 /509 pts. (**49.3%)** in control group (**HR, 1.20**; 95% CI, **1.01 to 1.42**; P = .041).

Higher 6-mo. mortality. 65.3% in recruitment group vs. **59.9%** (P = .04)

Less VFD (**5.3 vs 6.4**; P = .03) **More pneumothoraces** (**3.2% vs 1.2%**, P = .03), and **barotrauma** (**5.6% vs 1.6%**, P = .001).

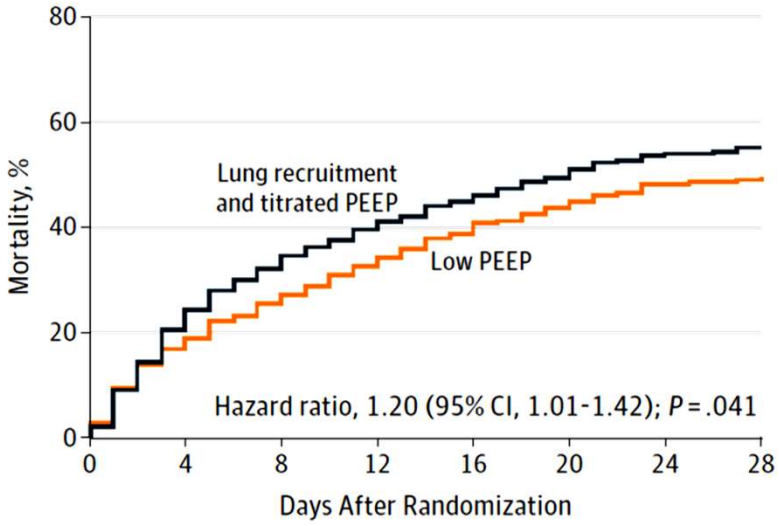
No diff in ICU and hospital LoS, or in ICU and in-hospital mortality.

Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et. al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. **JAMA. 2017 Oct 10;318(14):1335-45.**

7

ART- a well-intended study….but….

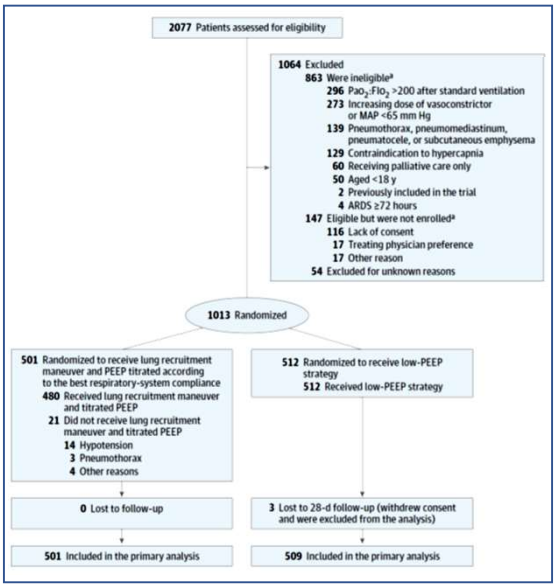
28-Day Mortality in Recruitment Manoeuver with Titrated PEEP Group vs Low-PEEP Group

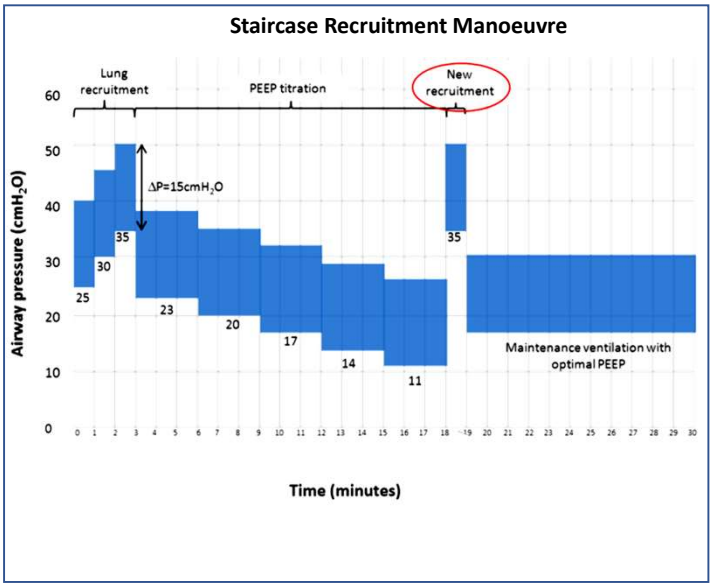


Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et. al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. ***JAMA. 2017 Oct 10;318(14):1335-45.***

8

ART- a well-intended study….but….

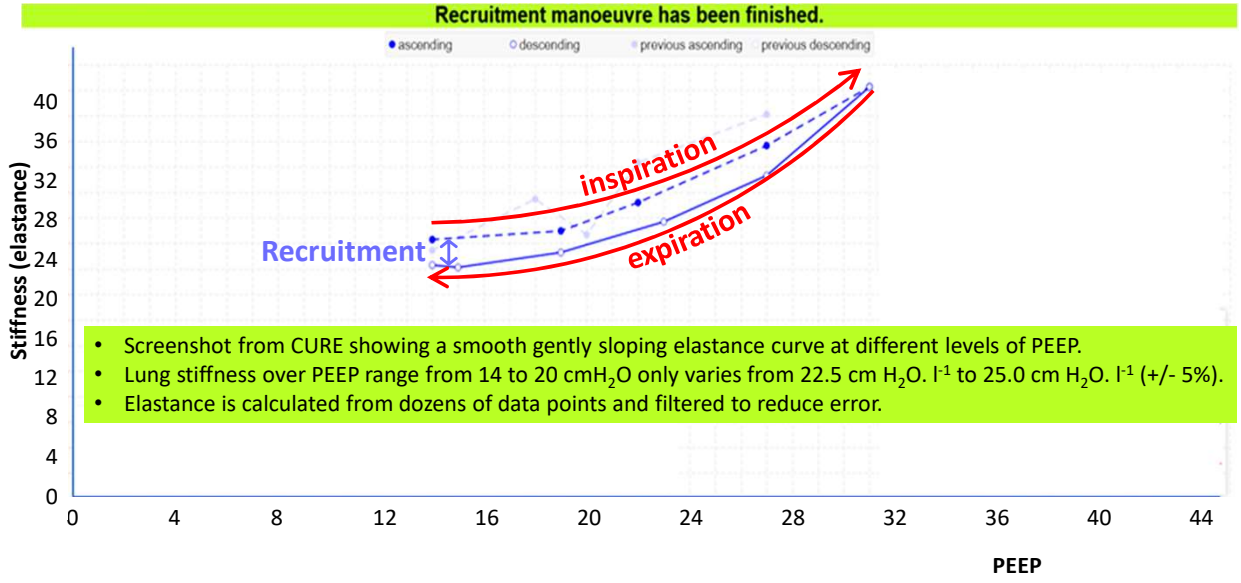




Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et. al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. ***JAMA. 2017 Oct 10;318(14):1335-45.***

9

Errors in Recruitment: why using a computer is essential

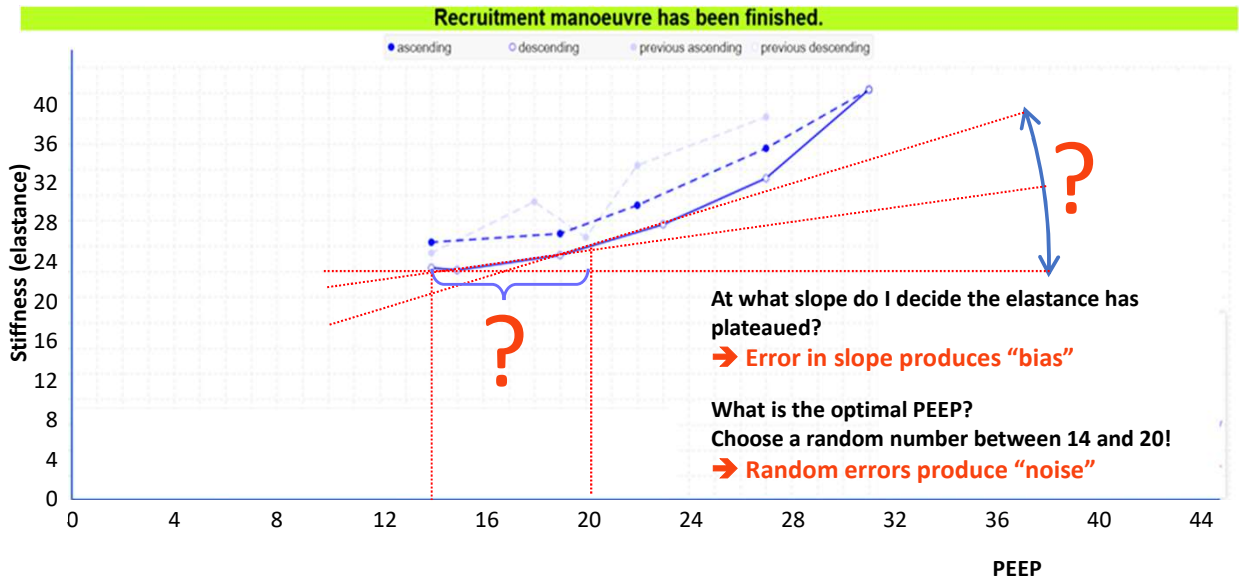


- Screenshot from CURE showing a smooth gently sloping elastance curve at different levels of PEEP.
- Lung stiffness over PEEP range from 14 to 20 cmH_2O only varies from 22.5 cm H_2O. l^{-1} to 25.0 cm H_2O. l^{-1} (+/- 5%).
- Elastance is calculated from dozens of data points and filtered to reduce error.

CUREsoft, staircase recruitment manoeuvre

10

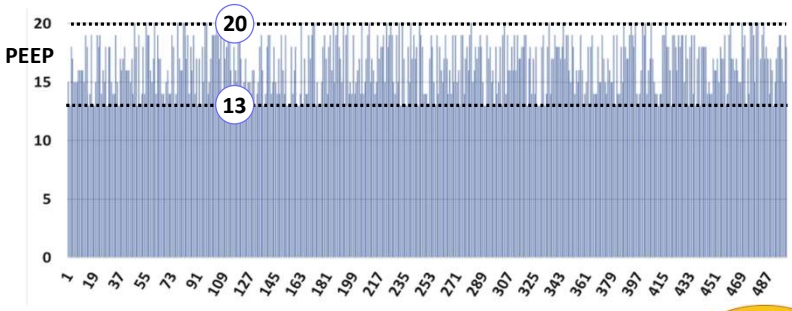
Errors in Recruitment: a random number generator?



CUREsoft, staircase recruitment manoeuvre

11

ART study simulation, 500 'titrated' PEEPs randomly generated between 13 and 20 cmH_2O



Variable	1hour	
	Lung Recruitment Maneuver with PEEP Titration Group	Control Group
PEEP, mean (95% CI), cmH_2O	16.4 (16.0 to 16.7)	13.0 (12.7 to 13.3)
No. of patients	499	507

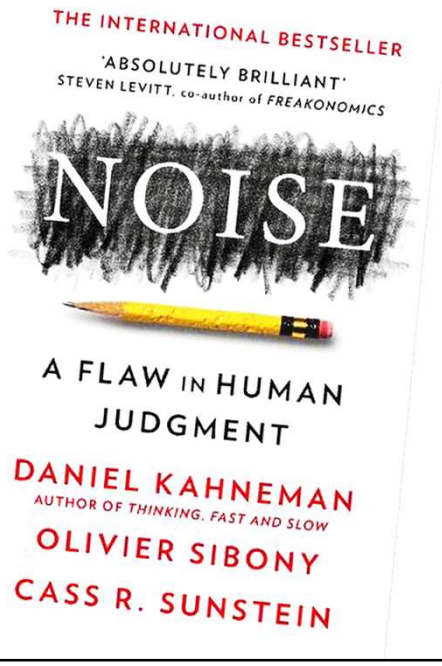
Mean =16.4 cm H_2O **[95% CI 16.0 -16.7] (Study results)**

Mean =16.5 cm H_2O **[95% CI 16.1 -16.9] (Random PEEP)**

Cavalcanti AB, Suzumura ÉA, Laranjeira LN, et.al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. **JAMA. 2017 Oct 10;318(14):1335-45.**

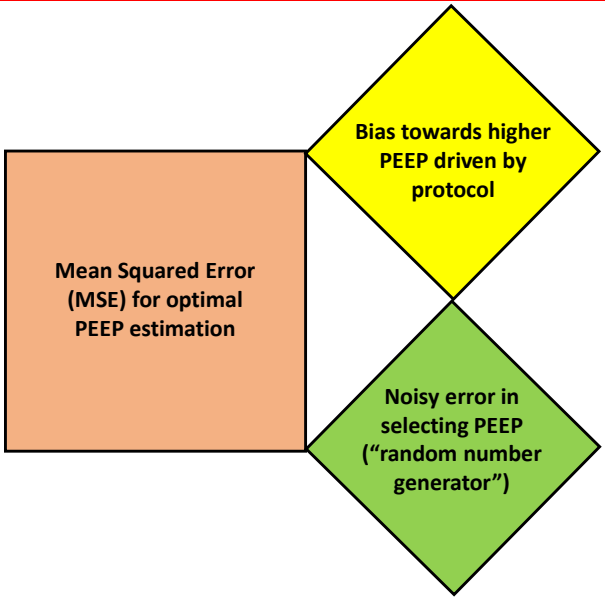
12

Errors in Recruitment: a random number generator?



13

Errors in Recruitment: a random number generator?



Brenner LA. Daniel Kahneman, Olivier Sibony, and Cass R. Sunstein. Noise: A Flaw in Human Judgment. **Harpercollins Publishers | William Collins, 2022, ISBN9780008309039**

14

Over PEEPed; too much dead space is associated with death

Variable	1hour	
	Lung Recruitment Maneuver with PEEP Titration Group	Control Group
Tidal volume, mean (95% CI), mL/kg of predicted body weight	5.4 (5.3 to 5.5)	5.5 (5.5 to 5.6)
Respiratory rate, mean (95% CI), breaths/min	29.7 (29.1 to 30.2)	28.1 (27.5 to 28.7)
$PaCO_2$, mean (95% CI), mmHg	59.7 (57.7 to 61.6)	55.9 (54.1 to 57.7)
V_E l.min^{-1} (estimated*)	9.78	9.43

*Based on PBW = 61 kg calculated from baseline characteristics

Calculating dead space minute ventilation ($V_{D'}$)

$V_{D\,(CONTROL)} = V_{D'\,(CONTROL)} / RR$
$= 5.66 / 28.1$
⇨ **$V_{D\,(CONTROL)} = 201$ ml**

$V_{D\,(INTERVENTION)}) = V_{D'\,(INTERVENTION)} / RR$
$= 6.25 / 29.7$
⇨ **$V_{D\,(INTERVENTION)}) = 212$ ml**

Change in V_D $= V_{D\,(INTERVENTION)}) / V_{D\,(CONTROL)}$
⇨ ΔV_D $= 0.211 / 0.201$
⇨ **$\Delta V_D = 1.05$**

- Physiological dead space fraction (V_D / V_T), estimated from literature in patients with ARDS is ~0.6.
- For **each increase of 0.05 the odds of death increases by 59% in the early phase** (OR 1.59, 95% CI 1.18-2.16, P = .003) and by **187% in the intermediate phase in ARDS** (OR 2.87, 95% CI 1.36-6.04, P = .005).

Nuckton TJ, Alonso JA, Kallet RH, Daniel BM, Pittet JF, Eisner MD, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. ***N Engl J Med. 2002;346(17):1281–6***.

Raurich JM, Vilar M, Colomar A, Ibanez J, Ayestaran I, Perez-Barcena J, et al. Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. ***Respir Care. 2010;55(3):282–7.***

Kallet RH, Zhuo H, Liu KD, Calfee CS, Matthay MA. The association between physiologic dead-space fraction and mortality in subjects with ARDS enrolled in a prospective multi-center clinical trial. ***Respir Care. 2014;59(11): 1611–8***

15

Over PEEPed; high ventilatory ratio is associated with death

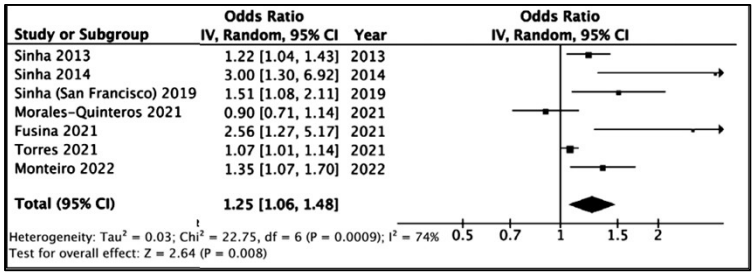
Dead-Space Ventilation Indices and Mortality in Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis*

Critical Care Medicine
Society of Critical Care Medicine

Pooled odds ratio of ventilatory ratio and mortality
Adjusted odds of mortality per 1 unit increase in ventilatory ratio

Variable	1hour	
	Lung Recruitment Maneuver with PEEP Titration Group	Control Group
$PaCO_2$, mean (95% CI), mmHg	59.7 (57.7 to 61.6)	55.9 (54.1 to 57.7)
V_E l.min^{-1}	9.78	9.43
Ventilatory Ratio*	2.55	2.30

***VR = ($PaCO_2$ X V_E[ml.min^{-1}]) / (37.5 X PBW x 100)**



- Using above OR of 1.25 for risk of death (ROD) per 1 unit increase, then ROD is 1.94 and 1.65 respectively for the intervention and control groups. **The relative increased ROD for the intervention group is 1.19**

Jayasimhan D, Chieng J, Kolbe J, Sidebotham DA. Dead-Space Ventilation Indices and Mortality in Acute Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis. ***Critical Care Medicine. 2023 May 19:10-97.***

16

Higher mechanical power is associated with death

	Baseline (Average)	Intervention	% Δ from baseline	Control	% Δ from baseline
RR (min^{-1})	25.3	29.7	+17.4	28.1	+11.1
V_T (ml)	354	329	-7.1	336	-5.1
V_E ($l.min^{-1}$)	8.9	9.78	+9.9	9.43	+6.0
Δ P (cm H_2O)	13.5	11.5	-14.8	13.0	-3.7
P plateau (cm H_2O)	26.0	27.9	+7.3	25.9	-0.4
PEEP (cm H_2O)	12.5	16.4	+31.2	13.0	+4.2
Mech Power ($J.min^{-1}$)*	16.9	21.2	+25.4	18.0	+6.2

Mech Power [MP] ($J.min^{-1}$) = 0.098 x V_T x RR x (P_{peak} - Δ P/2)

Wow!

- Even though **Δ P** in intervention group was 14.8 % less than baseline and **P plateau** was only slightly (7.3%) above baseline, **the MP was significantly higher (25.4%)**
- **This was almost entirely due to the higher respiratory rate. If this had not been increased, MP would have been just slightly higher than baseline (18 J $min.^{l-1}$)**
- What would have happened if the **PEEP had been left alone? (MP = 15.7; 7.4% less than baseline)**
- And if the **RR had also been left alone? (MP = 13.3; 27% less than baseline)**

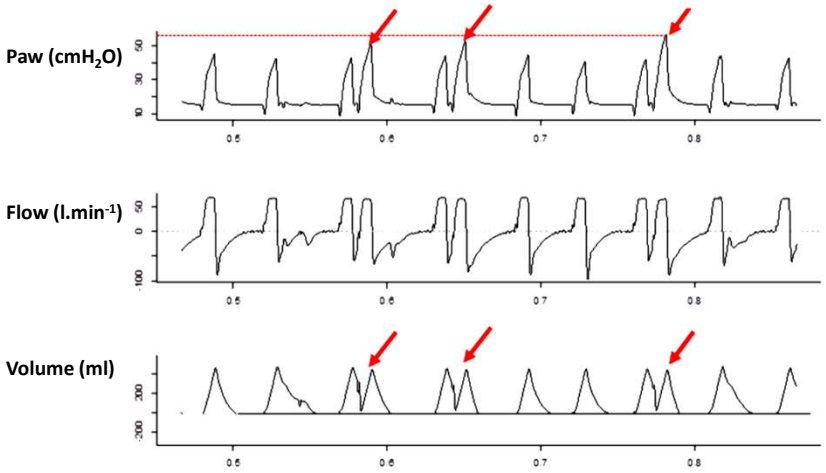
Serpa Neto A, Deliberato RO, Johnson AE, et. al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. ***Intensive care medicine. 2018 Nov;44:1914-22.***

17

Asynchrony is associated with death

Breath stacking

ART study used assist controlled ventilation (ACV) which the authors acknowledge and show causes breath stacking, such that a patient could receive twice the tidal volume prescribed. This has a nonlinear impact on lung strain exposing those at higher PEEP settings to risk of barotrauma and death.



18

Recruitability?

PEEP responsiveness

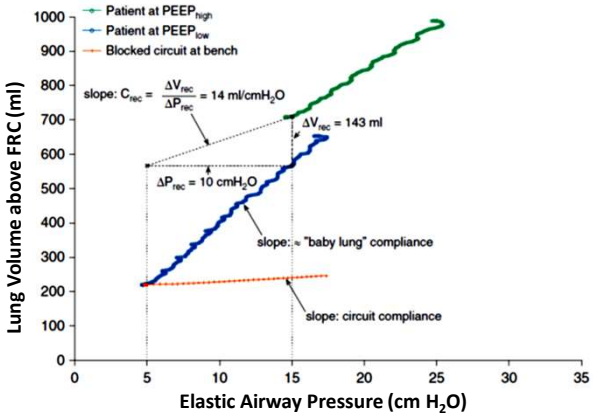
- The study did not attempt to identify responders to PEEP, furthermore it was acknowledged "only mild responses were observed in this trial as suggested by the small increments in the respiratory-system compliance and reductions in driving pressure. Furthermore, the driving pressure, a strong predictor of survival in ARDS, decreased by a mean of only less than 2 cm of water"
- Non-responsive patients do not benefit from recruitment!
- They just suffer all the risks….
  - Alveolar overdistention, lung injury/inflammation, barotrauma, pneumothoraces,, hypotension, poorer organ perfusion, renal failure, excess sedation and prolonged use of muscle relaxants, increased duration of MV, VAP, and delirium, etc.
- The lowest initial level of PEEP 11 +2 cm will be too high for this group, optimal PEEP ~5 to 10 cmH_2O.
- Hunting for best respiratory system compliance in non-responders is a fools game as the characteristics of the PEEP compliance curve has nothing to do with recruitability, but everything to do with the non-linear mechanical properties of the lung and chest wall….Oh dear….

19

How to fix this: Recruitment to Inflation Ratio (RI) to predict recritability

The ratio of Crec to the compliance of the baby lung is the recruitment to-inflation ratio (R/I ratio)

- The R/I ratio, reflects the proportion of volume distributed into the recruited lung to that into the baby lung with ΔPEEP
- No reference range for RI, but RI > 0.5 suggests recruitability



$$\text{Crec} = \frac{\Delta \text{Vrec}}{\text{PEEP}_{\text{high}} - \text{AOP}}$$

$$\frac{\text{R}}{\text{I}} \text{ ratio} = \frac{\text{Crec}}{\text{Crs at PEEP}_{\text{low}} \text{ or above AOP}}.$$

https://crec.coemv.ca/

Chen L, Del Sorbo L, Grieco DL, et. Al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome. A clinical trial. ***American Journal of Respiratory and Critical Care Medicine. 2020 Jan 15;201(2):178-87.***

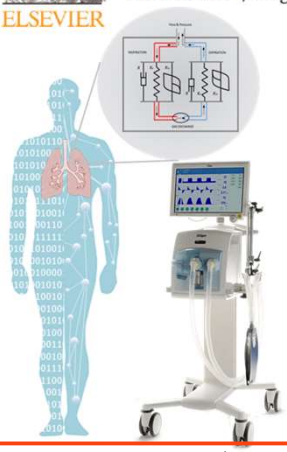
20

How to fix this: digital twins

Virtual patients for mechanical ventilation in the intensive care unit

Cong Zhou[a,b], J. Geoffrey Chase[b,*], Jennifer Knopp[b], Qianhui Sun[b], Merryn Tawhai[c], Knut Möller[d], Serge J Heines[e], Dennis C. Bergmans[e], Geoffrey M. Shaw[f], Thomas Desaive[g]

ELSEVIER



"A DT [digital twin] is defined as a digital copy of a physical system capable of accurately simulating, replicating, and predicting the behaviour of the physical system in various scenarios" [1]

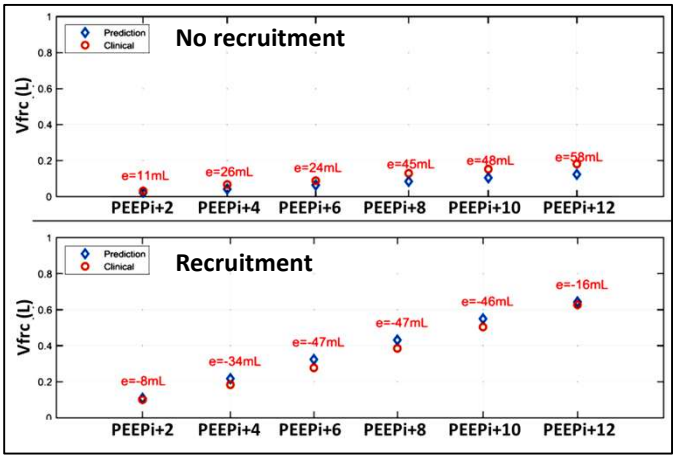
Virtual patients (digital twins) are created using methods from civil engineering mechanics and earthquake engineering. [2]

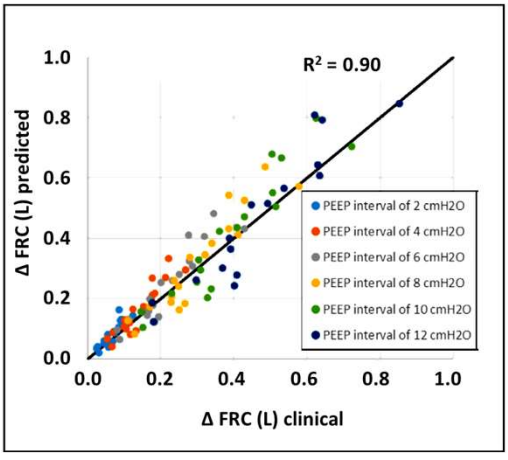
1 Ang CY, Lee JW, Chiew YS, Wang X, Tan CP, Cove ME, Nor MB, Zhou C, Desaive T, Chase JG. Virtual patient framework for the testing of mechanical ventilation airway pressure and flow settings protocol. ***Computer Methods and Programs in Biomedicine. 2022 Nov 1;226:107146***.

2 Zhou C, Chase JG, Knopp J, Sun Q, Tawhai M, Möller K, Heines SJ, Bergmans DC, Shaw GM, Desaive T. Virtual patients for mechanical ventilation in the intensive care unit. ***Computer Methods and Programs in Biomedicine. 2021 Feb 1;199:105912.***

21

How to fix this: digital twins





McREM cohort prediction under VC MV for all patients and PEEP prediction intervals (106 predictions).

Predictions can be made from a single breath!

Zhou C, Chase JG, Knopp J, Sun Q, Tawhai M, Möller K, Heines SJ, Bergmans DC, Shaw GM, Desaive T. Virtual patients for mechanical ventilation in the intensive care unit. ***Computer Methods and Programs in Biomedicine. 2021 Feb 1;199:105912.***

22

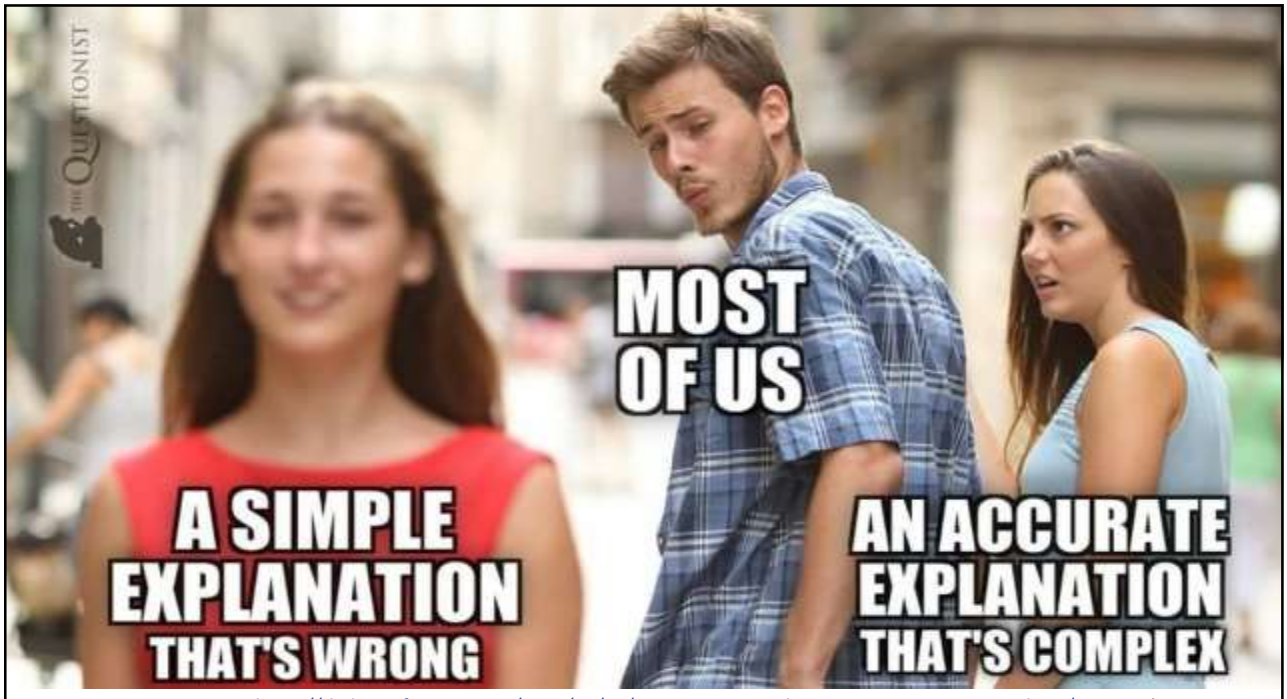
So…what went wrong?

TOO MUCH of doing things we think are going to help, because we can't get away from wanting better control of O_2, CO_2, and ventilation

- **TOO MUCH ventilation**
  High RR
- **TOO MUCH PEEP**
  Incorrectly estimated using a stair case recruitment manoeuvre; unreliable protocol with high bias and noise
- **TOO MUCH dead space (as a consequence of excessive PEEP)**
- **TOO MUCH asynchrony**
  Volume controlled ventilation, with high likelihood of causing asynchronous breathing and uncontrolled excessive lung strain
- **TOO MUCH Mechanical Power**
- **TOO heterogenous**
  Patients not responsive to recruitment should not have been randomised (no benefit)

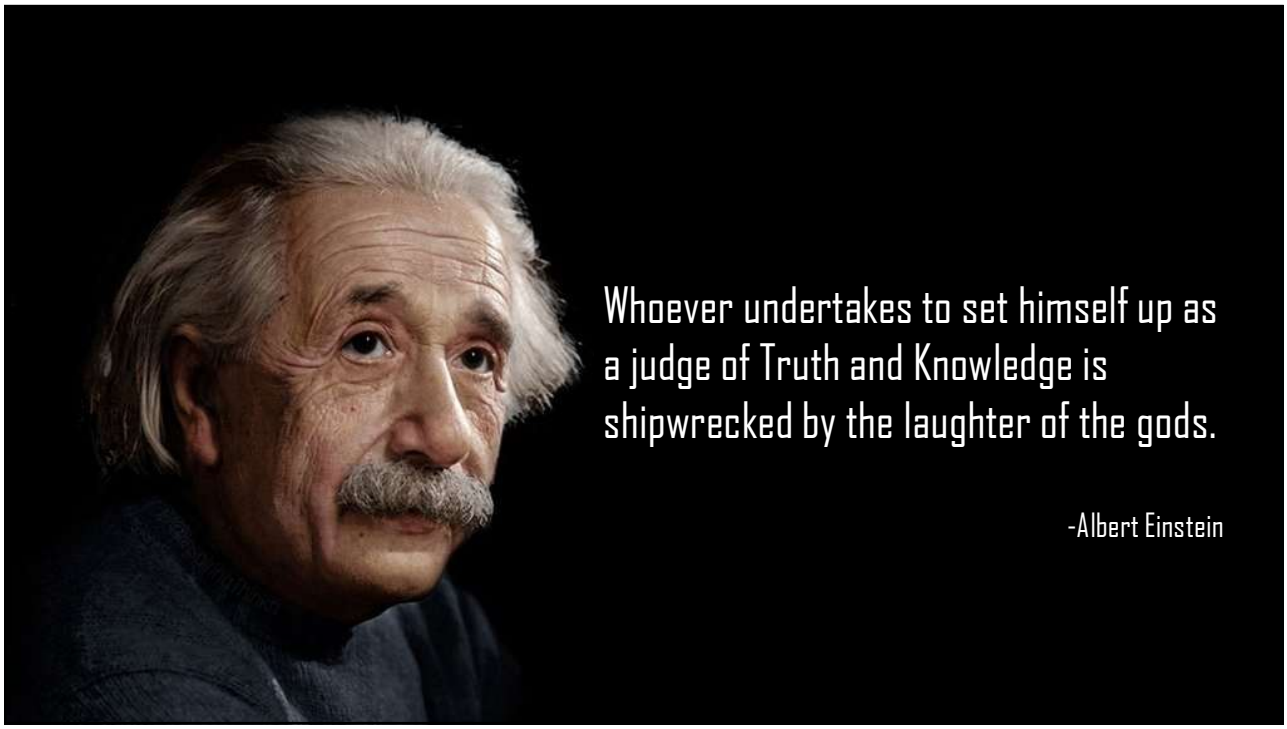
Finally, none of this has anything to do with recruitment per-se, but it has EVERYTHING to do with who you recruit, and how you ventilate them afterwards

23



https://thelogicofscience.com/2018/06/26/occams-razor-is-about-assumptions-not-simplicity/ accessed 12 Sept 2023

24


Whoever undertakes to set himself up as a judge of Truth and Knowledge is shipwrecked by the laughter of the gods.
-Albert Einstein

25