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ORIGINAL

Respiratory mechanics modifies the impact of ventilator settings on clinical outcome in patients with acute brain injury

Domenico Luca Grieco[1,2*], Alessandro Stronati[1,2], Chiara Robba[3,4], Tommaso Rosà[1,2], Ida G. Iavarone[3,4], Emanuele Rezoagli[5], Filippo Bongiovanni[1,2], Antonio M. Dell'Anna[1,2], Alessandro Cardu[1,2], Francesca Graziano[5,6,7], Stefania Galimberti[5,6,7], Anselmo Caricato[1,2], Nicolò Patroniti[3,4], Fabio Silvio Taccone[8], Giuseppe Citerio[5,9] and Massimo Antonelli[1,2]

Abstract

Purpose: To investigate whether respiratory system elastance (E_{RS}) modifies the associations of tidal volume (V_T) and respiratory rate with clinical outcomes in mechanically ventilated patients with acute brain injury.

Methods: In this post hoc analysis of the VENTIBRAIN study, E_{RS} was computed as the ratio of driving pressure (ΔP) to V_T/PBW. Effect modification by E_{RS} on outcome associations was assessed.

Results: In 1158 patients, V_T was similar across E_{RS} tertiles (median 7.9, 7.6 and 7.1 mL/kg), resulting in a marked ΔP gradient across tertiles (median 5, 9, and 12 cmH_2O). Higher V_T was associated with lower ICU mortality in patients with low E_{RS} (OR 0.52, 95%CI 0.36–0.74) but not in those with high E_{RS} (OR 1.16, 95% CI 0.89–1.51; $P_{int} < 0.001$). Higher respiratory rate was associated with worse outcomes, particularly at low E_{RS}, with the association attenuating at higher E_{RS}. The Bayesian optimal V_T/PBW decreased continuously with E_{RS}, from 11.4 mL/kg at E_{RS} 0.5 cmH_2O/(mL/kg) ($\approx \Delta P$ 6 cmH_2O) to 4.4 mL/kg at E_{RS} 2.5 cmH_2O/(mL/kg) ($\approx \Delta P$ 11 cmH_2O), while the optimal respiratory rate increased from 15 to 19 breaths/min. At constant alveolar ventilation, 1-cmH_2O ΔP increase had comparable prognostic impact to ≈ 3 breaths/min respiratory rate increases. These results were consistent irrespective of ARDS diagnosis.

Conclusions: The impact of ventilator settings is modulated by E_{RS}. A physiological framework for V_T adjustment could consider ΔP along with the respiratory rate required to maintain isocapnia, with outcome effects governed by a trade-off of ≈ 3 breaths/min per 1-cmH_2O change in ΔP.

Keywords: Acute brain injury, Respiratory mechanics, Tidal volume, Protective ventilation, Driving pressure

*Correspondence: domenicoluca.grieco@unicatt.it
[1] Department of Anesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Rome, Italy
Full author information is available at the end of the article

Domenico Luca Grieco and Alessandro Stronati have equally contributed to this work.

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Background

Low tidal volume (V_T) ventilation, originally proposed to prevent ventilator-induced lung injury in the acute respiratory distress syndrome (ARDS) [1–3], has shown mixed effects in broader populations [4–8]. Patients with acute brain injury have been excluded from major trials due to the need for precise $PaCO_2$ control to manage cerebral perfusion and intracranial pressure [9–11].

A recent randomized trial in patients with acute brain injury without ARDS showed that reducing V_T to 6 mL/kg may be neutral, or even detrimental, in terms of clinical outcome [12]. This may indicate that the effects of V_T depend on the broader ventilatory context, including the need for compensatory increases in respiratory rate to maintain $PaCO_2$ within a safe range [13]. These results raise the question of whether patient-level respiratory mechanics, rather than a fixed-V_T target, should guide ventilatory management.

In a recent large observational study (VENTIBRAIN) [14, 15], patients ventilated with higher V_T had better outcomes. However, higher driving pressure (ΔP) was associated with increased mortality. These findings may appear paradoxical at first glance, since ΔP is mathematically linked to V_T [16, 17]. However, ΔP also depends on respiratory system elastance ($\Delta P = V_T \times E_{RS}$), meaning that the same V_T may generate substantially different ΔP according to heterogeneous E_{RS}. These findings may reflect heterogeneity in E_{RS} across the VENTIBRAIN study population, which would be consistent with data indicating that E_{RS} modulates the impact of V_T on clinical outcome in ARDS [18]. These interactions may also help explain the U-shaped association observed between respiratory rate and outcomes, as the trade-off between V_T and respiratory rate at constant alveolar ventilation may shift depending on E_{RS}.

In this secondary analysis of the VENTIBRAIN study, we assessed whether E_{RS} modifies the associations of V_T and respiratory rate with clinical outcomes in patients with acute brain injury, and whether the V_T associated with the lowest mortality differs across levels of E_{RS}.

Methods

Study design and population

This is a secondary analysis of the VENTIBRAIN study, a prospective multicenter observational cohort that enrolled 2095 mechanically ventilated adults with acute brain injury across 74 intensive care units (ICU) in 26 countries between November 2020 and October 2023. The study design, inclusion and exclusion criteria, data collection procedures, and ethical approvals have been described elsewhere [14]. Briefly, eligible patients were adults (> 18 years) with a primary non-anoxic acute brain injury (traumatic brain injury, intracerebral hemorrhage, subarachnoid hemorrhage, or acute ischemic stroke) requiring intubation and mechanical ventilation in the ICU.

Take-home message

In mechanically ventilated patients with acute brain injury, respiratory system elastance modifies the impact of ventilator settings: higher tidal volume is associated with lower mortality when elastance is low, but not when elastance is high. Tidal volume associated with the best outcome falls continuously as respiratory system elastance rises, from ~11 to ~4 mL/kg PBW, irrespective of ARDS diagnosis. Ventilator settings could be individualized on respiratory mechanics rather than set at a fixed target, balancing driving pressure reduction against the respiratory rate required to maintain isocapnia — a trade-off of approximately 3 breaths/min per 1 cmH_2O of driving pressure.

From the parent cohort, patients were eligible for analysis if they had at least one valid plateau pressure or driving pressure recording during the ICU stay (allowing computation of E_{RS}) and a documented height for predicted body weight (PBW) calculation. After excluding patients with neither criterion met, 1158 patients were included in the analysis (Supplementary Fig. 1).

Data collection procedures, respiratory measurements, and outcome definitions have been reported in detail in the original VENTIBRAIN publication [14]. The VENTIBRAIN steering committee approved the project, and a data transfer agreement was signed in accordance with the original protocol. Ethical approval was obtained from the ethics committee of ASST-Monza (Approval 3425, 10/09/2020) and each participating center. No further ethical approval was necessary for this secondary analysis. The study was conducted according to the Declaration of Helsinki. Informed consent was managed according to local regulations.

Definition of E_{RS}

PBW was calculated using the ARDSNet formula (male: $50 + 0.91 \times$ [height in cm $-$ 152.4]; female: $45.5 + 0.91 \times$ [height in cm $-$ 152.4]) [1]. The primary exposure was E_{RS} adjusted for predicted body weight, defined as ΔP divided by V_T/PBW (algebraically equivalent to $E_{RS} \times$ PBW) and expressed in cmH_2O/(mL/kg). This normalization accounts for the physiological dependence of E_{RS} on body size, thereby providing a measure of the elastic load of the respiratory system that is comparable across patients of different statures.

Patients were classified into tertiles based on the empirical distribution of mean E_{RS} values during the first 7 days in the intensive care unit (ICU) stay (T1: < 0.99; T2: [0.99–1.42]; T3: > 1.42 cmH_2O/[mL/kg]).

Outcomes and subgroups

Four outcomes were examined: ICU mortality (available in 1077 of 1158 patients), hospital mortality ($n = 1055$), 6-month mortality ($n = 1120$), and unfavorable Glasgow Outcome Scale Extended (GOSE < 5; $n = 1001$). As a pre-specified subanalysis, results were compared between patients with and without ARDS ($n = 600$ and $n = 558$, respectively); ARDS was defined by clinician-reported recognition of the Berlin definition criteria at any time during the ICU stay [19]. This subanalysis was performed for the E_{RS} threshold analysis, the temporal stability of E_{RS}, and the E_{RS}-dependent optimal V_T models.

The primary pre-specified endpoint was ICU mortality; secondary endpoints, subgroup, and alternative timeframe analyses were exploratory.

Statistical analysis

Continuous variables were summarized as median (interquartile range) and compared across E_{RS} tertiles using the Kruskal–Wallis test. Categorical variables were summarized as *n* (%) and compared using the Chi-square test. All proportions were computed from available-case denominators; no imputation was performed for outcome variables. Two exposure timeframes were defined for E_{RS} and ventilatory variables. The primary timeframe was the individual patient mean computed across the initial 7 days (e.g., the observation period of the study) with valid measurements. For the isocapnic curve analysis, the baseline timeframe (day 0–1 average) was used as primary for consistency with the methodology of Costa et al. [20]. All primary analyses were replicated using the alternative timeframe as a pre-specified sensitivity analysis.

Assessment of selection bias. To assess potential selection bias from missing data, we compared 22 baseline characteristics and four clinical outcomes between included and excluded patients using standardized mean differences (SMD), with a threshold of $|\text{SMD}| > 0.1$ to identify meaningful imbalances.

Temporal stability of E_{RS}. To characterize the temporal behavior of E_{RS} during the first seven days of ICU stay, individual daily values were plotted by baseline tertile and summarized as geometric means with 95% Confidence Intervals (CI) computed on the log scale and back-transformed. A linear mixed-effects model was fitted on log-transformed E_{RS}, with random intercepts at both the center and the patient level. Fixed effects comprised time (centered at Day 1), tertile, their interaction, age, sex, APACHE II score, brain injury type (subarachnoid hemorrhage, intraparenchymal hemorrhage and acute ischemic stroke as indicators, traumatic brain injury as reference), ARDS status, and time-varying ventilatory parameters (V_T/PBW, PEEP, respiratory rate, ΔP; all *z*-scored).

Tertile-stratified logistic regression. To characterize effect modification of the V_T–outcome association by E_{RS}, we fitted separate logistic regression models within each E_{RS} tertile for each of the four outcomes. This approach avoids the linearity assumption of a single multiplicative interaction term and allows direct visual comparison of exposure–outcome curves across strata of lung mechanics. For each combination of E_{RS} tertile and outcome, the model was adjusted for age, sex, and APACHE II score, where all continuous predictors were *z*-scored within each tertile. Three exposures were examined: V_T/PBW, respiratory rate, and ΔP, all computed as the mean across the first 7 days of ICU stay. Results were reported as odds ratio (OR) with corresponding 95% CI and predicted probabilities were computed over clinically plausible ranges with 95% confidence intervals derived by the delta method. Effect modification was assessed by three complementary statistics: a likelihood ratio test for the continuous $E_{RS} \times$ exposure interaction (p_{int}), a pairwise *z* test comparing T3 and T1 slopes (p_{T3vsT1}), and a weighted meta-regression for linear trend across tertiles.

V_T and respiratory rate at constant alveolar ventilation (isocapnic curves). To evaluate the joint contribution of V_T and respiratory rate to the four outcomes at constant alveolar ventilation, we applied the isocapnic curve framework described by Costa et al. [20]. A logistic regression model was fitted as follows: $\text{logit(outcome)} = \beta_0 + \beta_{DP} \times \Delta P + \beta_{RR} \times$ respiratory rate + tertile indicators + covariates (i.e., for age, APACHE II score, $PaCO_2$, arterial pH, and PaO_2/FiO_2 ratio). Dead space was assumed as 1.5 mL/kg PBW (airway) plus 20% of V_T (alveolar), following Costa et al. and data available from patients with acute brain injury [13, 20]. Isocapnic curves were constructed for each subgroup by tracing combinations of V_T and respiratory rate maintaining constant alveolar ventilation at the sample median, using tertile-specific median E_{RS} and PBW values. The optimal ventilation point was defined as the V_T/PBW and respiratory rate combination yielding the minimum predicted OR (i.e., better outcome) along each isocapnic curve. The baseline timeframe for E_{RS} assessment (day 0–1 average) was used as primary for consistency with the Costa et al. methodology [20]; the mean timeframe served as sensitivity analysis (Electronic Supplementary Material).

Mechanical power was derived along each isocapnic curve using the simplified equation: $0.098 \times$ respiratory rate $\times V_T \times (P\text{peak} - 0.5 \times \Delta P)$, with V_T in liters [21, 22]. Peak airway pressure was reconstructed as $P0 + \Delta P$, where the tertile-specific $P0$ (the median PEEP-plus-resistive floor, computed as measured peak pressure minus measured ΔP) was held constant, so that ΔP,

plateau, and peak pressure all rose with V_T and, at each tertile's median observed V_T, reproduced the observed peak pressure.

Elastance threshold for V_T effect reversal. To quantify the E_{RS} threshold at which the direction of the V_T/PBW–outcome association reverses, we fitted Bayesian logistic regression models on the four outcomes with a continuous V_T/PBW × E_{RS} interaction term, adjusted for age, sex, and APACHE II score (all z-scored). Bayesian estimation used the No-U-Turn sampler (PyMC; 4 chains, 2000 draws per chain, 1000 warmup, target acceptance 0.95) with non-informative priors. Convergence was confirmed by Gelman–Rubin statistic (R) < 1.01 (this metric indicates adequate mixing and convergence of the chains to the stationary posterior) and effective sample sizes exceeding 400. The posterior probability that V_T 6 mL/kg yields lower mortality than V_T 10 mL/kg was computed at each point along the E_{RS} continuum, generating an S-curve. The comparison was made between V_T 6 mL/kg and V_T 10 mL/kg, as these represent the conventional protective and liberal targets commonly used as reference in clinical practice and in previous trials [12, 23–26]. The threshold, defined as the E_{RS} value where this probability equals 50%, was estimated with 95% highest density intervals. A region of practical equivalence (ROPE) was assumed to be |log(OR)| < 0.163 (OR 0.85–1.18).

Elastance-dependent optimal V_T and respiratory rate. To determine the E_{RS}-specific ventilatory settings that minimize the predicted probability of adverse outcomes for ICU mortality, we fitted quadratic logistic regression models with an exposure-by-E_{RS} interaction term, adjusted for age, sex, and APACHE II score (all z-scored). The optimal V_T/PBW and respiratory rate at a given E_{RS} were derived analytically as the vertex of the within-model parabola, back-transformed to the original scale, and clipped to clinically plausible ranges. Bayesian (80% credible intervals) estimates were obtained. The implied optimal ΔP at each E_{RS} was obtained deterministically as the product of the optimal V_T and E_{RS}. Separate analyses were performed for ARDS and non-ARDS subgroups.

All analyses were performed in Python 3.12 (Python Software Foundation, Wilmington, DE, USA) using statsmodels 0.14 for logistic regression, PyMC 5.26 (PyMC Labs, Basel, Switzerland) with ArviZ 0.22 for Bayesian estimation, SciPy 1.16 for statistical tests, and Matplotlib 3.10 with seaborn 0.13 for figure generation. Two-sided p values below 0.05 were considered statistically significant in frequentist analyses. Full details of the statistical analysis are provided in the electronic supplementary material (ESM).

Results

From the VENTIBRAIN cohort, 733 patients were excluded for missing E_{RS} (i.e., absence of both plateau pressure and driving pressure recordings) and 204 for PBW calculation, yielding an analytic cohort of 1158 patients (Supplementary Fig. 1).

Among 22 baseline characteristics and four outcomes compared between 1158 included and 937 excluded patients, 12 variables exceeded the |SMD| > 0.1 threshold (Supplementary Fig. 2). Patients included in this analysis presented a slightly better prognosis compared to those excluded (e.g., ICU mortality 27% vs 35%).

Patients' demographics and clinical characteristics according to E_{RS} tertiles are shown in Table 1.

Geometric mean E_{RS} remained essentially constant within each tertile across the first seven ICU days, with no significant time × tertile interaction (Supplementary Fig. 3). ARDS and non-ARDS patients followed parallel trajectories within each tertile.

V_T/PBW tended to be lower and respiratory rate higher with increasing E_{RS} ($p < 0.001$ for both), but these adjustments were insufficient to offset the differences in respiratory E_{RS}, resulting in a marked ΔP gradient across tertiles (Fig. 1).

Tertile-stratified logistic regression

The association between mean V_T/PBW and ICU mortality was modified by E_{RS} ($p_{int} < 0.001$; Fig. 1): higher V_T was associated with lower mortality in patients with low E_{RS} (T1: odds ratio [OR] 0.52, [95% CI 0.36–0.74]), but this protective effect progressively disappeared in patients with medium E_{RS} (T2: OR 0.82 [95% CI 0.61–1.11]) and reversed toward harm in patients with high E_{RS} (T3: OR 1.16 [95% CI 0.89–1.51]). Results on hospital ($p_{int} < 0.001$) and 6-month mortality ($p_{int} = 0.002$) were consistent (Supplementary Fig. 4). Higher respiratory rate was associated with worse outcomes across all tertiles; although the interaction with E_{RS} was not statistically significant (all $p_{int} \geq 0.15$), the magnitude of the association was considerably greater at low E_{RS} and tended to diminish at higher E_{RS} (Fig. 1 and Supplementary Fig. 4).

V_T and respiratory rate at constant alveolar ventilation

For ICU mortality, ΔP was significantly associated with outcome (OR per standard deviation increase 1.32, 95% CI 1.00–1.75, $p = 0.047$), with the overall effect of ΔP governed by patients with high E_{RS} (Fig. 1). At constant alveolar ventilation, ΔP carried consistently greater prognostic weight than respiratory rate across all outcomes: each 1 cmH_2O increase in ΔP had a similar impact on outcome as an approximately 3 breaths/min increase in respiratory rate. The V_T and respiratory rate

Table 1 Baseline characteristics, respiratory parameters, and outcomes stratified by tertiles of E_{RS}

Variable	Low E_{RS} < 0.99 cmH_2O/(mL/kg)	Medium E_{RS} [0.99–1.42 cmH_2O/(mL/kg)]	High E_{RS} > 1.42 cmH_2O/(mL/kg)	*p* value
No. of patients	386	386	386	
Clinical characteristics				
Age, years	61 (51–71)	57 (42–69)	57 (43–67)	< 0.001
Male sex	214 (55%)	238 (62%)	296 (77%)	< 0.001
Predicted body weight, kg	62 (52–70)	65 (57–71)	68 (62–73)	< 0.001
High-income country	172 (44%)	255 (66%)	275 (71%)	< 0.001
APACHE II score	18 (13–22)	17 (13–22)	19 (14–24)	0.001
Pupil reactivity				0.149
Both reactive	273 (73%)	297 (79%)	272 (73%)	
One reactive	27 (7%)	28 (7%)	28 (8%)	
Both unreactive	75 (20%)	50 (13%)	70 (19%)	
LIPS score	2 (0–4)	2 (0–5)	2 (0–5)	0.016
GCS motor score				0.526
1–4 (poor)	251 (66%)	237 (62%)	244 (65%)	
5–6 (good)	129 (34%)	143 (38%)	129 (35%)	
Brain injury type				< 0.001
Traumatic brain injury	118 (31%)	156 (40%)	168 (44%)	
Subarachnoid hemorrhage	106 (27%)	79 (20%)	50 (13%)	
Intracerebral hemorrhage	114 (29%)	105 (27%)	108 (28%)	
Ischemic stroke	48 (12%)	46 (12%)	60 (16%)	
Highly pathological CT scan	182 (47%)	192 (50%)	171 (44%)	0.317
Neuroworsening	122 (32%)	117 (30%)	107 (28%)	0.181
Gas exchanges and respiratory parameters (Day 0)				
Tidal volume, mL	480 (430–534)	470 (430–510)	477 (440–500)	0.420
Tidal volume/PBW, mL/kg	7.9 (7.1–8.8)	7.6 (6.8–8.3)	7.1 (6.5–7.9)	< 0.001
Respiratory rate, breaths/min	15 (14–18)	15 (14–18)	16 (14–20)	< 0.001
PEEP, cmH_2O	6 (5–8)	5 (5–7)	5 (5–6)	< 0.001
FiO_2, %	40 (30–45)	40 (35–50)	40 (40–50)	< 0.001
PaO_2, mmHg	105 (88–139)	112 (92–149)	116 (90–157)	0.064
PaO_2/FiO_2, mmHg	300 (228–383)	290 (213–394)	278 (200–390)	0.362
$PaCO_2$, mmHg	37 (33–41)	37 (34–41)	38 (35–42)	0.032
Driving pressure, cmH_2O	5 (3–7)	9 (8–11)	12 (10–15)	< 0.001
Compliance, mL/cmH_2O	82 (64–121)	50 (42–62)	38 (33–45)	< 0.001
Mechanical power, J/min	10.7 (8.5–14.2)	12.4 (9.2–17.7)	15.1 (11.2–21.2)	< 0.001
Respiratory system elastance (E_{RS}), cmH_2O/(mL/kg)	0.65 (0.39–0.88)	1.24 (1.11–1.38)	1.69 (1.49–1.94)	< 0.001
Intracranial pressure and pulmonary complications				
Lowest ICP, mmHg	4 (2–6)	5 (1–10)	5 (2–10)	0.333
Highest ICP, mmHg	16 (11–19)	14 (8–19)	15 (12–20)	0.373
ICP > 20 mmHg (ever)	54 (14%)	77 (20%)	100 (26%)	< 0.001
Pneumonia	54 (14%)	66 (17%)	83 (21%)	0.022
Pneumothorax	13 (4%)	21 (6%)	30 (9%)	0.034
Pleural effusion	103 (31%)	112 (33%)	122 (36%)	0.409
Atelectasis	124 (37%)	144 (43%)	148 (43%)	0.177
Pulmonary edema	10 (3%)	14 (4%)	22 (6%)	0.094
Diagnosis of ARDS (any severity)	210 (54%)	194 (50%)	196 (51%)	0.454
Outcomes*				
ICU mortality	72 (20%)	92 (26%)	125 (34%)	< 0.001

Table 1 (continued)

Variable	Low E_{RS} < 0.99 cmH_2O/(mL/kg)	Medium E_{RS} [0.99–1.42 cmH_2O/(mL/kg)]	High E_{RS} > 1.42 cmH_2O/(mL/kg)	*p* value
Hospital mortality	68 (20%)	103 (29%)	131 (37%)	< 0.001
6-month mortality	121 (33%)	134 (36%)	159 (42%)	0.021
Unfavorable GOSE (< 5)	200 (61%)	221 (65%)	243 (73%)	0.002

Data are median (IQR) or *n* (%). Continuous variables were compared across tertiles using the Kruskal–Wallis test; categorical variables were compared using the Pearson chi-square test. *p* values reported in the table refer to these tests

APACHE II Acute Physiology and Chronic Health Evaluation II, *ARDS* acute respiratory distress syndrome, *CT* computed tomography, *ERS* respiratory system elastance, FiO_2 fraction of inspired oxygen, *GCS* Glasgow Coma Scale, *GOSE* Glasgow Outcome Scale Extended, *ICP* intracranial pressure, *ICU* intensive care unit, *LIPS* Lung Injury Prediction Score, $PaCO_2$ arterial partial pressure of carbon dioxide, PaO_2 arterial partial pressure of oxygen, *PBW* predicted body weight, *PEEP* positive end-expiratory pressure

* Data availability varied across outcomes: ICU mortality, *n* = 1077; hospital mortality, *n* = 1055; 6-month mortality, *n* = 1120; unfavorable GOSE (< 5), *n* = 1001; total study population, *n* = 1158

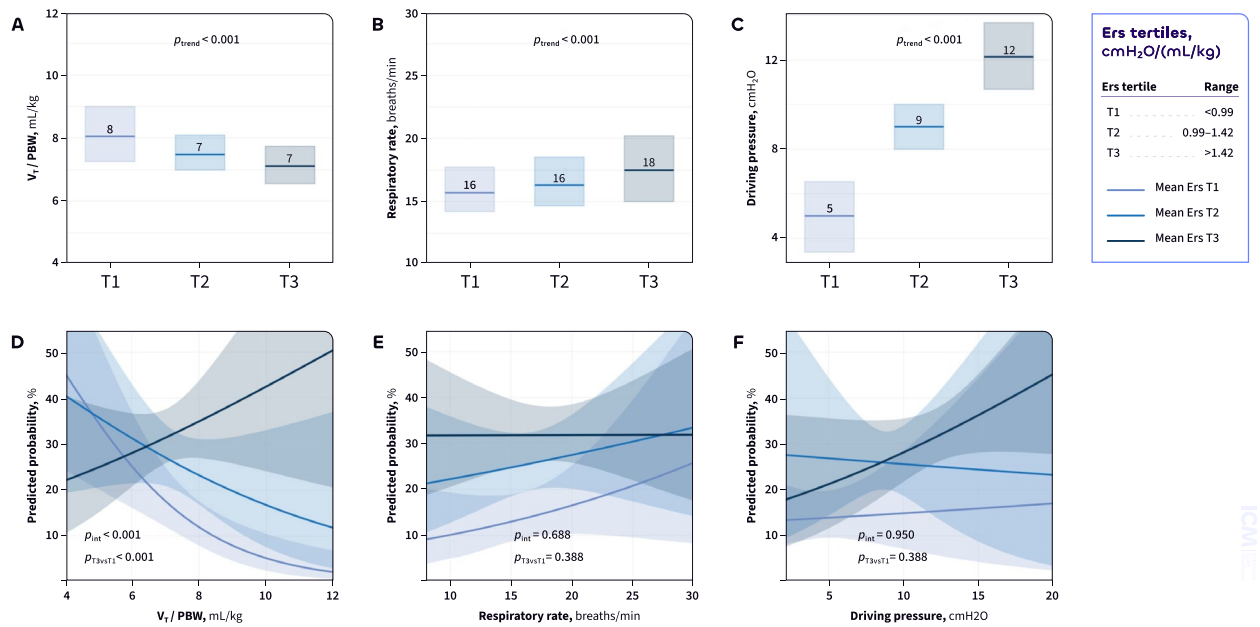

Fig. 1 Ventilatory settings across respiratory system elastance tertiles and effect modification by E_{RS} in the overall cohort. Top: panels **a**–**c** show the distribution (median and interquartile range of the first 7 days in ICU) of V_T/PBW; panel **a**), respiratory rate (panel **b**), and Δ*P* (panel **c**) across tertiles of mean E_{RS}. Despite a small decrease in V_T/PBW and a modest increase respiratory rate across tertiles, Δ*P* increased markedly. Bottom: panels **d**–**f** show the predicted probability of ICU mortality as a function of V_T/PBW (panel **d**), respiratory rate (panel **e**), and Δ*P* (panel **f**), stratified by E_{RS} tertiles. Lines represent E_{RS} tertiles. Shaded bands indicate 95% confidence intervals derived by the delta method. Each panel displays the continuous interaction *p* value (p_{int}) and the pairwise T3 vs T1 slope comparison *p* value (p_{T3vsT1}). Models adjusted for age, sex, and APACHE II score, with all continuous predictors *z*-scored within each tertile. Mean timeframe *N* = 1158

combination associated with the lowest odds of adverse outcome shifted across E_{RS} tertiles: in the low-E_{RS} tertile, the optimum favored higher V_T with lower respiratory rates, whereas in the high E_{RS} tertile, it favored lower V_T with higher respiratory rates (Fig. 2). Directionally consistent results were observed for hospital and 6-month mortality, and GOSE (Supplementary Fig. 5).

Elastance threshold for V_T effect reversal

The posterior probability that V_T 6 mL/kg yields lower ICU mortality than V_T 10 mL/kg varied from near 0% at the lowest observed E_{RS} values—where lower V_T were potentially harmful—to 100% at the highest, illustrating that the same V_T can be detrimental or beneficial depending on E_{RS}. The Bayesian analysis identified the E_{RS} value at which V_T 6 mL/kg and V_T 10 mL/kg become equally likely to be beneficial (or harmful), which

represents an equipoise threshold (Fig. 3). For ICU mortality, this threshold was 1.48 cmH_2O/(mL/kg) (95% HDI 1.15–1.98). The equipoise threshold was slightly lower for hospital mortality and 6-month mortality, indicating that for longer-term outcomes, the benefit of reducing V_T emerged at lower levels of E_{RS}.

Elastance-dependent optimal V_T and respiratory rate

Optimal V_T/PBW (i.e., the value associated with the lowest probability of adverse outcome) decreased from 11.4 mL/kg at E_{RS} 0.5 cmH_2O/(mL/kg) (yielding a $\Delta P \approx 6$ cmH_2O) to 4.4 mL/kg at E_{RS} 2.5 cmH_2O/(mL/kg) (yielding a $\Delta P \approx 11$ cmH_2O), a gradient of approximately 1.7 mL/kg per 0.5 cmH_2O/(mL/kg) increment in E_{RS} (posterior probability of a non-zero curvature in the optimal V_T/PBW–E_{RS} relationship = 100%). Because optimal V_T fell steeply as elastance rose, the corresponding optimal ΔP did not continue to increase but plateaued within a lung-protective range (~11–12 cmH_2O) at moderate-to-high E_{RS}. Optimal respiratory rate increased with E_{RS} (from 15 to 19 breaths/min across tertiles; posterior probability of a non-zero curvature in the optimal respiratory rate–E_{RS} relationship = 99%) (Fig. 4).

Influence of ARDS recognition on the V_T–E_{RS} interaction

The V_T–E_{RS} interaction was consistent across patients classified as having ARDS and those who were not (Supplementary Fig. 6). Accordingly the equipoise threshold at which V_T 6 mL/kg became favored over V_T 10 mL/kg was comparable between non-ARDS patients (E_{RS} 1.53 cmH_2O/[mL/kg]) and ARDS patients (1.42 cmH_2O/[mL/kg]), at near-identical baseline E_{RS} (1.24 vs 1.25 cmH_2O/[mL/kg]). Non-ARDS patients received higher V_T (median 7.6 vs 7.4 mL/kg) and higher ΔP (median 10 vs 9 cmH_2O). The optimal V_T/PBW vs E_{RS} gradient was consistent across ARDS and non-ARDS, declining steeply with elastance in both (Fig. 5).

Sensitivity analyses are reported in the Electronic Supplementary Material and confirmed these findings.

Discussion

In mechanically ventilated patients with acute brain injury, the impact of V_T setting depends on E_{RS}. Lower V_T only helps patients with high E_{RS}, where it meaningfully reduces ΔP. In the majority of patients with low E_{RS}, V_T restriction provides no advantage and forces an increase in respiratory rate, which in our data was independently associated with worse outcomes. The V_T associated with the highest probability of positive clinical outcome decreases continuously as E_{RS} rises, supporting individualized, mechanics-based settings rather than fixed thresholds. Clinically, V_T adjustment can be guided by a physiological framework that balances ΔP reduction against the respiratory rate needed for isocapnia, with outcomes governed by a trade-off of approximately 3 breaths/min per 1 cmH_2O change in ΔP.

Our findings provide a unifying mechanistic framework for several apparently discordant trials. In PReVENT trial [8], conducted in a heterogeneous non-ARDS ICU population, V_T 6 vs 10 mL/kg yielded no difference in outcome. Our data offer a direct explanation: when E_{RS} is not accounted for, a fixed-V_T comparison averages over patients with high E_{RS} (V_T restriction beneficial) and patients with low E_{RS} (V_T restriction unnecessary and forces a disproportionate compensatory rise in respiratory rate). These opposing effects cancel, driving the comparison toward the null. Results from the recent PROLABI sharpen this interpretation [12]: by enrolling brain-injured patients *without* ARDS, a population characterized predominantly by low E_{RS}, low V_T (6 mL/kg, bundled with higher PEEP) was precisely tested in the subgroup in which our analysis predicts that V_T restriction should be detrimental, because it costs significant increases in respiratory rate with minimal benefits on ΔP. Consistently, PROLABI reported higher mortality and a worse composite outcome with the protective strategy. Two caveats apply: the protective arm coupled lower V_T with higher PEEP, so V_T and PEEP effects cannot be separated, whereas our framework isolates the E_{RS}-conditioned tidal exposure; and PROLABI was stopped early for administrative reasons, so its estimates require confirmation. Both features, however, are concordant with our central thesis.

Taken together, PReVENT and PROLABI illustrate the two ways a fixed-V_T prescription fails: dilution of benefit in heterogeneous-E_{RS} populations, and frank harm when low V_T is imposed on predominantly low-E_{RS} patients. This mirrors, at the population level, the ARDS evidence

(See figure on next page.)

Fig. 2 Isocapnic curves showing the predicted odds ratio for ICU mortality as a function of tidal volume and respiratory rate combinations that maintain constant alveolar ventilation, stratified by E_{RS} tertile in the overall cohort. The odds ratio (top), corresponding driving pressure ($\Delta P = V_T \times E_{RS}$; middle), and mechanical power (bottom) are shown in three vertically stacked panels sharing a common tidal volume axis. Each curve traces a constant alveolar ventilation trajectory; the upper *x*-axis displays the corresponding respiratory rate. Circles indicate the optimal ventilation point (minimum odds ratio) for each tertile. Models adjusted for age, APACHE II score, $PaCO_2$, arterial pH, and $PaO2/FiO_2$ ratio, following Costa et al. [20]. Alveolar dead space is assumed as 1.5 mL/kg PBW (airway) plus 20% of V_T. Baseline timeframe (day 0–1 average) $N = 961$

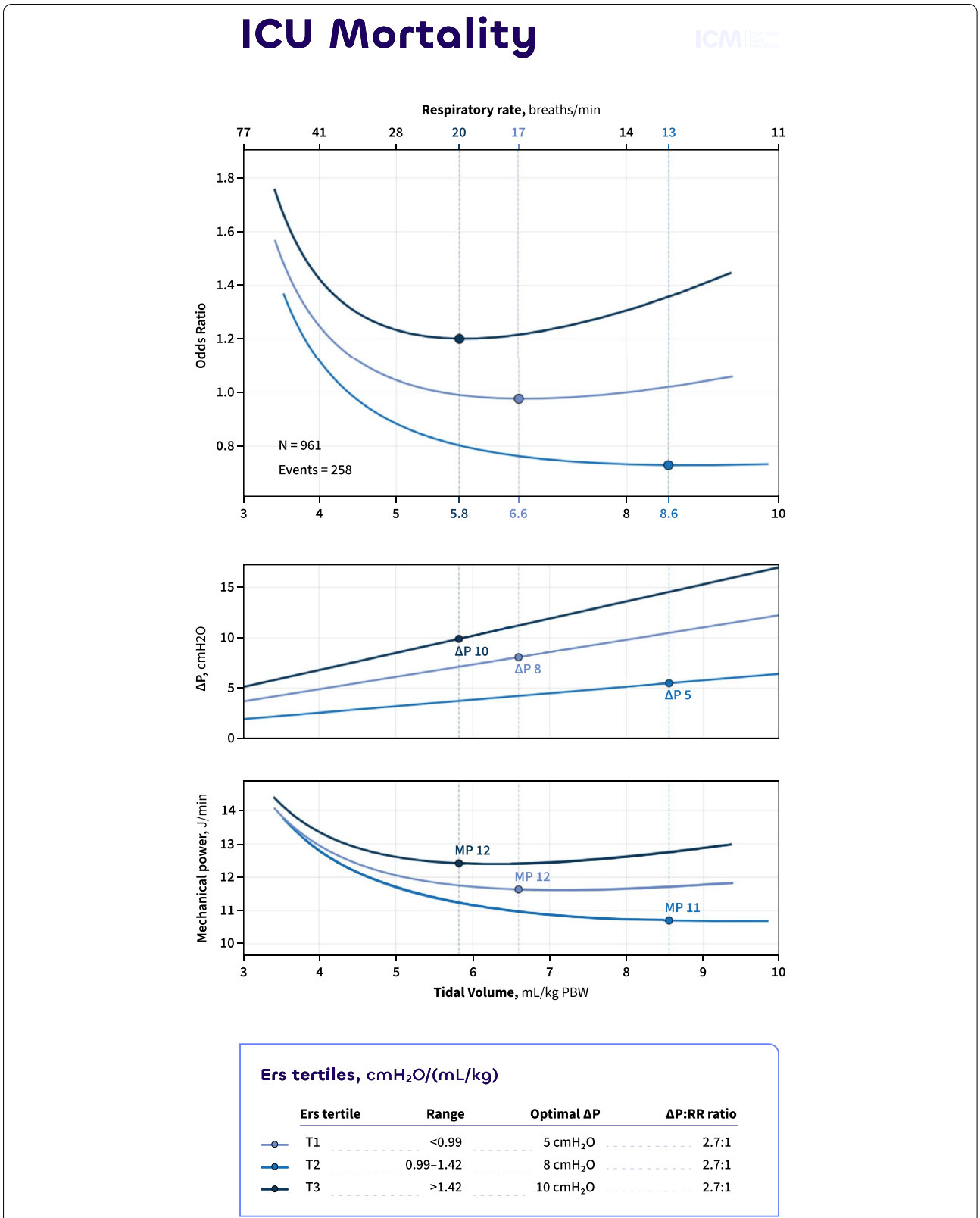

Fig. 2 (See legend on previous page.)

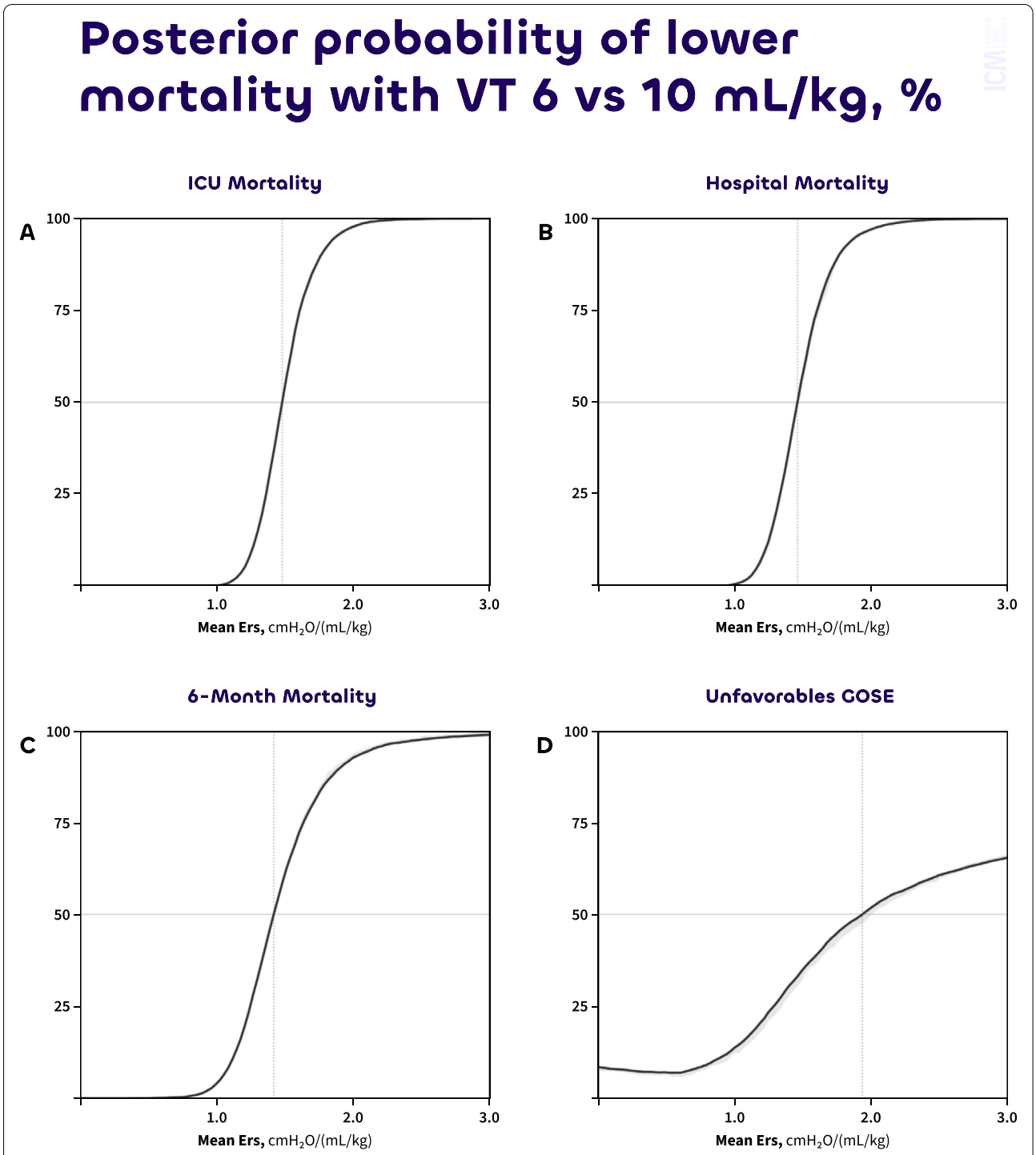

Fig. 3 Elastance threshold for tidal volume effect reversal in the overall cohort. Bayesian posterior probability (%) that V_T 6 mL/kg yields lower mortality or better neurological outcome than V_T 10 mL/kg, plotted across the mean E_{RS} continuum. The crossing point is the E_{RS} value where the posterior probability equals 50% (top row) or the odds ratio equals 1.0 (bottom row). Shaded bands indicate 95% credible intervals (Bayesian). Models adjusted for age, sex, and APACHE II score

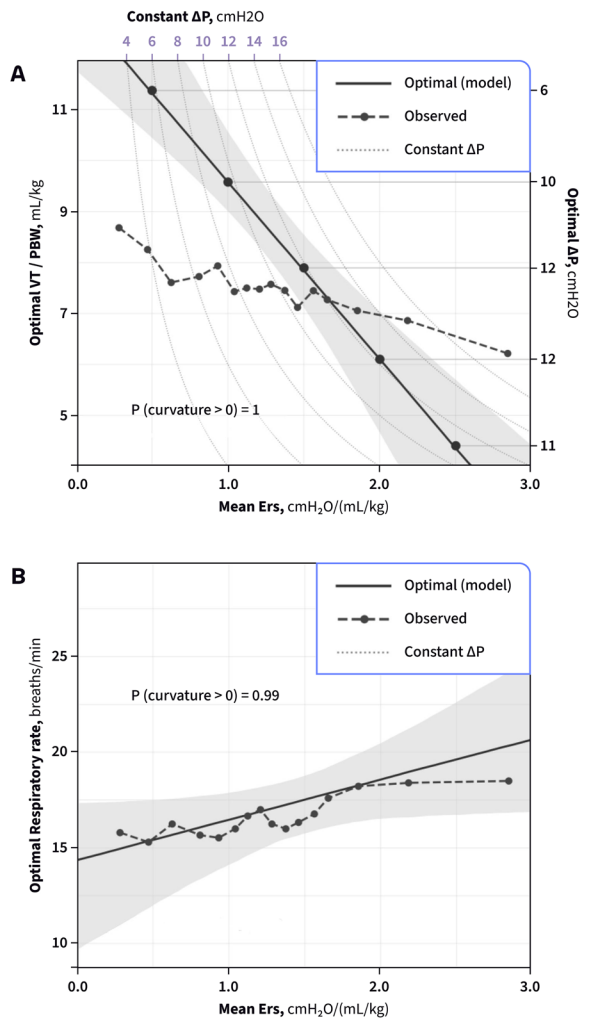

Fig. 4 Optimal V_T/PBW (panel **a**) and optimal respiratory rate (panel **b**) as a function of mean E_{RS} for ICU mortality in the overall cohort, estimated by Bayesian quadratic logistic regression (80% credible intervals). The optimal value at each E_{RS} level corresponds to the nadir of the U-shaped exposure–outcome curve; the dashed line shows observed median values within equally sized bins of E_{RS} in the VENTIBRAIN cohort. In panel **a**, the corresponding optimal ΔP ($= V_T \times$ ERS) increases from ~ 6 to ~ 11–12 cmH_2O across the E_{RS} range (right axis); because optimal V_T falls steeply with elastance, the optimal ΔP does not continue to rise but remains within a lung-protective range. Because ΔP depends on both V_T and E_{RS}, the right axis reports ΔP along the optimal-V_T (model) line only; the ΔP at any other combination is given by the dotted iso-ΔP contours (constant ΔP). In this analysis, the optimal V_T is derived from the V_T–outcome relationship as a continuous function of E_{RS} and is not constrained to maintain constant alveolar ventilation; the ΔP shown is therefore that generated by this unconstrained optimal V_T. The clinically applicable optimum, in which V_T and respiratory rate are coupled to maintain constant alveolar ventilation, is shown in Fig. 2 and yields lower optimal V_T and ΔP values. P(curvature > 0) denotes the Bayesian posterior probability that the quadratic term is positive. Models adjusted for age, sex, and APACHE II score

itself: meta-analyses pooling heterogeneous low- versus high-V_T definitions show no mortality benefit [27], and only trials with a large V_T separation (6 vs 12 mL/kg) demonstrated survival advantage [1, 28]. The common thread is that V_T per se is not the operative variable; the E_{RS}-conditioned tidal exposure—ultimately ΔP—is, consistent with the classical study by Amato et al. [17].

Our findings may help reconcile some observations questioning ΔP-outcome associations in non-ARDS patients [29, 30], in whom E_{RS} is generally low. This generates limited variance in ΔP, carrying no prognostic signal, because it does not reflect meaningful mechanical stress. The prognostic relevance of ΔP depends on E_{RS} being sufficiently high for V_T to generate injurious mechanical stress [16].

This observation has a clear physiological explanation. An increase in E_{RS} reflects a decrease in functional lung size, even in lungs without ARDS [31–33]. For a given V_T to generate injurious strain, lung size must be sufficiently reduced, so that the ratio of V_T to resting lung volume becomes harmful [34]. When compliance (low E_{RS}) is preserved and the lung is large, the same V_T distributes over a greater volume of aerated tissue, generating low strain per individual alveolar unit. In this setting, reducing V_T offers no protection from strain but imposes the cost of higher respiratory rate, whose potential harmful effects, related to strain rate, are not offset by any meaningful reduction in tidal stretch [35, 36]. This is particularly relevant in patients with acute brain injury, who may require higher alveolar ventilation for tight $PaCO_2$ control [37].

Our data indicate that there is no single optimal ΔP. Because ΔP is the product of V_T and E_{RS}, the ΔP compatible with the best outcome is conditional on E_{RS} and rises with it before reaching a plateau within a lung-protective range. The point is not that a low ΔP is undesirable, but that the benefit of lowering it depends on what it costs in respiratory rate to remain isocapnic: at low E_{RS}, where ΔP is already low and reflects little strain, reducing it further requires a disproportionate rise in respiratory rate and is not worthwhile, whereas at high E_{RS}, the same reduction in V_T lowers ΔP substantially at modest respiratory-rate cost—because the V_T-to-ΔP gain (E_{RS}) is itself steeper when the lung is stiff. For this reason, we have framed titration around V_T, which, together with respiratory rate, is the variable the clinician sets, rather than around ΔP, which is its consequence. ΔP nonetheless remains a useful bedside signal, provided that it is read not against a fixed target but as a quantity to be exchanged against respiratory rate along the isocapnic curve. Mechanical power integrates these variables into a single index of energy delivery and provides a useful global ceiling [21, 38]; it does not, however, uniquely determine how a

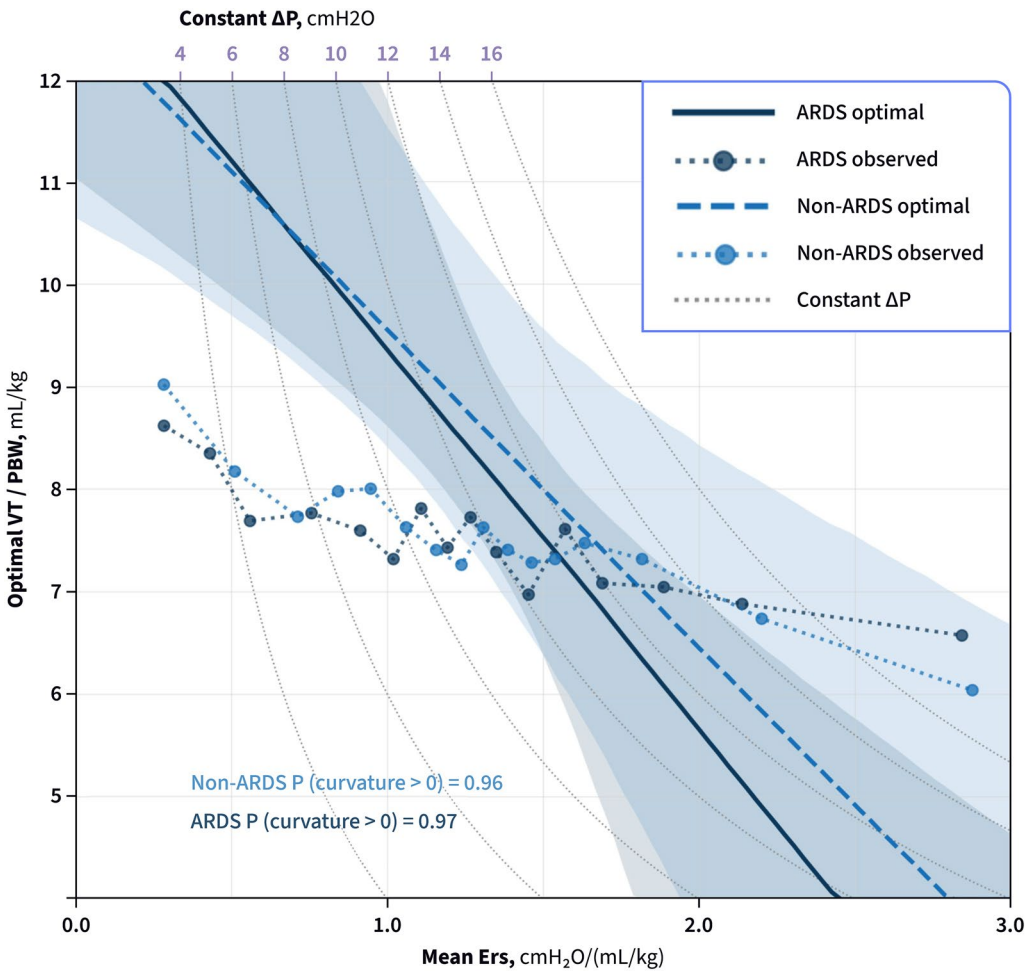

Fig. 5 ARDS vs non-ARDS comparison of optimal V_T/PBW as a function of mean E_{RS}, estimated by Bayesian quadratic logistic regression. Solid lines represent ARDS patients; dashed lines represent non-ARDS patients. Dotted lines with circle markers show observed median V_T/PBW computed from 15 quantile bins of E_{RS} (minimum 8 patients per bin), separately for each subgroup. Diagonal contours are lines of constant driving pressure, calculated as $V_T \times$ ERS, with the corresponding ΔP shown on the top axis. Consistently with Fig. 4, for a given E_{RS}, the ΔP associated with the optimal V_T/PBW is identified by the constant-ΔP contour intersecting the optimal V_T/PBW curve at that E_{RS}; this optimal ΔP therefore varies along the E_{RS} axis. P(curvature > 0) denotes the Bayesian posterior probability that the quadratic term is positive. Models adjusted for age, sex, and APACHE II score

given alveolar ventilation should be partitioned between V_T and respiratory rate, since multiple V_T–respiratory-rate combinations may yield the same power. The ΔP–respiratory-rate exchange we describe can be viewed as the operational rule for this partition within an acceptable energy envelope, not as an alternative to mechanical power.

These results have relevant clinical implications.

First, VENTIBRAIN data show that, in clinical practice, V_T was characterized by minimal clinically meaningful variation across E_{RS} tertiles. Our findings suggest that this strategy may be harmful in both directions: in patients with high E_{RS}, V_T commonly used in practice may still generate excessive ΔP, whereas in patients with low E_{RS}, unnecessarily restrictive V_T may require compensatory increases in respiratory rate to maintain alveolar ventilation, incurring the cost of a higher respiratory rate for a negligible reduction in ΔP, and hence in mechanical stress [21, 36].

Second, V_T–E_{RS} interaction was consistent across ARDS and non-ARDS patients. Notably, 190 patients in the highest E_{RS} tertile were never diagnosed with ARDS, despite having respiratory mechanics indistinguishable from the 196 ARDS patients in the same stratum. This observation, together with the fact that ARDS diagnosis in VENTIBRAIN relied on clinician-reported recognition, suggests that a substantial proportion of lung injury in this population may have been clinically unrecognized.

Failure to recognize ARDS not only precludes protective V_T selection, but may also result in the omission of other evidence-based interventions [39]. The absence of a broader protective bundle may amplify the injurious impact of inappropriate V_T in patients that were not formally classified as ARDS. This is consistent with LUNG SAFE data, which showed that ARDS diagnosis is missed in 40% of patients [40, 41]. These findings argue against using the clinical diagnosis of ARDS as the only trigger for adjusting mechanical ventilation settings. Instead, E_{RS}, and hence ΔP, may provide a more reliable and continuous signal for individualizing V_T prescription, regardless of whether formal ARDS criteria are recognized at the bedside.

Third, any intervention on V_T must be accurately weighed against its impact on respiratory rate to maintain isocapnia. We found that each 1 cmH_2O increase in ΔP had a comparable impact on outcome to an increase of approximately 3 breaths/min in respiratory rate. A practical approach is therefore to reduce V_T only when the resulting increase in respiratory rate does not exceed 3 breaths/min per 1 cmH_2O reduction in ΔP at constant alveolar ventilation, a threshold below which the benefit of lower ΔP is likely to outweigh the cost of increased respiratory rate. Conversely, if respiratory rate can be reduced by more than 3 breaths/min at the cost of increasing V_T so that ΔP increases by 1 cmH_2O, then it is beneficial to increase V_T. This trade-off critically depends on E_{RS}, as compliance ($1/E_{RS}$) determines how many mL of V_T increase ΔP by 1 cmH_2O. Accordingly, the values of V_T/PBW and respiratory rate yielding the highest posterior probability of benefit shifted from 11.4 mL/kg and 15 breaths/min at low E_{RS} to 4.4 mL/kg and 19 breaths/min at high E_{RS}. When V_T and respiratory rate were instead constrained to lie along isocapnic curves (Fig. 2), the optimal combination spanned a narrower range, from 8.6 mL/kg and 13 breaths/min at low E_{RS} to 5.8 mL/kg and 20 breaths/min at high E_{RS} (evaluated at tertile-median E_{RS}).

These exchange rates are empirical, outcome-derived equivalences rather than mechanical-injury constants. In ARDS, the injurious potential of ΔP and respiratory rate is approximately 1:4, indicating that the trade-off favors more aggressive V_T reduction [20]. In our population, this was lower (≈ 3), suggesting a narrower margin for exchanging V_T for respiratory rate. This is physiologically plausible: this difference likely reflects the higher E_{RS} of the ARDS population studied by Costa et al. [20], in which each unit of V_T reduction yields a proportionally larger decrease in ΔP because of lower compliance ($1/E_{RS}$). Conversely, patients with acute brain injury had on average lower E_{RS}, meaning that the same V_T reduction produces a smaller absolute decrease in ΔP, while the need for tight $PaCO_2$ control in the injured brain amplifies the clinical consequences of even modest increases in respiratory rate. In this population, the cost of each additional breath may therefore be higher than in ARDS, making indiscriminate V_T restriction less justified and mechanics-based titration particularly useful.

This study has limitations. First, as a post hoc observational analysis, findings are hypothesis-generating; confounding and unmeasured variables cannot be excluded, and prospective validation is needed. Second, 45% of the parent cohort was excluded due to missing data, though excluded patients had higher mortality across all endpoints; although residual confounding cannot be excluded, this suggests selection bias toward the null and that our estimates are conservative. The proposed trade-off between ΔP and respiratory rate is also physiologically bounded: it cannot be applied beyond the respiratory-rate range compatible with effective CO_2 clearance, since extreme V_T reduction and respiratory rate increases approach dead-space ventilation. Finally, spontaneous breathing efforts may have affected mechanics measurements; however, sensitivity analyses restricted to baseline, when patients were more likely passively ventilated, yielded concordant results.

Conclusions

In mechanically ventilated patients with acute brain injury, the effect of V_T on clinical outcomes depends on E_{RS}. In clinical practice, V_T is generally set too low in patients with preserved lung mechanics and too high in those with increased E_{RS}, with insufficient adaptation to individual compliance. These observational findings generate the hypothesis that V_T and respiratory rate could be titrated jointly along the isocapnic curve, reducing V_T only when the resulting increase in respiratory rate does not exceed 3 breaths/min per cmH_2O reduction in ΔP, a threshold at which the benefit of lower ΔP outweighs the cost of increased respiratory rate. Conversely, increasing V_T is acceptable when this allows a reduction in respiratory rate of at least 3 breaths/min per cmH_2O increase in ΔP, as the benefit of a lower respiratory rate would then outweigh the cost of higher ΔP. This physiology-grounded approach warrants confirmation in prospective trials.

Supplementary Information
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Author details
[1] Department of Anesthesiology and Intensive Care Medicine, Catholic University of the Sacred Heart, Rome, Italy. [2] Department of Anesthesia, Emergency and Intensive Care Medicine, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. [3] Department of Surgical Science and Integrated Diagnostic, University of Genova, Genoa, Italy. [4] IRCCS Ospedale Policlinico San

Martino, Genoa, Italy. [5] School of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [6] Biostatistics and Clinical Epidemiology, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy. [7] Bicocca Bioinformatics Biostatistics and Bioimaging B4 Center, School of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy. [8] Department of Intensive Care, Hôpital Universitaire de Bruxelles (HUB), Université Libre de Bruxelles (ULB), Brussels, Belgium. [9] NeuroIntensive Care Unit, Department Neuroscience, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy.

Author contributions
DLG, TR, AC, and MA designed the study. AS, FG, and SG performed statistical analysis. All authors contributed to manuscript drafting and critical review. All the authors reviewed the final draft of the manuscript and agreed on submitting it to Intensive Care Medicine.

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Data availability
Not applicable.

Declarations

Conflicts of interest
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