RESPIRATORY CARE

Research Article | *Original Research*

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https://doi.org/10.4187/respcare.12269

Cite as: RESPCARE 2024; 10.4187/respcare.12269

Received: 11 June 2024
Accepted: 1 September 2024

Pressure Control Surrogate Formula for Estimating Mechanical Power in ARDS is Associated with Mortality

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Word Count:

Abstract: 283

Text: 2,753

COI: Mr. Kallet has received honoraria from ContinuED

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Key Words: *acute respiratory distress syndrome, Berlin Definition, driving pressure, mechanical power, plateau pressure, pressure control ventilation, ventilator-induced lung injury, volume control ventilation.*

Elements of this paper were published in abstract form in Respiratory Care October 2023, 68 (Suppl 10):3934725 (14,25,49,76 and 95).

Contributions:

R H. Kallet: Data collection and analysis, manuscript development and revisions.

M.S. Lipnick: manuscript development and revisions.

Abstract

BACKGROUND: Mechanical power applied to the respiratory system (MP_{RS}) is associated with ventilator-induced lung injury (VILI) and ARDS mortality. Absent automated ventilator MP_{RS} measurements, the alternative is clinically unwieldy equations. However, simplified surrogate formulas are now available and accurately reflect values produced by airway pressure-volume curves. This retrospective, observational study examined whether the surrogate pressure-control equation alone could accurately assess mortality risk in ARDS subjects managed almost exclusively with volume-control ventilation. **METHODS:** 948 subjects were studied in whom invasive mechanical ventilation and implementation of ARDSNet ventilator protocols commenced ≤ 24hr after ARDS onset, and who survived > 24hr. MP_{RS} was calculated as 0.098 x respiratory frequency x V_T x (PEEP + driving pressure [P_{DR}]). MP_{RS} was assessed as a risk factor for hospital mortality, and compared between non-survivors and survivors across Berlin Definition classifications. In addition, mortality was compared across 4 MP_{RS} thresholds associated with VILI or mortality (ie. 15, 20, 25 and 30 J/m). **RESULTS:** MP_{RS} was associated with increased mortality risk: Odds Ratio (95% CI) of 1.06 (1.04-1.07) per J/m, P<0.001). Median MP_{RS} differentiated non-survivors from survivors in Mild (24.7 vs. 18.5 J/m, respectively, P==0.034); Moderate (25.7 vs. 21.3 J/m, P<0.001); and Severe ARDS (28.7 vs. 23.5 J/m, P<0.001). Across 4 MP_{RS} thresholds mortality increased from 23-29% when MP_{RS} was ≤ threshold vs. 38-51% when MP_{RS} was > threshold (P<0.001). In the > cohort the Odds Ratio (95%CI) increased from 2.03 (1.34-3.12) to 2.51 (1.87-3.33). **CONCLUSION:** The pressure control surrogate formula is sufficiently accurate to assess mortality in ARDS, even when using volume control ventilation. In our subjects when MP_{RS} exceeds established cut-off values for VILI or mortality risk, we found mortality risk consistently increased by a factor of > 2.0.

Introduction

Mechanical power (MP) represents energy over time that, when applied to the respiratory system (lungs and chest wall: MP_{RS}), is linked to both ventilator-induced lung injury (VILI) and ARDS mortality.[1-4] In the absence of ventilators calculating MP_{RS} directly from airway pressure (P_{AW})-volume curves (ie. "geometric" measurements once provided by the Bicore™ pulmonary mechanics monitor), now mathematical formulas are needed. However, estimating MP_{RS} by formula is complex and unwieldy, as it includes the variables minute ventilation, peak P_{AW}, PEEP and inspiratory flow rate in order to approximate the gold standard (geometric area within P_{AW} - volume curve).

In an attempt to address this obstacle, Chiumello et.al.[5] devised simplified ("surrogate") formulas to calculate MP_{RS} during either volume control (VC) or pressure control (PC) continuous mechanical ventilation (CMV) modes. They found both surrogate equations were highly correlated with direct (geometric) measurements of MP_{RS}. Surrogate MP_{RS} values averaged 0.8J/m greater than direct, geometric measurements (8.64±2.62 vs. 7.84±2.62, respectively, P=0.01).[5]

In this retrospective, observational study we assessed whether reliance on the PC surrogate formula *alone* could accurately assess hospital mortality risk in ARDS subjects managed with lung-protective ventilation (LPV), and when VC-CMV was used almost exclusively. The basis for doing so was that we recorded plateau pressure (Pplat) and driving pressure (P_{DR}) as part of our quality assurance monitoring; not peak P_{AW} and inspiratory flow rate. The justification for applying the PC surrogate formula in subjects managed with VC-CMV is described below in the methods section (see Design Rationale).

Essentially this study asks whether the fraction of MP applied by the ventilator needed to overcome flow resistance properties of the ventilator-patient system is *essential* to assess

mortality-risk in ARDS from excessive MP_{RS}? We approached answering this question by assessing: 1) the association between PC surrogate MP_{RS} and mortality; 2) whether MP_{RS} increased correspondingly with increasing ARDS severity (ie. Berlin classifications) and its associated mortality risk; and 3) whether mortality differed at-or-below, versus above MP_{RS} thresholds previously association either with VILI or mortality as reported in other studies.[3, 4, 6, 7]

Methods

Design Rationale

The PC surrogate formula (ie. $MP_{RS} = 0.098 \times V_T \times RR \times (PEEP + P_{DR})$[5] was used to assess mortality risk, without distinguishing CMV modes (ie. P_{DR} = Pplat-PEEP vs. Peak P_{AW}-PEEP, and excluding the corresponding inspiratory flow rate). The rationale for applying this simplified equation to both VC and PC- CMV is as follows:

1) Pplat not peak P_{AW} reflects the stress applied to the lungs and chest wall at end-inspiration. In contrast, peak P_{AW} and inspiratory flow rate largely reflect endotracheal tube resistance. Even when tube deformation and lumen occlusion (which occurs clinically) are absent, its frictional resistance approximates that of lung resistance in early ARDS (~10 cmH_2O).[8, 9] Moreover, in terms of VILI risk, the relevance of accounting for frictional resistive forces is controversial.[2, 10]

2) In ARDS the primary source of VILI is the uneven distribution of lung strain and stress during inspiration. Uneven lung strain-stress is reflected in measure of *viscoelastic resistance*: a phenomenon that only can be captured during s a 2-5s end-inspiratory pause when gases redistribute and lung pressures equilibrate (see Supplementary Materials Part 1).[11-13]

3) Clinically, we used a 0.5s pause time per-ARDSNet ventilator protocols.[14] Therefore, Pplat measured at 0.5s likely reflects some portion of the mechanical unevenness believed to cause VILI.

4) MP_{RS} also reflects the energy needed to overcome the elastic, viscoelastic and resistive properties of the chest wall, as well as its inertial properties.[15] In the presence of morbid obesity or abdominal compartment syndrome chest wall elastance is markedly increased,[16] and inertial forces are no longer negligible.[17] In light of these factors, as well as the absence of esophageal manometry (to isolate the pulmonary component), all MP_{RS} techniques are crude approximations for estimating its impact on VILI and ARDS mortality. Likewise, similar limitations apply when trying to separate artificial airway frictional resistance from that of the pulmonary airways.

Subjects

The 1,995 subjects in our ARDS LPV quality assurance data base (2002-2017) have been described previously.[18, 19] In this study a subset (948 subjects) were selected based on the following criteria: 1) having met the Berlin definition of ARDS,[20] 2) both CMV and ARDSNet protocols[21, 22] were initiated within 24h of ARDS onset, and 3) subjects having survived > 24h after protocol initiation (Fig 1).

The justification for these criteria are: First, those mechanically ventilated prior to ARDS onset may have been exposed to VILI. Second, our focus was the impact of MP_{RS} on mortality in the exudative phase of ARDS. After ~48h lung injury begins to transition to a proliferative or fibrotic stage;[23] therefore possibly producing changes in lung mechanics and MP_{RS}. Thus, excluding subjects in whom ARDS onset preceded ARDSNet protocol initiation would introduce interpretive ambiguity by mixing subjects at different stages of ARDS evolution. Third, evaluating subjects who survived beyond the day of ARDS onset allowed time for potential optimization of LPV. Fourth, excluding those who died on the day of ARDS onset eliminated additional ambiguity because whatever MP moribund subjects were exposed to over a matter hours prior to death cannot reasonably be attributed to mortality risk.

Our sample consisted of 108 subjects with mild (11%), 440 with moderate (46%) and 400 with severe ARDS (42%). During the study period subjects were managed almost exclusively with VC-CMV, as stipulated by the ARDSNet protocols.[21, 22] Approval to use our quality assurance data was granted by the University of California, San Francisco Institutional Review Board (Approval Reference number: 268589).

Measurements and Calculations

Lung and chest wall subcomponents of MP_{RS} (MP_L and MP_{CW} respectively) were estimated using respiratory system elastance (E_{RS}) data, and its lung (E_L) and chest wall (E_{CW}) subcomponents in ARDS subjects from our previous study:[24] E_L/E_{RS} (0.74), E_{CW}/E_{RS} (0.26). These values were consistent with other studies (Supplementary Materials, Part 2). Other calculations included comparing MP_{RS} to normal resting power (MP_{RS} Ratio)[25] using a value of 4 J/m,[26] MP_{RS} Index adjusted power to predicted body weight (PBW)[27] and Δ MP_{RS} as the change in power ~24h after protocol initiation (ie. a signifier for LPV optimization).

Assessments

MP_{RS} and its subcomponents were assessed from several perspectives: 1) the overall mortality risk for sample population, 2) mortality differences between non-survivors and survivors across Berlin Definition classifications, and 3) changes in MP_{RS} from initiation of LPV to the first full day of ARDSNet protocol management between non-survivors and survivors, 4) mortality risk between subjects falling at-or-below versus above MP_{RS} thresholds of 15, 20, 25, 30 J/m. These corresponded with estimated MP_L thresholds of 11, 14, 18 and 22 J/m respectively.

We tested threshold values that approximated those of preclinical studies of VILI induced in normal lungs, and a clinical study of ARDS. One preclinical study found an MP_{RS} threshold of

25 J/m (MP_L of 13 J/m) was associated with greater lung damage.[28] In their subsequent study MP_{RS} thresholds of 15 and 30 J/m produced morphologic and histologic injury,[6] In another preclinical study, an MP_L 15 J/m (MP_{RS} of 18 J/m) produced whole lung edema.[7] The clinical study found that an MP_{RS} threshold of 19 J/m was associated with increased mortality risk.[4]

Statistical Analysis

Data are expressed as median and (25-75%) inter-quartile range, as all variables failed a normality test (D'Agostoni and Pearson method). Direct comparisons between non-survivors and survivors were analyzed by Mann-Whitney test. Cross-group comparisons were done by Kruskal-Wallis and Dunn's post-test. The Fisher Exact test was used to assess mortality risk above and below the aforementioned thresholds. Univariate logistic regression was used to assess the mortality risk of each MP-associated variable (eg. MP_{RS}, MP_L, MP_{CW}) Alpha was set at 0.05.

Results

Achieving LPV Goals

Regarding traditional pulmonary mechanics measured ~24h after ARDSNet protocol initiation, the most salient findings (for both non-survivors and survivors) were 75% of Pplat and V_T values met protocol goals (Supplementary Table 1). Respiratory system compliance was significantly lower and P_{DR} was significantly higher among non-survivors.

Mortality and MP

Hospital mortality was 35.6% and all MP variables were significant predictors of mortality risk (Table 1). For every 1 J/m increase in MP_{RS}, mortality risk increased by 6%. The MP_{RS} Ratio of 5.8 (4.4-7.8). was ~ 6-fold greater than normal (ie. ~4 J/m). MP_{CW} was associated with a higher mortality risk than MP_L. MP_{RS} Index appeared to carry a more pronounced mortality risk.

Mechanical Power Characteristics Across Berlin Definition ARDS Classifications

All MP measures increased significantly with increasing ARDS intensity: moderate vs. mild (P=0.02), severe vs. moderate (P<0.001) and severe vs. mild (P<0.001) (Fig 2). The median increase in MP_{RS} was 113% between mild to moderate ARDS, 116% between moderate and severe ARDS and 131% between mild and severe ARDS. Likewise, MP_{RS} Index increased with ARDS intensity: 0.30, 0.36 and 0.42 J/m per Kg PBW for mild, moderate and severe ARDS respectively; with the same proportional increases and associated P values described above.

Mortality and Changes in MP from ARDS Onset to the Following Day

Particularly noteworthy was that from ARDSNet protocol initiation to the following day, MP_{RS} among all subjects decreased by -0.9 (-4.2 to 2.4) J/m from 24.7 (18.5-32.7) to 23.3 (17.6-31.3) J/m (P=0.020). However, non-survivors had an *increase* in MP_{RS} of 0.9 (-5.1 to 6.8) J/m whereas, in survivors MP_{RS} *decreased* by -1.5 (-5.9 to 2.5) J/m (P<0.001). The corresponding change in MP_L among non-survivors and survivors was 0.7 (-3.7 to 4.9) J/m vs. -1.1 (-4.3 to 1.8) J/m (P<0.001). In other words, by ~24h into ARDS a difference in MP_{RS} of 2.4 J/m (MP_L of 1.8 J/m) had already separated non-survivors from survivors.

Differences in MP and Mortality Between Berlin Classifications

When differences in MP_{RS} and its subcomponents were compared between non-survivors and survivors across Berlin classifications, median MP_{RS} among non-survivors always exceeded 24 J/m in contrast to survivors (< 24J/m) irrespective of ARDS severity (Table 2). Extrapolating these findings to corresponding estimates of MP_L, the median values amongst non-survivors always exceeded 17 J/m regardless of ARDS severity. Likewise, MP_{RS} ratio was > 6 times normal values in non-survivors and < 6 in survivors. Mortality rates observed with increasing ARDS severity were consistent with previous findings.[20]

MP Thresholds and Mortality Risk

Across the four MP_{RS} and corresponding MP_L thresholds, mortality steadily increased for both *at-or-below* and *above* cohorts at each threshold level. However, mortality in the *above* cohort was consistently and substantially greater: its associated risk factor always exceeded 2.0 **(**Table 3). The absolute cumulative mortality increased by 6% (23-29%) in the *at-or-below* cohort compared to 14% (38-51%) in the *above* cohort. This translated into total mortality rate increases of 126% versus 134% respectively. The highest separation in mortality between cohorts (Δ 22%) occurred at the MP_{RS} (MP_L) threshold of 30 (22) J/m, with a mortality of 51% **(**Fig 3).

Discussion

Our main finding was the PC surrogate MP_{RS} equation[5] was strongly associated with mortality across all ARDS severity classifications. This despite subjects managed almost exclusively with VC-CMV. Eighty five percent of our subjects had MP_{RS} levels > 15 J/m (associated with VILI in animals with normal lungs),[6] and 65% had MP_{RS} levels above 20 J/m that exceeded a mortality threshold found in subjects with various etiologies of acute respiratory failure (Table 3).[4]

Interestingly, 34% of subjects who met ARDSNet study mortality risk-exclusion criteria with corresponding $MP_{RS} \leq 25$ J/m had similar mortality to three ARDSNet trials that occurred during our data collection period (24-27% vs. 25-28% respectively).[22, 29, 30] Yet, a particularly worrisome finding was mortality exceeding 50% in those whose MP_{RS} exceeded 30 J/m (MP_L > 22 J/m): a mortality rate associated with late 20th Century ventilator management prior to the adoption of LPV.[31, 32]

Elevated levels of MP_{RS} associated with VILI also were observed in our subjects. This has practical implications for achieving *safer* threshold levels (ie. MP_{RS} < 15 J/m, MP_L of < 12 J/m,)

proposed by others.[33] Our results suggests the likelihood of achieving these stringent threshold (without liberalizing sedation usage or dosing) is improbable. Moreover, in severe ARDS such thresholds might require extracorporeal membrane oxygenation in cases that otherwise wouldn't meet salvage criteria. The vast majority of *survivors* across ARDS severity classes were managed with MP_{RS} > 15 J/m: 74% (mild), 81% (moderate) and 87% (severe). Overall, 59% of our survivors required MP_{RS} > 20 J/m (MP_L > 14 J/m).

Our results support our hypothesis accounting for resistive work is unnecessary for clinical purposes. It also supports our reasoning that the major sources of VILI are elastic and viscoelastic properties of a heterogeneously injured lung: a substantial portion of which might be captured with a brief pause time (0.5s) that we adopted by adhering to the ARDSNet protocols.[34]

In reviewing the literature a nettlesome problem became apparent: how should MP_{RS} be targeted since studies have used different equations with varying complexity? Among surrogate formulas relevant to our study, some excluded PEEP (ie. static MP), but included 50% of peak airway pressure multiplied by P_{DR}.[2] Others included PEEP and used 50% of P_{DR}. Although not explained, a 50% correction factor is an attempt to estimate the absorption of pressure (*energy*) across the lung parenchyma.[2, 3]

Of particular interest to us were studies done by Xie et.al.[10] and Costa et.al.[35] who used a 50% correction factor as a means of estimating "elastic power" (EP) (Supplementary Materials Part 3): Xie and colleagues[36] found EP was highly accurate in identifying severe ARDS (threshold of 14.6 J/m). Costa and colleagues[2] parsed EP into its static and dynamic subcomponents (as well as a resistive subcomponent) to estimate total MP. Their relevance to our study, was that only the dynamic EP (and not the resistive subcomponent) was associated with mortality risk: OR (95%CI) of 1.31(1.19-1.45).[35]

These two studies are directly related to our estimates of MP_L (0.74 correction factor) compared with their estimates of EP (0.5 correction factor).[10, 35] In our post hoc analysis we found that our MP_L and EP using their equations produced the same results (Supplementary Materials, Part 3). However, because the equations differ the conversion factors are not interchangeable. Ours requires a conversion factor more reflective of the E_L/E_{RS} relationship reported in ARDS.

We also compared our mortality to that found by Wu et.al.[37] who used the same surrogate formula as we used. They also observed elevated levels of mean MP_{RS} at baseline ~28 J/m (V_T 8.4 mL/kg PBW) compared to our baseline measurements (when expressed as mean) of ~27 J/m (V_T 7.1 mL/kg PBW). A similar finding was that after 2 days of LPV, they reported average MP_{RS} had decreased in survivors and increased in non-survivors (mean total difference of Δ 5.1 J/m). In our subjects, the total difference between non-survivors and survivors after ~1day was Δ 2.5 J/m.

We feel compelled to comment upon two of our other findings. First, that MP_{CW} carried a greater mortality risk than MP_L was baffling (being a derived variable not directly relevant to VILI). The only cogent explanation we can offer is that MP_{CW} was a latent signifier for subjects with intra-abdominal hypertension, and therefore associated with heightened mortality risk.[38] Unfortunately our database lacked supporting information. Second, the higher mortality risk associated with MP_{RS} index is concerning. We speculate that E_{CW} was lower in smaller stature, leaner subjects so that a higher fraction of MP_{RS} was applied to the lungs, thereby increasing VILI risk.

The limitations of our study were its retrospective nature and the limitations of our quality assurance data. Most vexing was the potential contribution of subject effort to MP_{RS} during assisted CMV. Our sedation practice (particularly during the first days after ARDS onset, was to promote synchrony while maintaining V_T and Pplat targets. Passive ventilation was

pharmacologically induced when asynchrony interfered with LPV goals and gas exchange stabilization. This practice was followed with particular fidelity during the initial days after implementing ARDSNet protocols.

In summary, for bedside management in the absence of automated ventilator measurements of MP_{RS}, the PC-CMV surrogate formula is a reasonable method to estimate MP_{RS} even when using VC-CMV. Despite the ambiguities and limitations described above, surrogate estimates of MP_{RS} are strongly associated with mortality risk across threshold values and degrees of ARDS severity. Our data suggests that exceeding an MP_{RS} threshold of 30 J/m (MP_L of 22 J/m) greatly increases mortality risk when it occurs early in the exudative phase of ARDS. Prospective trials are needed to examine varying MP_{RS} safety thresholds across both different severity classifications and pathological stages ARDS. Of equal importance, it would behoove such studies to assess the impact of MP_{RS} thresholds on competing needs such as its impact on sedation requirements and the related issues of duration of mechanical ventilation and ventilator-associated events.

References

1. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med 2016;42(10):1567-1575.
2. Costa ELV, Slutsky AS, Brochard LJ, Brower R, Serpa-Neto A, Cavalcanti AB, et al. Ventilatory Variables and Mechanical Power in Patients with Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2021;204(3):303-311.
3. Azizi BA, Munoz-Acuna R, Suleiman A, Ahrens E, Redaelli S, Tartler TM, et al. Mechanical power and 30-day mortality in mechanically ventilated, critically ill patients with and without Coronavirus Disease-2019: a hospital registry study. J Intensive Care 2023;11(1):14.
4. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, et al. Mechanical power of ventilation is associated with mortality in critically ill patients: an analysis of patients in two observational cohorts. Intensive Care Med 2018;44(11):1914-1922.
5. Chiumello D, Gotti M, Guanziroli M, Formenti P, Umbrello M, Pasticci I, et al. Bedside calculation of mechanical power during volume- and pressure-controlled mechanical ventilation. Crit Care 2020;24(1):417.
6. Vassalli F, Pasticci I, Romitti F, Duscio E, Assmann DJ, Grunhagen H, et al. Does Iso-mechanical Power Lead to Iso-lung Damage?: An Experimental Study in a Porcine Model. Anesthesiology 2020;132(5):1126-1137.
7. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, et al. Mechanical Power and Development of Ventilator-induced Lung Injury. Anesthesiology 2016;124(5):1100-1108.
8. El-Khatib MF, Husari A, Jamaleddine GW, Ayoub CM, Bou-Khalil P. Changes in resistances of endotracheal tubes with reductions in the cross-sectional area. Eur J Anaesthesiol 2008;25(4):275-279.
9. Broseghini C, Brandolese R, Poggi R, Polese G, Manzin E, Milic-Emili J, Rossi A. Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction. Am Rev Respir Dis 1988;138(2):355-361.
10. Xie Y, Yan Y, Shi J, Luo J, Wang Y, Chen H, Li X. Elastic power, a novel predictor of the severity and prognosis of ARDS. J Crit Care 2023;78:154380.
11. Eissa NT, Ranieri VM, Corbeil C, Chasse M, Robatto FM, Braidy J, Milic-Emili J. Analysis of behavior of the respiratory system in ARDS patients: effects of flow, volume, and time. J Appl Physiol (1985) 1991;70(6):2719-2729.
12. D'Angelo E, Calderini E, Robatto FM, Puccio P, Milic-Emili J. Lung and chest wall mechanics in patients with acquired immunodeficiency syndrome and severe Pneumocystis carinii pneumonia. Eur Respir J 1997;10(10):2343-2350.
13. Auler JO, Jr., Saldiva PH, Martins MA, Carvalho CR, Negri EM, Hoelz C, Zin WA. Flow and volume dependence of respiratory system mechanics during constant flow ventilation in normal subjects and in adult respiratory distress syndrome. Crit Care Med 1990;18(10):1080-1086.

14. Kallet RH, Corral W, Silverman HJ, Luce JM. Implementation of a low tidal volume ventilation protocol for patients with acute lung injury or acute respiratory distress syndrome. Respir Care 2001;46(10):1024-1037.
15. Polese G, Rossi A, Appendini L, Brandi G, Bates JH, Brandolese R. Partitioning of respiratory mechanics in mechanically ventilated patients. J Appl Physiol (1985) 1991;71(6):2425-2433.
16. Ranieri VM, Brienza N, Santostasi S, Puntillo F, Mascia L, Vitale N, et al. Impairment of lung and chest wall mechanics in patients with acute respiratory distress syndrome: role of abdominal distension. Am J Respir Crit Care Med 1997;156(4 Pt 1):1082-1091.
17. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. Total Respiratory Inertance and Its Gas and Tissue Components in Normal and Obese Men. J Clin Invest 1964;43(3):503-509.
18. Kallet RH, Zhuo H, Ho K, Lipnick MS, Gomez A, Matthay MA. Lung Injury Etiology and Other Factors Influencing the Relationship Between Dead-Space Fraction and Mortality in ARDS. Respir Care 2017;62(10):1241-1248.
19. Kallet RH, Lipnick MS, Zhuo H, Pangilinan LP, Gomez A. Characteristics of Nonpulmonary Organ Dysfunction at Onset of ARDS Based on the Berlin Definition. Respir Care 2019;64(5):493-501.
20. Force ADT, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307(23):2526-2533.
21. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301-1308.
22. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 2004;351(4):327-336.
23. Tomashefski JF, Jr. Pulmonary pathology of the adult respiratory distress syndrome. Clin Chest Med 1990;11(4):593-619.
24. Kallet RH, Hemphill JC, 3rd, Dicker RA, Alonso JA, Campbell AR, Mackersie RC, Katz JA. The spontaneous breathing pattern and work of breathing of patients with acute respiratory distress syndrome and acute lung injury. Respir Care 2007;52(8):989-995.
25. Gattinoni L, Collino F, Camporota L. Mechanical power: meaning, uses and limitations. Intensive Care Med 2023;49(4):465-467.
26. Roussos CCE. Respiratory muscle energetics. In: Mead J, editor. Handbook of Physiology Section 3, The Respiratory System, Mechanics of Breathing. Vol. III. Bethesda, MD.: American Medical Association, 1986.
27. Zhang Z, Zheng B, Liu N, Ge H, Hong Y. Mechanical power normalized to predicted body weight as a predictor of mortality in patients with acute respiratory distress syndrome. Intensive Care Med 2019;45(6):856-864.
28. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, et al. Positive End-expiratory Pressure and Mechanical Power. Anesthesiology 2019;130(1):119-130.
29. National Heart L, Blood Institute ACTN, Truwit JD, Bernard GR, Steingrub J, Matthay MA, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. N Engl J Med 2014;370(23):2191-2200.

30. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354(24):2564-2575.
31. Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? Eur Respir J 1997;10(6):1297-1300.
32. Bone RC, Fisher CJ, Jr., Clemmer TP, Slotman GJ, Metz CA. Early methylprednisolone treatment for septic syndrome and the adult respiratory distress syndrome. Chest 1987;92(6):1032-1036.
33. Silva PL, Pelosi P, Rocco PRM. Understanding the Mysteries of Mechanical Power. Anesthesiology 2020;132(5):949-950.
34. Kallet RH, Jasmer RM, Pittet JF, Tang JF, Campbell AR, Dicker R, et al. Clinical implementation of the ARDS network protocol is associated with reduced hospital mortality compared with historical controls. Crit Care Med 2005;33(5):925-929.
35. Roussos C, Fixley M, Gross D, Macklem PT. Fatigue of inspiratory muscles and their synergic behavior. J Appl Physiol Respir Environ Exerc Physiol 1979;46(5):897-904.
36. Smoller JW, Pollack MH, Otto MW, Rosenbaum JF, Kradin RL. Panic anxiety, dyspnea, and respiratory disease. Theoretical and clinical considerations. Am J Respir Crit Care Med 1996;154(1):6-17.
37. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015;372(8):747-755.
38. Malbrain ML, Chiumello D, Pelosi P, Bihari D, Innes R, Ranieri VM, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. Crit Care Med 2005;33(2):315-322.
39. Kallet RH, Campbell AR, Dicker RA, Katz JA, Mackersie RC. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. Respir Care 2005;50(12):1623-1631.

Figure Legends.

Fig 1. Subject selection flow chart

Fig 2. Respiratory system mechanical power (MP_{RS}) and its lung (MP_L) and chest wall (MP_{CW}) subcomponents across Berlin Definition classifications. *P<0.001 compared to severe ARDS, †P=0.02 compared to moderate ARDS.

Fig 3. Mortality across 4 respiratory system mechanical power (MP_{RS}) thresholds. Percentages listed above the bars reflect the difference in mortality between the *above-threshold* cohort versus the *at-or-below threshold* cohort. *P<0.001 for mortality comparisons between cohorts measured at each threshold.

Supplementary Fig 1. Scalar waveform of airway pressure during an extended (~4-5s) end-inspiratory pause. See supplementary text for detailed description.

Supplementary Fig 2. The dispersion of lung elastance (E_L) to respiratory system elastance (E_{RS}) ratio findings reported in pulmonary mechanics studies of ARDS.*chapter by Agostoni describing the elastic properties of chest mechanics in normal subjects.

Supplementary Fig 3. Comparisons between 3 surrogate equations of mechanical power applied to the lungs (MPL) in the current study, versus those referred to as elastic power (EP) in the studies of Costa (C) and Xie (X) among non-survivors (NS) and survivors (S).

Supplementary Figure 4. Total mechanical power (MPtot) representing both ventilator and patient contributions. The box represents the 25-75% interquartile range. The line inside denotes the median value. The horizontal lines at the bottom and the top represents the corresponding minimum and maximum values. Data from the study by Kallet et al.

QUICK LOOK

Current Knowledge

Mechanical power applied to the respiratory system (MP_{RS}) is associated with ventilator-induced lung injury (VILI) and ARDS mortality. Because power is energy transferred to lungs (and is a composite of all variables known to cause and perpetuate lung injury), it is widely considered the most important variable to monitor in mechanically ventilated patients. Because ventilators currently don't calculate power from the airway pressure-volume loops they generate, cumbersome mathematical formulas are used to estimate power. However, simplified surrogate formulas accurately estimate power and can be used to assess mortality risk at the bedside.

What this paper contributes to our knowledge

The current study demonstrates that estimating MP_{RS} using only the pressure control surrogate equation (even in subjects managed with volume control ventilation) discriminates survivors from non-survivors across both ARDS severity classifications, as well as MP threshold levels associated with increased VILI and mortality risk. This indicates complex equations accounting for the resistive components of MP are not necessary to assess the mortality risk from MP in ARDS.

Table 1. Mortality risk for various aspects of mechanical power in ARDS.

	Odds Ratio (95% CI)*	AUC (95% CI)
MP_{RS} (J/m)	1.06 (1.04-1.07)	0.650 (0.613-0.686)
MP_{L} (J/m)	1.08 (1.06-1.10)	0.650 (0.613-0.687)
MP_{CW} (J/m)	1.22 (1.17-1.29)	0.649 (0.613-0.686)
MP_{RS} Ratio	1.25 (1.18-1.32)	0.649 (0.612-0.686)
MP_{RS} Index (J/m per Kg)	44.1 (18.9-106.9)	0.666 (0.630-0.703)
Δ MP_{RS} (J/m)	1.02 (1.01-1.04)	0.584 (0.544-0.623)

Key: AUC = area under (receiver operating) curve, MP_{RS} = power applied to the respiratory system, MP_{L} = power applied to the lungs, MP_{CW} = power applied to the chest wall, MP_{RS} Ratio = applied power relative to power transfer under normal physiologic conditions at rest (ie. 4 J/m), MP_{RS} Index = power normalized to predicted body weight, Δ MP_{RS} = Change in applied power 1 day following initiation of lung-protective ventilation. *all tested variables $P<0.001$

Table 2. Power distribution across Berlin Definition categories between non-survivors and survivors.

	Non-Survivors	Survivors	Mortality
	Mild		
N	28	80	26%
MP_{RS} (J/m)	24.7 (14.1-33.2)	18.5 (14.6-25)*	
MP_{L} (J/m)	17.8 (10.1-23.9)	13.3 (10.5-18)†	
MP_{CW} (J/m)	6.9 (4.0-9.3)	5.2 (4.1-7.0)‡	
MP_{RS} Ratio	6.2 (3.5-8.3)	4.6 (3.7-6.3)‡	
MP_{RS} Index (J/m-Kg)	0.37 (0.29-0.50)	0.29 (0.23–0.38)†	
	Moderate		
N	142	298	32%
MP_{RS} (J/m)	25.7 (19.5-34.5)	21.3 (16.6-27.2)†	
MP_{L} (J/m)	18.5 (14.1-24.9)	15.4 (12-19.6)†	
MP_{CW} (J/m)	7.2 (5.5-9.7)	4.6 (3.7-6.3)†	
MP_{RS} Ratio	6.4 (4.9-8.6)	5.3 (4.2-6.8)†	
MP_{RS} Index (J/m-Kg)	0.43 (0.33-0.55)	0.34 (0.27-0.44)†	
	Severe		
N	168	232	42%
MP_{RS} (J/m)	28.7 (21.6-38.7)	23.5 (18.1-31.8)†	
MP_{L} (J/m)	20.6 (15.6-27.9)	16.9 (13-22.9)†	
MP_{CW} (J/m)	8.0 (6.1-10.8)	6.6 (5.0-8.9)†	
MP_{RS} Ratio	7.2 (5.4-9.7)	5.9 (4.5-8.9)†	
MP_{RS} Index (J/m-Kg)	0.49 (0.35-0.63)	0.38 (0.30-0.50)†	

Key: MP_{RS} = power applied to the respiratory system, MP_{L} = power applied to the lungs, MP_{CW} = power applied to the chest wall, MP_{RS} Ratio = applied power relative to that at rest under normal physiologic conditions (ie. 4J/m), MP_{RS} Index = power normalized to predicted body weight, *P = 0.034, †P <0.001, ‡P = 0.033.

Table 3. Mortality rates and risk for ARDS subjects above and below mechanical power thresholds.

MP_{RS} (MP_L) Thresholds (J/m)	Mortality at/below	Odds Ratio (95% CI)	Mortality* above	Odds Ratio (95%CI)	% Sample > Threshold
15 (11)	23%	0.49 (0.32-0.75)	38%	2.03 (1.34-3.12)	85%
20 (14)	24%	0.43 (0.32-0.58)	42%	2.33 (1.72-3.16)	65%
25 (18)	27%	0.43 (0.33-0.56)	47%	2.34 (1.77-3.07)	43%
30 (22)	29%	0.40 (0.3-0.54)	51%	2.51 (1.87-3.33)	29%

Key: MP_{RS} = mechanical power applied to the respiratory system, MP_L = mechanical power applied to the lung.*P<0.001 for all mortality differences between each power threshold.

Supplementary Table 1. Common mechanics measurements by outcome on the day after ARDS onset.

Variable	Non-Survivors	Survivors
N	338	610
Pplat (cmH_2O)	26 (22-30)	23 (20-27)*
PEEP (cmH_2O)	10 (8-14)	10 (8-11) *
Mean Paw (cmH_2O)	18 (15-21)	15 (10-16) *
P_{DR} (cmH_2O)	15 (12-18)	13 (10-16) *
V_T (mL/Kg PBW)	6.2 (5.9-6.7)	6.1 (5.9-6.5)†
Minute Ventilation (L/m)	10.7 (8.8-13.1)	9.7 (8.1-11.7) *
F (breaths/m)	29 (23-34)	25 (21-30) *
C_{RS} (mL/cmH_2O)	28 (21-35)	31 (24-39) *
E_{RS} (cmH_2O/L)	36 (29-49)	33 (26-41)*

Key: E_{RS} = respiratory system elastance, Pplat = plateau pressure, Paw = airway pressure, P_{DR} = driving pressure, V_T = tidal volume, $\dot{V}_E$ = minute ventilation, F = frequency (total), C_{RS} = respiratory system compliance, *P < 0.001, †P=0.69

Supplementary Table 2. Literature review of clinical studies measuring chest elastance in ARDS.

Study Subjects	E_{RS}	E_L	E_{CW}	E_L/E_{RS}	E_{CW}/E_{RS}
ARDS Surgical[16]	33.7	24.7	8.9	0.73	0.36
ARDS Medical[16]	30.2	26.1	5.4	0.86	0.18
ARDS[10]	20.6	14.6	6.7	0.71	0.33
Mixed ARDS-AHRF[11]	24.7	14.2	10.6	0.57	0.43
LIS < 2.5 PEEP+10[1]	24.6	15.4	8.8	0.63	0.36
LIS < 2.5 PEEP+15[1]	27.6	17.6	9.9	0.64	0.36
LIS > 2.5 PEEP+10[1]	37.8	26.5	11.4	0.70	0.30
LIS > 2.5 PEEP+15[1]	42.1	31	11.1	0.74	0.26
ARDS PEEP+10[12]	24.4	17.6	6.8	0.72	0.28
ARDS PEEP+15[12]	27	20	7	0.74	0.26
ARDS PCP[13]	36.2	29.4	6.8	0.81	0.19
Mixed ARDS-AHRF[14]	25.5	18.3	7.2	0.72	0.28
AHRF (~ARDS)[15*]	28.9	19.6	9.4	0.67	0.33
ARDS[17]	35.7	25.6	8.9	0.74	0.26

Key: AHRF = acute hypoxemic respiratory failure, ERS = total elastance of the respiratory system (ie. lung and chest wall), EL = elastance of the lung, ECW = elastance of the chest wall, LIS = lung injury score, PCP = pneumocystis carinii pneumonia (as it was referred during that historic period), * subjects studied in ~1980 prior to codified criteria for defining ARDS. However, most study subjects appeared to have ARDS risk factors.

Supplementary Table 3. Different surrogate estimates of mechanical power associated with elastic forces in ARDS between survivors and non-survivors.

	Kallet & Lipnick	Xie et.al.*	Costa et.al.†	
Variable	MP_L (J/m)	EP (J/m)	EP (J/m)	P
Survivors	15.6 (12.1-20.5)	15.3 (12-20.4)	15.3 (12-20.4)	0.85
Non-Survivors	19.7 (15.1-27)	19.3 (14.6-26)	19.3 (14.6-26)	0.71

Key: MP_L = lung mechanical power, EP = elastic power. *Xie et.al. J Crit Care 2023, †Costa et.al. Am J Respir Crit Care Med 2021.

Fig.1

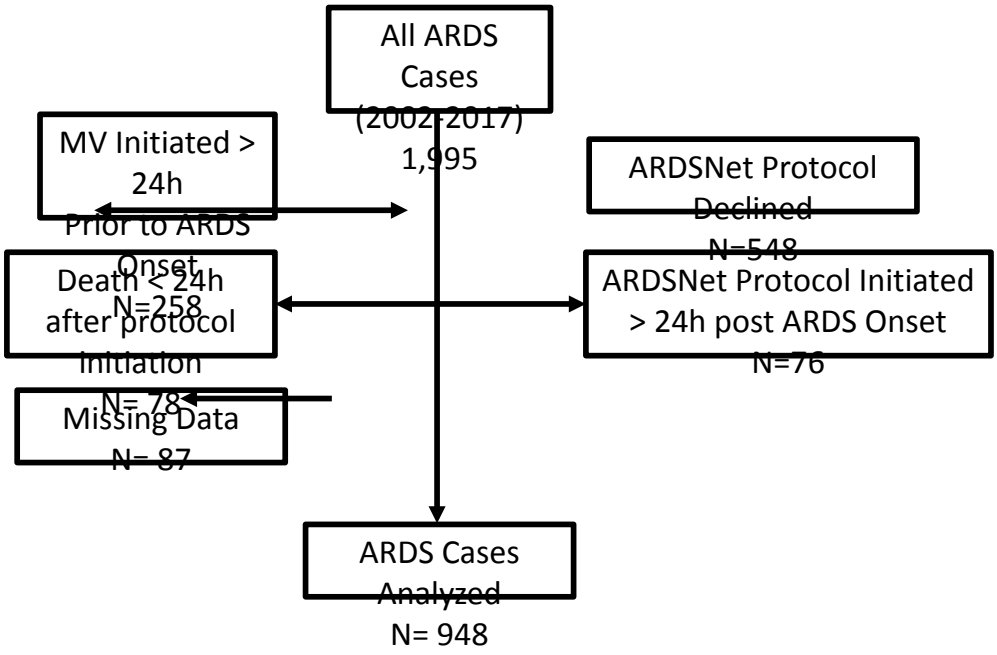


Fig 2

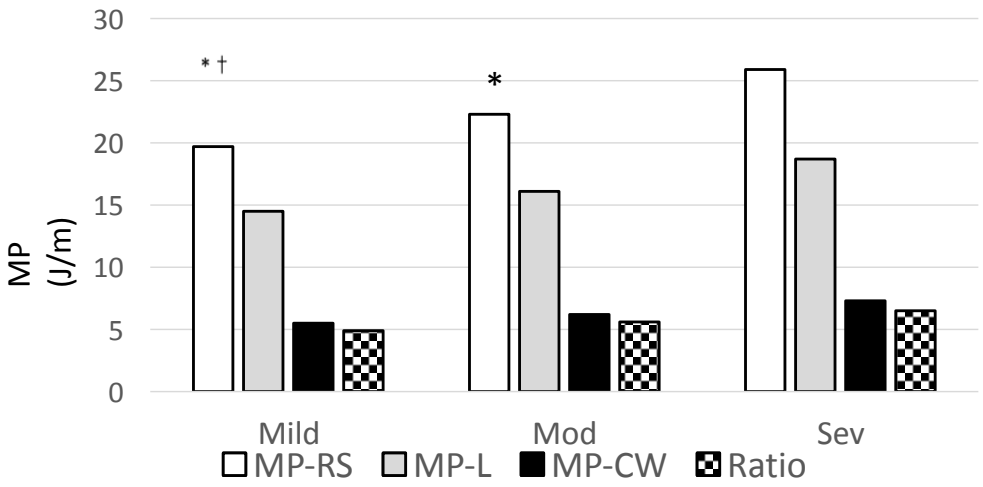
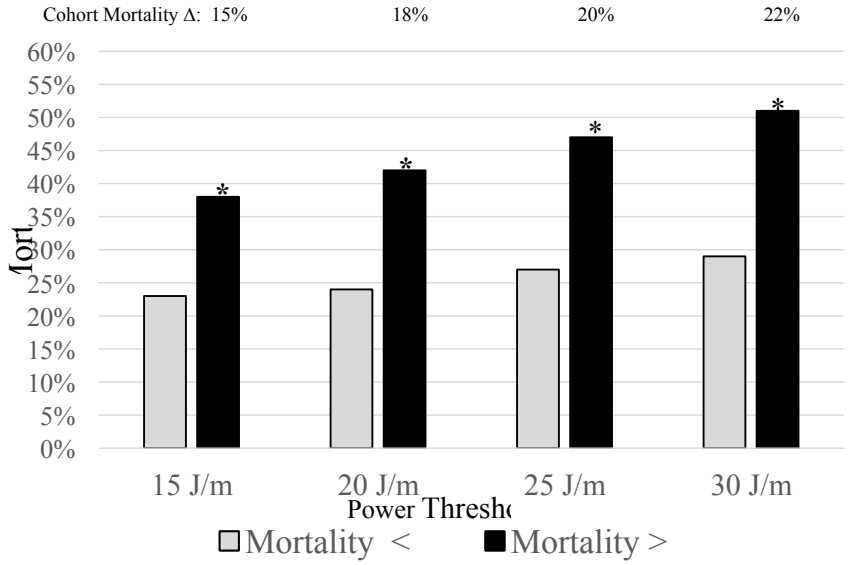
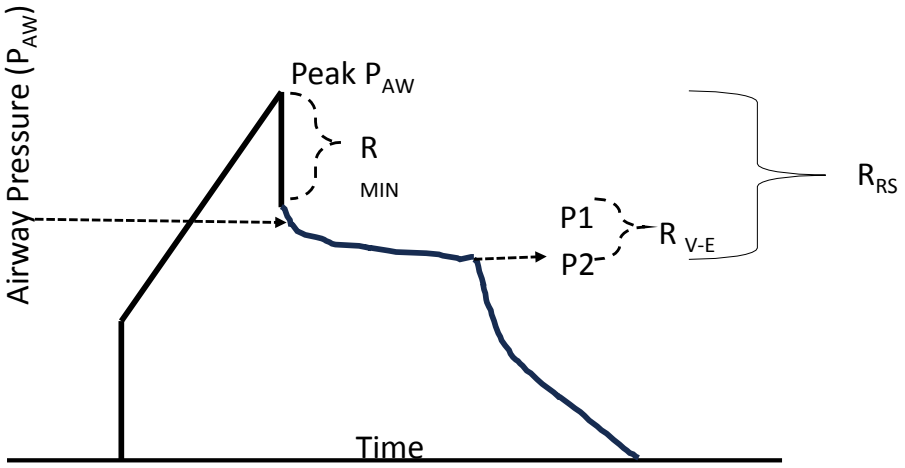


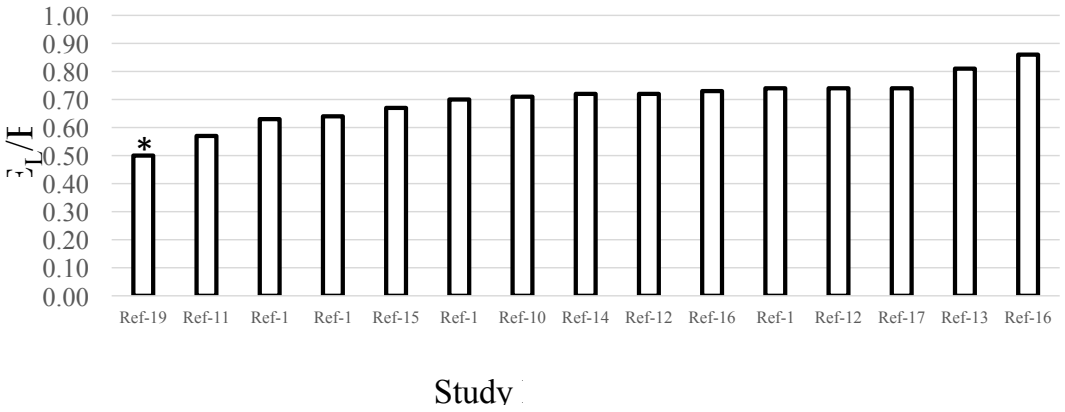
Fig 3



Supplementary Fig 1



Supplementary Fig 2



Supplementary Fig 3