TITLE

Tidal volume response to incremental NAVA levels identifies distinct ventilatory phenotypes associated with potential risk of patient self-inflicted lung injury

AUTHORS:

Nicolò Sella[1,2]**#**, Tommaso Pettenuzzo[1,2]**#**, Piero Dissegna[1], Stefano De Marchi[1,3], Dimitri Portale[4], Mara Bassi[1], Alessandro De Cassai*[1,2], Francesco Zarantonello[1,2], Chiara Romondia[1], L. Felipe Damiani[5], Gianmaria Cammarota[6,7], Federico Longhini[8], Eugenio Garofalo[8], Marina Munari[3], Paolo Navalesi[1], Annalisa Boscolo[1,2], and PadovaICU Group^

#*These authors equally contributed to the work.*

^*Members of* the PadovaICU Group *are listed in the Acknowledgements.*

AUTHORS INFORMATION:

1) Department of Medicine (DIMED), University of Padova, Padova (PD) Italy.
2) Institute of Anesthesia and Intensive Care, Padova University Hospital, Padova, Italy.
3) Padova Neuroscience Center, Padova, Italy.
4) Neurological and Neurosurgical Intensive Care Unit, Padova University Hospital, Padova, Italy.
5) Facultad de Medicina, Escuela de Ciencias de La Salud, Departamento de Kinesiología, Pontificia Universidad Catolica de Chile, Santiago, Chile.
6) Department of Translational Medicine, Università degli Studi del Piemonte Orientale, Novara, Italy.
7) Anesthesia and General Intensive Care Unit, University Hospital of Alessandria, Alessandria, Italy.
8) Anesthesia and Intensive Care, Department of Medical and Surgical Sciences, Magna Græcia University, Catanzaro, Italy.

Abstract

Background. Patient self-inflicted lung injury contributes to lung damage, but tools for risk stratification remain limited. Neurally adjusted ventilatory assist (NAVA) provides support proportional to respiratory drive. We investigated whether the tidal volume (Vt) response to increasing NAVA level could identify distinct physiological patterns associated with different risk profiles.

Methods. We conducted a prospective physiological study in two intensive care units. Adult intubated patients underwent a stepwise increase of NAVA level from 0.5 to 3.0 $cmH_2O/\mu V$. At each step, Vt, respiratory drive and effort indices, and lung stress parameters were measured. The relationship between NAVA level and Vt was modeled using multiple candidate functions, and the best model was selected based on Akaike Information Criterion. Unsupervised clustering (finite mixture models) was applied to identify distinct response patterns.

Results. Forty-seven patients were included. The relationship between NAVA level and Vt was best described by a B-spline model. Three clusters were identified: “safe response” (10/47, 21%), “intermediate response” (16/47, 34%), and “dangerous response” (21/47, 45%). In the “safe response” cluster, Vt normalized to ideal body weight increased from 4.78 (4.31; 5.46) to 6.10 (5.34; 7.26) mL/kg, whereas in the “dangerous response” cluster it increased from 8.00 (7.38; 8.59) to 10.35 (9.37; 11.45) mL/kg. Despite similar reductions in diaphragm electrical activity across clusters, quasi static driving pressure and dynamic transpulmonary pressure were higher in the “dangerous response” cluster at NAVA levels ≥2.0 $cmH_2O/\mu V$ ($p<0.05$), reaching 14.0 (8.0; 16.0) and 25.6 (16.4; 36.7) cmH_2O at NAVA 3 $cmH_2O/\mu V$, respectively. Baseline characteristics and arterial blood gas analysis did not differ between clusters. Duration of mechanical ventilation ($p=0.015$) and intensive care unit length of stay ($p=0.029$) were shorter in the “safe response” cluster.

Conclusions. The Vt response to increasing NAVA level is heterogeneous and identifies distinct physiological phenotypes associated with different lung stress profiles and clinical outcomes, thus providing a simple bedside tool to stratify risk, although further validation is required.

Trial registration. ClinicalTrials.gov, NCT05689476. Registered January 20,2023.

Keywords

Mechanical ventilation. Acute respiratory failure. Respiratory drive. Respiratory effort. Patient self-inflicted lung injury. Neurally adjust ventilatory assist.

Background

Increasing attention has been recently directed toward patient self-inflicted lung injury (P-SILI), an injurious phenomenon driven by excessive spontaneous respiratory effort during assisted mechanical ventilation [1,2]. While ventilator-induced lung injury (VILI) is a well-established contributor to morbidity and mortality in patients with acute respiratory failure and lung-protective ventilation strategies are now standard of care worldwide [3,4], P-SILI continues to be an area of active debate and investigation [2,5].

Excessive respiratory drive, which is frequently observed in patients with hypoxemia and lung injury, is hypothesized to play a central role in the pathogenesis of P-SILI [1]. An increased neural drive, resulting in vigorous inspiratory efforts, may generate high transpulmonary pressures, regional lung overdistension, heterogeneous stress distribution, and pulmonary edema [1,6]. These mechanisms may promote lung injury through pendelluft, cyclic recruitment–derecruitment, increased vascular pressures, and elevated mechanical power, even when global tidal volume (Vt) appears within protective ranges [5-10]. Thus, the occurrence of excessive effort during assisted ventilation may establish a vicious cycle in which worsening lung injury further increases respiratory drive, perpetuating additional damage [1,5,11].

Neurally adjusted ventilatory assist (NAVA) is a mode of assisted ventilation that delivers support in proportion to and in synchrony with the electrical activity of the diaphragm (EAdi), thereby closely coupling ventilatory assistance to the patient's neural respiratory drive [12]. By using a trigger that originates near the respiratory centers, NAVA improves patient–ventilator synchrony and has been associated with better diaphragm protection than conventional modes [13-16]. Ideally, this tight coupling should optimize the matching between patient demand and ventilatory support [16]. Indeed, in a model of acute respiratory distress syndrome, this tight coupling between the patient's ventilatory demand and the delivered inspiratory support downregulates inspiratory effort and limits Vt through physiological neural feedback [13,17]. However, clinical data suggest that, in hypoxemic patients with resolving acute respiratory distress syndrome, after switching to partial support ventilation, NAVA, compared with pressure support ventilation (PSV), was associated with increased inspiratory drive, effort, and transpulmonary driving pressure and, even after adjustment for inspiratory effort,

with higher pendelluft magnitude [18]. Moreover, although primarily mediated by chemical inputs from the central and peripheral chemoreceptors, breathing drive in patients with AHRF might also be affected by stimuli coming from mechanoreceptors, vagal inputs, and inflammatory chemokines [19]. Consequently, despite its physiological advantages, NAVA does not eliminate the risk of P-SILI, and careful titration of assistance and monitoring of respiratory drive remain essential [2,15,18].

We hypothesized that the relationship between NAVA level (i.e. the adjustable factor converting Eadi signal into ventilatory pressure assist) and Vt reflects the underlying regulation of respiratory drive and may serve as a marker of P-SILI risk. Specifically, we postulated that patients with persistently elevated and poorly regulated respiratory drive would exhibit a progressive increase in Vt with escalating NAVA levels, reflecting the absence of effective feedback control mechanisms. In contrast, patients not at risk of P-SILI would demonstrate a more regulated response, with stabilization or limitation of Vt despite increasing assistance. The aims of the present study were to investigate the relationship between stepwise incremental NAVA levels and Vt in intubated patients with acute respiratory failure, and to assess whether distinct clusters of Vt response to increasing NAVA levels can be identified, reflecting different patterns of respiratory effort and lung stress and potential risk of P-SILI.

Methods

Study design and ethical approval

This was a prospective, physiological study conducted in two intensive care units (ICUs). The study was approved by the Ethics Committee of the University Hospital of Padova (approval number 5542/AO/22) and conducted in accordance with the Declaration of Helsinki. The study protocol was registered in ClinicalTrial.gov (ID: NCT05689476) on January 20th 2023. Written informed consent was obtained according to local regulations.

Study population

From June 1st 2024, to June 1st 2025, we consecutively screened adult patients (≥18 years) receiving invasive mechanical ventilation for acute respiratory failure and equipped with a NAVA catheter.

In both participating centers, placement of a NAVA catheter is part of routine clinical practice in patients ventilated for more than 48 hours, who failed the first spontaneous breathing trial.

Patients were enrolled when deemed ready to undergo weaning by the attending physician, according to predefined criteria [20,21], including: ability to sustain assisted spontaneous breathing; rapid shallow breathing index <105; stable hemodynamics (heart rate ≤110 beats/min and low-dose vasopressor support, defined as epinephrine or norepinephrine ≤0.1 μg/kg/min); positive end-expiratory pressure (PEEP) ≤8 cmH_2O and fraction of inspired oxygen (FiO_2) ≤0.5; absence of acidosis (pH ≥7.35); body temperature <38°C; adequate level of consciousness and cooperation as assessed by motor activity assessment scale 2–4.

Exclusion criteria were: tracheostomy, ongoing extracorporeal membrane oxygenation or extracorporeal CO_2 removal, hemodynamic instability, ex-vivo lung perfusion before lung transplantation, lung retransplantation, pregnancy, and pre-existing neuromuscular disorders or phrenic nerve dysfunction impairing reliable EAdi measurement [22].

Endpoints and outcome variables

The primary endpoint was to identify distinct patterns of Vt response to stepwise increases in NAVA level. This was operationalized through *i)* characterization of the shape and slope of the Vt response curve to increasing NAVA levels and its variability among patients; and *ii)* clustering analysis of the individual NAVA level/Vt relationships. In accordance with the study hypothesis, we specifically evaluated whether a pattern characterized by a progressive increase in Vt at stepwise escalating NAVA levels could identify a subgroup of patients at higher risk of patient P-SILI.

The secondary endpoint was to compare the identified clusters in terms of:

- markers of respiratory drive and effort, including respiratory rate, EAdi, neuromuscular efficiency index (NME) [23], airway pressure deflection generated by the patient's respiratory effort against the occluded airway (ΔPocc) [24], and pressure generated by the respiratory muscles during inspiration (Pmus) [24];
- lung stress parameters, including quasi static driving pressure (DP) [25], and the ΔPocc-derived dynamic transpulmonary driving pressure (ΔPLdyn) [24];
- arterial blood gases (ABG) exchange;
- clinical baseline characteristics;
- clinically relevant outcomes, i.e. successful weaning [26], ICU and hospital length of stay, and ICU and hospital survival.

Study protocol and ventilatory strategy

After enrollment, patients underwent a baseline assessment of Vt, respiratory rate, and ABG analysis during PSV.

They were then switched to NAVA mode, starting from a NAVA level of 0.5 $cmH_2O/\mu V$. A stepwise NAVA titration was performed from 0.5 $cmH_2O/\mu V$ up to 3.0 $cmH_2O/\mu V$, in increments of 0.5 $cmH_2O/\mu V$, with each step lasting 20 minutes (**Figure 1**). At the end of each step, the following study variables were recorded as the average of three consecutive cycles:

- Vt and respiratory rate;
- EAdi peak and NME [23];

- ΔPocc [24], Pmus [24], DP [25], and ΔPLdyn [24].

ABGs were also obtained during PSV and at NAVA levels of 0.5, 2, and 3 $cmH_2O/\mu V$.

PEEP and FiO2 remained unchanged throughout the study period.

Model selection and clustering analysis

To characterize the relationship between NAVA level and Vt at the individual level, multiple candidate models were fitted for each patient, including linear, exponential, logarithmic, and B-spline (cubic splines) models. Model performance was assessed using the Akaike Information Criterion (AIC): the model with the lowest mean AIC across patients was selected as the reference model for subsequent analyses [27,28].

Clustering analysis was performed using finite mixture models implemented in the flexmix package in R (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria). To reduce the risk of overfitting, a minimum cluster probability of 10% was imposed, corresponding to at least five patients per cluster [29].

Statistical analysis

Continuous variables were summarized as mean (standard deviation) if normally distributed and as median (first quartile; third quartile) if skewed. Normality was assessed using the Shapiro–Wilk test and visual inspection of distributions. Homogeneity of variances was evaluated using Levene's test. Comparisons of continuous variables across groups were performed using one-way analysis of variance (ANOVA) when assumptions of normality and equal variances were met, Welch's ANOVA when variances were unequal, and the Kruskal–Wallis test when normality assumptions were violated. When overall tests were significant, post hoc pairwise comparisons were conducted using Tukey's honestly significant difference test following ANOVA or Dunn's test with Bonferroni correction following Kruskal–Wallis tests.

Categorical variables were expressed as count (percentage) and compared using Pearson's chi-square test or Fisher's exact test, as appropriate. When contingency tables were sparse or larger than 2 × 2, Monte Carlo simulation was applied. Post hoc pairwise comparisons were performed using Fisher's exact test with Bonferroni correction.

All analyses were conducted using R software (version 4.5.2; R Foundation for Statistical Computing, Vienna, Austria). A two-sided p-value < 0.05 was considered statistically significant. For post hoc multiple comparisons, statistical significance was based on adjusted p-values.

Results

Study population

During the study period, 51 eligible patients were identified across the two participating ICUs. Four patients were excluded (two due to unstable EAdi signal at baseline preventing reliable measurements despite repeated repositioning attempts, and two due to lack of informed consent), resulting in a final cohort of 47 patients (**Supplementary Figure 1**).

Baseline demographic characteristics and clinical variables at enrollment are reported in **Table 1**.

Relationship between NAVA level and tidal volume

The relationship between NAVA level and Vt normalized to the ideal body weight (IBW) for the overall cohort is shown in **Figure 2A**.

Multiple candidate models and model performance, assessed using the AIC, are summarized in **Supplementary Table 1**. The B-spline model, defined as piecewise polynomial functions of degree 4 (cubic splines), demonstrated the lowest mean AIC across patients and was therefore selected for subsequent analyses and clustering.

Clustering analysis based on the B-spline–modeled NAVA level/Vt relationship identified three distinct clusters (**Figure 2A-B**):

- ten patients (21%) were classified into a cluster termed “safe response”, characterized by maintenance of Vt/IBW within ranges conventionally considered lung-protective across increasing NAVA levels [1,4], from 4.78 (4.31; 5.46) ml/kg at NAVA level 0.5 cmH2O/μV up to 6.10 (5.34; 7.26) ml/kg at NAVA level 3 cmH2O/μV (**Table 2, Figure 3A**);
- twenty-one patients (45%) were assigned to the “dangerous response” cluster, in which Vt/IBW progressively increased with escalating NAVA levels, reaching values considered injurious [1,4], from 8.00 (7.38; 8.59) ml/kg at NAVA level 0.5 cmH2O/μV up to 10.35 (9.37; 11.45) ml/kg at NAVA level 3 cmH2O/μV (**Table 2, Figure 3A**);
- the remaining 16 patients (34%) formed an intermediate cluster, termed “intermediate response”, characterized by a moderate increase in Vt/IBW with increasing NAVA levels,

from 6.12 (5.37; 6.87) ml/kg at NAVA level 0.5 cmH2O/μV up to 7.77 (6.95; 8.69) ml/kg at NAVA level 3 cmH2O/μV (**Table 2, Figure 3A**).

Comparison across clusters

Comparisons across clusters of markers of respiratory drive and effort, as well as ventilatory and lung injury–related parameters, are presented in **Table 2** and **Figure 3A-G**. Additional data are also available in **Supplementary Tables 2-4**. In particular, while NME values were similar across clusters at all NAVA levels (all $p > 0.05$), EAdi peak presented a significant difference across groups at NAVA level 3.0 cmH2O/μV ($p = 0.029$), when EAdi peak was 4.0 (3.4; 7.5), 4.5 (3.0; 7.4), and 7.2 (5.0; 11.0) μV in the "safe", "intermediate", and "dangerous response" clusters, respectively. ΔPocc and Pmus decreased with increasing NAVA levels, both with significant differences among clusters at NAVA level 1.0 cmH2O/μV ($p = 0.018$, and $p = 0.019$, respectively) and at NAVA level 3.0 cmH2O/μV (both $p = 0.047$). Both DP and ΔPLdyn increased with higher NAVA levels, especially in the "dangerous response" cluster, where DP and ΔPLdyn raised up to 14.0 (8.0; 16.0) and 25.6 (16.4; 36.7) cmH_2O at NAVA 3 cmH_2O/μV, respectively. Significant differences in DP and ΔPLdyn among groups were found at NAVA levels greater than 2.0 cmH2O/μV (all $p < 0.05$).

ABG parameters were not different among clusters at all tested NAVA levels (all $p > 0.05$), as shown in **Table 3**.

Cluster-specific demographic and clinical characteristics, as well as variables associated with cluster membership, are reported in **Table 1**. Except for a different proportion of patients with connective tissue diseases ($p = 0.032$), no baseline demographic or clinical characteristics differed across the three clusters (all $p > 0.05$). In particular, baseline Vt/IBW was not different across clusters ($p = 0.349$), as shown in **Supplementary Figure 2**.

The discriminative ability of Vt/IBW at different NAVA levels to predict cluster assignment was assessed using receiver operating characteristic (ROC) analysis, as shown in **Supplementary Figure 3** and **Supplementary Table 5**. In particular, Vt/IBW showed high accuracy in identifying both the "safe" and "dangerous response" clusters across all tested NAVA levels, with area under the curve (AUC) values consistently above 0.93 for the "safe response" cluster and above 0.94 for the "dangerous response" cluster. In contrast, the "intermediate response" cluster was less well

discriminated, with AUC values ranging from 0.62 to 0.71. When considering cluster assignment as an ordinal outcome (low to high risk of P-SILI), Vt/IBW demonstrated excellent overall discriminative performance, with ordinal AUC values between 0.94 and 0.96 across NAVA levels, peaking at NAVA levels 2.0 and 2.5 $cmH_2O/\mu V$.

Comparisons of clinically relevant outcomes across clusters are summarized in **Table 4**. While ICU and hospital survival were not different among clusters ($p = 0.330$, and $p = 0.170$, respectively), the duration of invasive mechanical ventilation and the length of ICU stay were significantly lower in the "safe response" cluster compared to the others ($p = 0.015$, and $p = 0.029$, respectively).

Discussion

In this prospective physiological study including 47 patients at risk of difficult weaning, the Vt/IBW response to incremental NAVA levels was highly heterogeneous and was best described by a B-spline model, enabling the identification of three distinct response clusters with different potential risk profiles for P-SILI. In the “safe response” cluster, Vt/IBW remained within ranges conventionally considered lung-protective [1,4], accompanied by a trend towards a progressive reduction in respiratory drive and effort and stable, non-injurious values of DP and ΔPLdyn [30,31]. In contrast, in the “dangerous response” cluster, Vt/IBW increased to potentially injurious levels [1,4], paralleled by higher and risky values of DP and ΔPLdyn [30,31]. ABG parameters, including pH, $PaCO_2$, and oxygenation, did not differ across clusters and therefore did not explain the divergent ventilatory patterns. Also, baseline demographic and clinical characteristics were not able to discriminate patients belonging to the “dangerous response” cluster [32]. However, clinically relevant outcomes, including duration of invasive mechanical ventilation and ICU length of stay, were shorter in the “safe response” cluster.

The relationship between NAVA level and Vt observed in our study extends previous physiological findings. Indeed, increasing NAVA levels was associated with overall modest and non-linear changes in Vt, despite a reduction in respiratory drive, as reflected by decreasing EAdi [13,17,33]. Coisel and coworkers have shown that Vt typically increases slightly at lower NAVA levels and then plateaus at higher assist, reflecting the interplay between ventilatory support and intrinsic feedback control of breathing [33]. However, our results highlight a marked inter-individual variability in this relationship, which is only partially captured in previous studies. While the “plateau” behavior of Vt has been described at the population level, our clustering approach demonstrates that this pattern does not apply uniformly to all patients. Specifically, only a subset of patients exhibited a controlled Vt response with early plateauing (i.e., the “safe response” cluster), whereas others showed a progressive increase in Vt with escalating NAVA levels, without evidence of effective feedback limitation (i.e., the “dangerous response” cluster).

Importantly, our findings are in line with previous reports that have also documented that higher NAVA levels may be associated with increased Vt variability and a higher proportion of breaths

exceeding lung-protective thresholds [13,17,18], although this phenomenon has generally been considered limited. Our data extend these observations by identifying a distinct subgroup of patients in whom Vt consistently increased to potentially injurious levels at higher NAVA settings. This suggests that, despite its proportional nature, NAVA does not universally guarantee protection from excessive tidal volumes and that patient-specific regulation of breathing plays a key role in determining ventilatory output.

The identification of three distinct ventilatory response clusters in our study provides a novel, data-driven framework to interpret heterogeneity in potential P-SILI risk. Current understanding of P-SILI is largely based on pathophysiological mechanisms—namely excessive respiratory drive and effort leading to injurious transpulmonary pressures, regional overdistension, and pendelluft—rather than on formally defined phenotypes [7,8,10]. At the bedside, risk stratification relies on surrogate markers of effort, such as respiratory rate, ΔPocc, esophageal pressure swings, or clinical signs of increased work of breathing, but these approaches remain descriptive and not standardized into reproducible phenogroups [18,19]. In this context, our findings extend the current paradigm by applying an unsupervised clustering approach to physiological data, identifying three clusters of patients with different magnitudes of Vt response to increasing NAVA levels, which were associated with different profiles of lung stress and clinical outcomes. While previous studies have emphasized the central role of respiratory drive and effort in determining P-SILI risk [1,5,18], our results suggest that the behavioral response of the respiratory system to ventilatory assist—captured by the Vt–NAVA level relationship—may represent an additional and integrative marker of risk. Notably, the “dangerous response” cluster exhibited a pattern consistent with sustained exposure to potentially injurious tidal volumes and transpulmonary pressures, despite a trend towards a reduction in EAdi and effort, highlighting a dissociation between neural drive and mechanical output that is not fully captured by conventional monitoring.

Importantly, formal clustering approaches to define P-SILI phenotypes are currently lacking in the literature, despite growing recognition of heterogeneity in acute respiratory distress syndrome and spontaneous breathing patterns [2,4]. In other clinical domains, unsupervised learning applied to multidimensional data has successfully identified phenogroups in critically ill ICU populations with distinct prognostic implications, often outperforming traditional risk stratification methods [34,35]. Our

study represents a first step in this direction for P-SILI, suggesting that similar approaches applied to respiratory mechanics and ventilatory signals may allow identification of clinically meaningful risk clusters. However, whether these phenotypes are reproducible across populations and can be used to guide clinical decision-making—such as timing of extubation or titration of assisted ventilation—requires further investigation and external validation.

From a practical perspective, this phenotyping approach suggests that NAVA may serve not only as a mode of ventilatory support but also as a simple bedside tool for P-SILI risk stratification, whereby an incremental NAVA trial and the corresponding tidal volume response can provide immediate insight into patient-specific risk profiles. Interestingly, the high discriminative performance of Vt/IBW for identifying patients at the extremes of risk suggests that tidal volume behavior during assisted ventilation reflects meaningful differences in the interaction between respiratory drive, mechanics, and ventilatory support, while the excellent ordinal AUC across all NAVA levels may indicate that Vt/IBW captures a continuous gradient of risk, rather than discrete categories, reinforcing the hypothesis of P-SILI as a spectrum. This phenotyping approach may be particularly valuable given that, as also observed in our study, baseline demographic and clinical characteristics alone are insufficient to reliably identify patients at higher risk. Identifying a patient's risk profile may, in turn, facilitate a more tailored and consensual therapeutic strategy, particularly with regard to the choice and adjustment of ventilatory support modalities.

The observed behavior of respiratory drive, inspiratory effort, and lung stress across increasing NAVA levels in our study is consistent with the complex and non-linear interaction between ventilatory assistance and patient effort described in previous literature [36,37]. Indeed, in line with prior physiological studies [36,37], increasing assist was associated with a trend towards a progressive reduction in indices of respiratory drive and effort, including EAdi, ΔPocc, and Pmus. However, this reduction did not uniformly translate into lower lung stress, as reflected by the divergent behavior of quasi static driving pressure and ΔPLdyn across clusters. This finding supports the concept that decreasing respiratory effort does not necessarily imply protection from injurious lung mechanics, particularly when tidal volume increases.

Previous studies have shown that respiratory effort may remain elevated despite the application of ventilatory support, particularly when respiratory drive persists [36,37]. For example, during pressure

support ventilation, reductions in assistance lead to compensatory increases in inspiratory effort aimed at preserving tidal volume, while excessive assistance may suppress effort and shift control of ventilation toward passive mechanics [36]. Our findings extend these observations by showing that this physiological framework also applies to NAVA, but with important inter-individual variability. While all patients exhibited a reduction in neural drive with increasing NAVA levels, only some demonstrated a corresponding stabilization of tidal volume and lung stress. In others, tidal volume and ΔPLdyn continued to increase despite reduced effort, suggesting that once a certain level of assistance is reached, ventilatory output may become increasingly determined by respiratory system mechanics rather than by neural control. This is consistent with the concept of a transition toward a "quasi-passive" state described during pressure support ventilation, in which inspiratory effort approaches zero and tidal volume becomes primarily dependent on compliance and applied pressure [2,36]. From a P-SILI perspective, these findings reinforce the notion that the key determinant of injury is not respiratory drive or effort per se, but the resulting transpulmonary pressures and lung deformation. Although increasing assistance may reduce effort, it may simultaneously expose the lung to higher Vt and mechanical stress if not appropriately titrated. This is in agreement with experimental and computational data showing that excessive tidal volume and transpulmonary pressure swings—regardless of their origin—are central drivers of lung injury progression [1,8,10,38]. Therefore, effective prevention of P-SILI requires not only control of respiratory drive and effort but also careful monitoring of the mechanical consequences of ventilation [1,2,18].

Finally, the association between ventilatory response patterns and clinically relevant outcomes observed in our study is consistent with the growing body of evidence linking P-SILI–related mechanisms to worse prognosis [1,2,5,8,9,11]. In our cohort, patients belonging to the "safe response" cluster exhibited shorter duration of invasive mechanical ventilation and ICU length of stay compared with the other groups, suggesting a more favorable clinical trajectory. Although direct evidence quantifying the impact of P-SILI on duration of mechanical ventilation remains limited, several studies have shown that markers of increased respiratory drive and effort—such as P0.1, Pmus, and driving pressure—are associated with lower ICU survival and prolonged ventilatory support, supporting the clinical relevance of P-SILI pathophysiology [1,2,5,9]. Our findings extend

these observations by suggesting that not only the presence of high respiratory drive or effort, but also the resulting ventilatory pattern—specifically the Vt response to ventilatory assist—may identify patients at higher risk of unfavorable outcomes. In this context, the persistence of increasing Vt and lung stress despite ventilatory support without chemoregulation may represent a functional expression of ongoing injurious mechanisms, potentially contributing to delayed recovery and prolonged need for organ support. However, it is important to acknowledge that, to date, no interventional study has definitively demonstrated that strategies aimed at limiting P-SILI translate into improved survival or shorter duration of mechanical ventilation, and causality cannot be inferred from observational data. Interestingly, and somewhat unexpectedly, the intermediate Vt response cluster appeared to be associated with the least favorable overall prognosis. Although this finding should be interpreted with caution and considered hypothesis-generating, one possible explanation is that patients in the “dangerous response” cluster may have been more easily recognized as being at risk and therefore more readily transitioned to fully controlled ventilation [19,32]. In contrast, patients in the “intermediate response” cluster, characterized by a more subtle and less overtly injurious pattern, may have remained on assisted ventilation, potentially continuing to be exposed to a self-perpetuating cycle of P-SILI that went unrecognized at the bedside [1].

This study has several limitations that warrant careful consideration. First, its physiological design precludes any inference of causality. The associations observed between ventilatory response patterns and clinical outcomes should therefore be interpreted with caution and considered purely hypothesis-generating. Second, the study population consisted of a selected cohort of patients at risk of difficult weaning. While clinically relevant, this selection may introduce bias and substantially limits the generalizability of our findings to the broader population of mechanically ventilated ICU patients, particularly those in earlier or more severe phases of acute respiratory failure. Third, the study was conducted in centers with specific expertise in EAdi monitoring. This may limit external validity, as both the feasibility of the protocol and the interpretation of physiological signals may differ in less experienced settings or where such monitoring tools are not routinely available. Fourth, the relatively small sample size and the use of unsupervised clustering techniques raise the possibility of overfitting and instability of the identified clusters. Although methodological precautions were adopted, including constraints on cluster size, the reproducibility and robustness of these

phenotypes remain uncertain and require validation in larger, independent cohorts. Fifth, the study protocol relied on short-term physiological assessments during a controlled NAVA titration. These conditions may not reflect the complexity and variability of real-world clinical practice, where factors such as sedation, disease progression, clinician-driven ventilator adjustments, and patient–ventilator interactions over time may substantially influence respiratory behavior. In addition, as this represents a point-in-time assessment, it reflects the patient's physiological condition at the moment of measurement; however, the individual risk profile may change over time and repeated assessments may be necessary as clinical conditions evolve. Sixth, although multiple surrogate markers of respiratory drive, effort, and lung stress were evaluated, direct measurements of transpulmonary pressure using esophageal manometry were not systematically performed, potentially limiting the accuracy of lung stress assessment. In addition, several variables relevant to P-SILI pathophysiology—such as regional lung mechanics, pendelluft, or mechanical power—were not directly quantified. Finally, the study was not designed or powered to assess clinical outcomes. Observed differences in duration of mechanical ventilation and ICU length of stay may be influenced by unmeasured confounders, including clinician decision-making, variability in weaning strategies, and differences in case mix. Therefore, any interpretation linking the identified phenotypes to outcomes should be considered exploratory and not definitive.

Conclusions

In patients at risk of difficult weaning, the Vt response to incremental NAVA levels is highly heterogeneous and allows identification of distinct clusters associated with different profiles of respiratory effort, lung stress and clinical outcomes. These findings suggest that the dynamic interaction between patient effort and ventilatory assist—captured by the Vt response to NAVA level—may represent a clinically relevant marker of potential P-SILI risk that is not identifiable using baseline characteristics or conventional monitoring alone. If confirmed in larger studies, this approach could provide a simple and reproducible bedside strategy to individualize assisted ventilation and improve risk stratification during spontaneous breathing. However, the clinical

implications of this phenotyping approach, and its potential to guide management and improve outcomes, require larger validation.

List of abbreviations

- ABG – Arterial blood gas
- AIC – Akaike Information Criterion
- ANOVA – One-way analysis of variance
- AUC – Area under the curve
- DP – Quasi static driving pressure
- ΔPLdyn – Dynamic transpulmonary driving pressure
- ΔPocc – Airway pressure deflection during occlusion
- EAdi – Electrical activity of the diaphragm
- FiO_2 – Fraction of inspired oxygen
- IBW – Ideal body weight
- ICU – Intensive care unit
- NAVA – Neurally adjusted ventilatory assist
- NME – Neuromechanical efficiency
- $PaCO_2$ – Partial pressure of carbon dioxide in arterial blood
- PaO_2 – Partial pressure of oxygen in arterial blood
- PEEP – Positive end-expiratory pressure
- Pmus – Pressure generated by respiratory muscles
- P-SILI – Patient self-inflicted lung injury
- PSV – Pressure support ventilation
- ROC – Receiver operating characteristic
- VILI – Ventilator-induced lung injury
- Vt – Tidal volume

Figure legend

Figure 1. Study protocol.

Abbreviations. PSV, pressure support ventilation. NAVA, neurally adjusted ventilatory assist. ABG, arterial blood gas analysis. Vt, tidal volume. RR, respiratory rate. Eadi, electrical activity of the diaphragm. NME, neuromuscular efficiency index. DP, quasi static driving pressure. ΔPLdyn, dynamic transpulmonary driving pressure. ΔPocc, airway pressure deflection generated by the patient's respiratory effort against the occluded airway. Pmus, pressure generated by the respiratory muscles during inspiration. PEEP, positive end expiratory pressure. FiO2, fraction of inspired oxygen.

Figure 2. The relationship between NAVA level and tidal volume normalized to the ideal body weight. A) Individual patients' relationship and clustering analysis based on the B-spline–modeled relationship identified three distinct clusters: the "safe response" cluster (red lines), the "dangerous response" cluster (green lines), and the "intermediate response" cluster (blue lines). **B)** Clustering synthesis, showing for each cluster the mean B-spline function of the relationship between NAVA level and tidal volume normalized to the ideal body weight (continuous lines) with 95% confidence interval (shaded areas). The "safe response" cluster is depicted in red, the "dangerous response" in green, and the "intermediate response" cluster in blue.

Abbreviations. NAVA, neurally adjusted ventilatory assist. Vt, tidal volume. IBW, ideal body weight.

Figure 3. Evolution of respiratory drive, inspiratory effort, and lung stress parameters across increasing NAVA levels. A) Tidal volume normalized to ideal body weight (Vt/IBW). **B)** Peak electrical activity of the diaphragm (EAdi). **C)** Neuro-muscular efficiency index (NME). **D)** Airway pressure deflection generated by the patient's respiratory effort against the occluded airway (ΔPocc). **E)** Pressure generated by the respiratory muscles during inspiration (Pmus). **F)** Quasi static driving pressure (DP). **G)** Dynamic transpulmonary driving pressure (ΔPLdyn). Red dotted line represents

the safety threshold [4,24,30,31]. *p-value < 0.05 for difference with the value registered at NAVA level 0.5 $cmH_2O/\mu V$ (intra-cluster variability). #p-value < 0.05 for intercluster difference.

Abbreviations. NAVA, neurally adjusted ventilatory assist.

Supplementary Figure legend

Supplementary Figure 1. Study enrollment flowchart.

Abbreviations. IMV, invasive mechanical ventilation. NAVA, neurally adjusted ventilatory assist. Vt, tidal volume. Eadi, electrical activity of the diaphragm.

Supplementary Figure 2. Baseline tidal volume distribution across ventilatory response clusters. Individual values of tidal volume normalized to ideal body weight measured at baseline during pressure support ventilation are shown for each cluster (safe, intermediate, and dangerous response). Data are presented as individual points (jittered for visualization), with median (horizontal line) and interquartile range (vertical line) overlaid. Shaded areas represent a smoothed distribution (raincloud plot).

Abbreviations. Vt, tidal volume. IBW, ideal body weight.

Supplementary Figure 3. Receiver operating characteristic curves of Vt/IBW for prediction of ventilatory response clusters across NAVA levels. Receiver operating characteristic (ROC) curves showing the discriminative performance of tidal volume normalized to ideal body weight at different NAVA levels (0.5–3.0 $cmH_2O/\mu V$) for the identification of the three response clusters: low "safe", "intermediate", and "dangerous response". Each panel represents a one-vs-rest analysis for the corresponding cluster. No significant differences were observed between the AUC values obtained at different NAVA levels for any of the clusters (all $p > 0.10$).

Abbreviations. NAVA, neurally adjusted ventilatory assist. AUC, area under the curve.

References

1. Brochard L, Slutsky A, Pesenti A. Mechanical Ventilation to Minimize Progression of Lung Injury in Acute Respiratory Failure. Am J Respir Crit Care Med. 2017 Feb 15;195(4):438-442.
2. Piquilloud L, Demoule A. P-SILI and the Dangers of the Transition Phase. Am J Respir Crit Care Med. 2025 Oct 22. Epub ahead of print.
3. Tonetti T, Marini JJ. Mechanical power and VILI: modeling limits and unknowns. Intensive Care Med Exp. 2025 Jan 6;13(1):1.
4. Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018 Feb 20;319(7):698-710.
5. Balzani E, Alcala GC, Bellani G, Pesenti A. Patient self-inflicted lung injury an important phenomenon. Curr Opin Crit Care. 2026 Feb 1;32(1):9-16.
6. Cornejo R, Telias I, Brochard L. Measuring patient's effort on the ventilator. Intensive Care Med. 2024 Apr;50(4):573-576.
7. Carteaux G, Parfait M, Combet M, Haudebourg AF, Tuffet S, Mekontso Dessap A. Patient-Self Inflicted Lung Injury: A Practical Review. J Clin Med. 2021 Jun 21;10(12):2738.
8. Yoshida T, Grieco DL, Brochard L, Fujino Y. Patient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathing. Curr Opin Crit Care. 2020 Feb;26(1):59-65.
9. Weaver L, Das A, Saffaran S, Yehya N, Scott TE, Chikhani M, Laffey JG, Hardman JG, Camporota L, Bates DG. High risk of patient self-inflicted lung injury in COVID-19 with frequently encountered spontaneous breathing patterns: a computational modelling study. Ann Intensive Care. 2021 Jul 13;11(1):109.
10. Marongiu I, Slobod D, Leali M, Spinelli E, Mauri T. Clinical and Experimental Evidence for Patient Self-Inflicted Lung Injury (P-SILI) and Bedside Monitoring. J Clin Med. 2024 Jul 10;13(14):4018.
11. Merola R, Rocco PRM, Battaglini D. Patient Self-Inflicted Lung Injury in ARDS: From Physiological Concept to Clinical Syndrome. J Clin Med. 2026 Feb 11;15(4):1412.

12. Sinderby C, Navalesi P, Beck J, Skrobik Y, Comtois N, Friberg S, Gottfried SB, Lindström L. Neural control of mechanical ventilation in respiratory failure. Nat Med. 1999 Dec;5(12):1433-6.
13. Brander L, Sinderby C, Lecomte F, Leong-Poi H, Bell D, Beck J, Tsoporis JN, Vaschetto R, Schultz MJ, Parker TG, Villar J, Zhang H, Slutsky AS. Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med. 2009 Nov;35(11):1979-89.
14. Shimatani T, Shime N, Nakamura T, Ohshimo S, Hotz J, Khemani RG. Neurally adjusted ventilatory assist mitigates ventilator-induced diaphragm injury in rabbits. Respir Res. 2019 Dec 23;20(1):293.
15. Tian X, Alizadeh M, Qi H, Shang Y. Application of neurally adjusted ventilatory assist (NAVA): a narrative review. J Thorac Dis. 2025 Oct 31;17(10):9178-9199.
16. Sinderby C, Beck J, Spahija J, de Marchie M, Lacroix J, Navalesi P, Slutsky AS. Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest. 2007 Mar;131(3):711-717.
17. Brander L, Leong-Poi H, Beck J, et al. Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest. 2009;135 3:695-703.
18. Arellano DH, Brito R, Morais CCA, Ruiz-Rudolph P, Gajardo AIJ, Guiñez DV, Lazo MT, Ramirez I, Rojas VA, Cerda MA, Medel JN, Illanes V, Estuardo NR, Bruhn AR, Brochard LJ, Amato MBP, Cornejo RA. Pendelluft in hypoxemic patients resuming spontaneous breathing: proportional modes versus pressure support ventilation. Ann Intensive Care. 2023 Dec 20;13(1):131.
19. Pettenuzzo T, Sella N, Zarantonello F, De Cassai A, Geraldini F, Persona P, Pistollato E, Boscolo A, Navalesi P. How to recognize patients at risk of self-inflicted lung injury. Expert Rev Respir Med. 2022 Sep;16(9):963-971.
20. Boles JM, Bion J, Connors A, Herridge M, Marsh B, Melot C, Pearl R, Silverman H, Stanchina M, Vieillard-Baron A, Welte T. Weaning from mechanical ventilation. Eur Respir J. 2007;17:1033–1056.

21. MacIntyre NR, Cook DJ, Ely EW Jr, Epstein SK, Fink JB, Heffner JE, Hess D, Hubmayer RD, Scheinhorn DJ. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest. 2001;17:375–395.
22. Mandyam S, Qureshi M, Katamreddy Y, Parghi D, Patel P, Patel V, Anshul F. Neurally Adjusted Ventilatory Assist Versus Pressure Support Ventilation: A Comprehensive Review. J Intensive Care Med. 2024 Dec;39(12):1194-1203.
23. Liu L, Liu H, Yang Y, Huang Y, Liu S, Beck J, Slutsky AS, Sinderby C, Qiu H. Neuroventilatory efficiency and extubation readiness in critically ill patients. Crit Care. 2012 Jul 31;16(4):R143.
24. Bertoni M, Telias I, Urner M, Long M, Del Sorbo L, Fan E, Sinderby C, Beck J, Liu L, Qiu H, Wong J, Slutsky AS, Ferguson ND, Brochard LJ, Goligher EC. A novel non-invasive method to detect excessively high respiratory effort and dynamic transpulmonary driving pressure during mechanical ventilation. Crit Care. 2019 Nov 6;23(1):346.
25. Cammarota G, Verdina F, De Vita N, Boniolo E, Tarquini R, Messina A, Zanoni M, Navalesi P, Vetrugno L, Bignami E, Corte FD, De Robertis E, Santangelo E, Vaschetto R. Effects of Varying Levels of Inspiratory Assistance with Pressure Support Ventilation and Neurally Adjusted Ventilatory Assist on Driving Pressure in Patients Recovering from Hypoxemic Respiratory Failure. J Clin Monit Comput. 2022 Apr;36(2):419-427.
26. Pham T, Heunks L, Bellani G, Madotto F, Aragao I, Beduneau G, Goligher EC, Grasselli G, Laake JH, Mancebo J, Peñuelas O, Piquilloud L, Pesenti A, Wunsch H, van Haren F, Brochard L, Laffey JG; WEAN SAFE Investigators. Weaning from mechanical ventilation in intensive care units across 50 countries (WEAN SAFE): a multicentre, prospective, observational cohort study. Lancet Respir Med. 2023 May;11(5):465-476.
27. Pan W. Akaike's information criterion in generalized estimating equations. Biometrics. 2001;57:120–125.
28. Mauri T, Alban L, Turrini C, Cambiaghi B, Carlesso E, Taccone P, Bottino N, Lissoni A, Spadaro S, Volta CA, Gattinoni L, Pesenti A, Grasselli G. Optimum support by high-flow

nasal cannula in acute hypoxemic respiratory failure: effects of increasing flow rates. Intensive Care Med. 2017 Oct;43(10):1453-1463.

29. Leisch F. FlexMix: A General Framework for Finite Mixture Models and Latent Class Regression in R. Journal of Statistical Software. 2004 11(8).
30. Bellani G, Grassi A, Sosio S, Gatti S, Kavanagh BP, Pesenti A, Foti G. Driving Pressure Is Associated with Outcome during Assisted Ventilation in Acute Respiratory Distress Syndrome. Anesthesiology. 2019 Sep;131(3):594-604.
31. Grassi A, Bianchi I, Teggia Droghi M, Miori S, Bruno I, Balzani E, Morris IS, Schaedler D, Becher T, Valdivia Marchal M, Serrano JM, Caritg O, Roca O, Costa E, Amato M, Barriga F, Roldan R, Boffi A, Piquilloud L, Mitchon GJ, Musch G, Piva S, Bertoni M, Castagna L, Grasselli G, Riccardo M, Spadaro S, Nita C, McNicholas B, Sklar MC, Magliocca A, Rezoagli E, Foti G, Laffey J, Brochard LJ, Goligher EC, Bellani G. Increased Driving Pressure During Assisted Ventilation for Hypoxemic Respiratory Failure Is Associated with Lower ICU Survival: The ICEBERG Study. Am J Respir Crit Care Med. 2025 Nov;211(11):2169-2179.
32. Pacchiarini G, Monteleone F, Zarantonello F, Sella N, Bassi M, Zambianchi A, Fincati V, Bolzon A, Pistollato E, De Cassai A, Boscolo A, Navalesi P, Pettenuzzo T. Recognizing and managing excessive respiratory drive and effort: an expert narrative review. Expert Rev Respir Med. 2026 Jan 28:1-17.
33. Coisel Y, Chanques G, Jung B, et al. Neurally Adjusted Ventilatory Assist in Critically Ill Postoperative Patients: A Crossover Randomized Study. Anesthesiology. 2010;113:925-935.
34. Sikora A, Rafiei A, Rad MG, Keats K, Smith SE, Devlin JW, Murphy DJ, Murray B, Kamaleswaran R; MRC-ICU Investigator Team. Pharmacophenotype identification of intensive care unit medications using unsupervised cluster analysis of the ICURx common data model. Crit Care. 2023 May 2;27(1):167.
35. Zampieri F, Salluh J, Azevedo LC, et al. ICU staffing feature phenotypes and their relationship with patients' outcomes: an unsupervised machine learning analysis. Intensive Care Medicine. 2019;45:1599 - 1607.

36. Docci M, Rezoagli E, Teggia-Droghi M, Coppadoro A, Pozzi M, Grassi A, Bianchi I, Foti G, Bellani G. Individual response in patient's effort and driving pressure to variations in assistance during pressure support ventilation. Ann Intensive Care. 2023 Dec 20;13(1):132.
37. Docci M, Foti G, Brochard L, Bellani G. Pressure support, patient effort and tidal volume: a conceptual model for a non linear interaction. Crit Care. 2024 Nov 6;28(1):358.
38. Yoshida T, Uchiyama A, Matsuura N, Mashimo T, Fujino Y. Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: High transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. Critical Care Medicine. 2012;40:1578–1585.

Declarations

Ethics approval and consent to participate

The study was designed following the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Padua University Hospital, Padua, Italy (approval number 5542/AO/22). Patient consent was obtained according to the national regulation. In cases the patient was incompetent because of critical illness or the use of sedative drugs, consent could be delayed, and a provision for delayed consent was applied: as soon as competent, each patient was fully informed on what had been done, and a written permission of using data collected was obtained. The patients or their legal surrogates were informed of their right to refuse the study-related use of their medical records.

Consent for publication

Not applicable.

Availability of data and materials

Individual participant data that underlie the results reported in this article, after de-identification, data dictionary, study protocol, statistical analysis plan, informed consent form, and analytic code will be available to any researchers who provide a methodologically sound proposal, immediately following publication and without end date. Proposals should be directed to the corresponding author. To gain access, data requestors will need to sign a data access agreement.

Competing interests

NS, TP, FZ, and PN received lecturing fees from Getinge. The other authors declare no competing interests.

Funding

None to declare.

Authors' contributions

All authors directly accessed and verified the underlying data reported in the manuscript, and accepted responsibility to submit for publication.

All authors approved the final version of the manuscript to be published.

All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Substantial contributions to the conception or design of the work: N.S., T.P., P.N., A.B., A.D.C., F.Z., G.C., F.L.

The acquisition, analysis, or interpretation of data for the work: N.S., T.P., P.D., S.D.M., D.P., M.B., A.D.C., F.Z., C.R., L.F.D., E.G., M.M.

Drafting the work: N.S., T.P., A.D.C.

Reviewing it critically for important intellectual content: P.D., S.D.M., D.P., M.B., F.Z., C.R., L.F.D., G.C., F.L., E.G., M.M., P.N., A.B.

Acknowledgments

We are indebted with all ICU personnel who made this work possible.

Members of the PaduaICU Group are listed below, following their respective affiliations:

- Institute of Anesthesia and Intensive Care, Padova University Hospital, Padova, Italy: Francesco Monteleone, Luisa Muraro, Giorgia Pacchiarini, Arianna Peralta, Silvia Piovesan;
- Department of Neuroscience, University of Padova, Padova, Italy: Elisa Pistollato.

Table 1. Baseline demographic characteristics and clinical variables at enrollment.

Data are expressed as mean (standard deviation), number (percentage), or median (interquartile range).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
DEMOGRAPHICS					
Age, *years*	59 (14)	54 (17)	59 (17)	62 (9)	0.304
Male, *n (%)*	33 (70)	6 (60)	12 (75)	15 (71)	0.762
BMI, *kg/m^2*	25.7 (23.1; 29.4)	28.1 (25.0; 31.2)	25.9 (23.7; 29.7)	24.7 (21.9; 27.0)	0.181
Comorbidities, *n (%)*					
- CHF	2 (4)	0 (0)	0 (0)	2 (9)	0.338
- PVD	5 (11)	1 (10)	1 (6)	3 (14)	0.806
- Stroke	15 (32)	3 (30)	7 (44)	5 (24)	0.508
- Hemiplegia	6 (13)	1 (10)	1 (6)	4 (19)	0.566
- Dementia	3 (6)	0 (0)	1 (6)	2 (9)	0.655
- COPD	17 (36)	4 (40)	4 (25)	9 (43)	0.583
- CTD	2 (4)	2 (20)	0 (0)	0 (0)	**0.032**
- Gastric ulcer	1 (2)	1 (10)	0 (0)	0 (0)	0.212
- Liver	7 (15)	3 (30)	1 (6)	3 (14)	0.319
- Diabetes	9 (19)	3 (30)	2 (13)	4 (19)	0.611
- CKD	2 (4)	1 (10)	0 (0)	1 (5)	0.529
- Cancer	4 (8)	0 (0)	1 (6)	3 (14)	0.458
- Leukemia	2 (4)	1 (10)	1 (6)	0 (0)	0.462

- Lymphoma	1 (2)	0 (0)	0 (0)	1 (5)	0.608
- Immunosuppression	0 (0)	0 (0)	0 (0)	0 (0)	
Charlson CI	3 (2; 6)	4 (3; 5)	3 (1; 4)	4 (3; 6)	0.265
ICU ADMISSION					
Cause, *n (%)*					
- hARF	10 (21)	2 (20)	5 (31)	3 (14)	0.880
- BLTx	13 (28)	3 (30)	2 (13)	8 (38)	0.220
- Acute brain injury	17 (36)	2 (20)	8 (50)	7 (33)	0.320
SOFA score	7.5 (3.4)	6.8 (2.7)	8.1 (3.9)	7.4 (3.5)	0.659
DDimer, *mcg/L*	3176 (1663; 9462)	6908 (3176; 11854)	1858 (1191; 10202)	3050 (2015; 3792)	0.397
CRP, *mg/L*	47 (24; 115)	33 (16; 47)	59 (29; 137)	51 (29; 139)	0.426
PCT, *mcg/L*	0.40 (0.10; 1.30)	0.20 (0.10; 1.40)	0.45 (0.10; 1.00)	0.60 (0.10; 1.30)	0.857
IMV length, *days*	7 (3; 14)	5 (3; 7)	10 (4; 20)	8 (3; 11)	0.310
ENROLLMENT					
RASS:					0.162
- >0	0 (0)	0 (0)	0 (0)	0 (0)	
- 0; -2	39 (83)	9 (90)	11 (69)	19 (91)	
- < -2	8 (17)	1 (10)	5 (31)	2 (9)	
CCPOT:					0.916
- 0	39 (83)	8 (80)	13 (81)	18 (86)	
- 1; 3	7 (15)	1 (10)	3 (19)	3 (14)	
- $\geq$ 4	1 (2)	1 (10)	0 (0)	0 (0)	
PS t0, *cmH2O*	8 (6; 10)	8 (5; 8)	8 (7; 8)	8 (7; 10)	0.723

PEEP t0, *cmH2O*	8 (6; 12)	8 (5; 12)	8 (6; 10)	8 (7; 10)	0.777
FiO_2 t0	0.30 (0.25; 0.40)	0.30 (0.25; 0.40)	0.30 (0.25; 0.40)	0.40 (0.30; 0.40)	0.352
Vt/IBW t0, *mL/kg*	7.71 (6.36; 8.61)	6.84 (5.68; 7.36)	7.58 (6.47; 8.61)	7.70 (6.28; 8.06)	0.349
RR t0, *breath/minute*	18 (14; 23)	20 (19; 25)	19 (16; 25)	16 (12; 20)	0.100
Crs t0, *mL/cmH_2 O*	61.3 (49.1; 73.0)	72.5 (43.9; 86.1)	60.4 (54.2; 70.0)	62.9 (49.3; 71.2)	0.777
PaO_2/FiO_2 t0, *mmHg*	273 (213; 334)	304 (272; 327)	270 (213; 331)	270 (207; 334)	0.929
pH t0	7.45 (7.42; 7.48)	7.45 (7.43; 7.49)	7.45 (7.43; 7.48)	7.45 (7.40; 7.48)	0.713
$PaCO_2$ t0, *mmHg*	39.5 (36.9; 44.6)	42.8 (38.3; 45.7)	39.3 (36.0; 44.3)	38.7 (37.2; 44.6)	0.300

Abbreviations. BMI, body mass index. CHF, chronic heart failure. PVD, peripheral vascular disease. COPD, chronic obstructive pulmonary disease. CTD, connective tissue disease. CKD, chronic kidney disease. CI, comorbidity index. ICU, intensive care unit. hARF, hypoxemic acute respiratory failure. BLTx, bilateral lung transplant. SOFA, sequential organ failure assessment. CRP, C-reactive protein. PCT, procalcitonin. IMV, invasive mechanical ventilation. RASS, Richmond agitation sedation scale. CCPOT, critical care pain observation tool. t0, baseline assessment at the time of enrollment. PS, pressure support. PEEP, positive end-expiratory pressure. FiO_2, fraction of inspired oxygen. Vt, tidal volume. IBW, ideal body weight. RR, respiratory rate. Crs, quasi static respiratory system compliance during inspiratory hold maneuver. PaO_2, arterial partial pressure of oxygen. $PaCO_2$, arterial partial pressure of carbon dioxide.

Table 2

Table 2. Markers of respiratory drive and effort, and ventilatory and lung injury–related parameters.

Data are expressed as median (interquartile range).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
Vt/IBW, *mL/kg*					
Vt NAVA level 0.5	6.67 (5.45; 7.81)	4.78 (4.31; 5.46)	6.12 (5.37; 6.87)	8.00 (7.38; 8.59)	**< 0.001**
Vt NAVA level 1.0	7.47 (6.16; 9.66)	5.86 (5.25; 6.00)	7.23 (6.46; 7.47)	8.90 (8.16; 10.01)	**< 0.001**
Vt NAVA level 1.5	8.23 (6.68; 10.03)	6.09 (5.68; 6.90)	7.28 (6.68; 7.67)	9.27 (8.62; 10.54)	**< 0.001**
Vt NAVA level 2.0	7.91 (6.35; 9.68)	6.15 (5.49; 6.35)	7.44 (6.98; 8.89)	9.40 (8.46; 10.36)	**< 0.001**
Vt NAVA level 2.5	8.79 (6.10; 10.19)	5.99 (5.45; 6.10)	7.63 (6.95; 8.79)	9.48 (9.06; 10.57)	**< 0.001**
Vt NAVA level 3.0	8.78 (6.81; 10.87)	6.10 (5.34; 7.26)	7.77 (6.95; 8.69)	10.35 (9.37; 11.45)	**< 0.001**
Respiratory rate, *bpm*					
Resp rate NAVA level 0.5	20 (17; 26)	24,5 (19; 29)	25 (19; 28)	18 (16; 22)	0.412
Resp rate NAVA level 1.0	20 (16; 26)	24,5 (16; 29)	25 (19; 27)	16 (14; 22)	0.398
Resp rate NAVA level 1.5	20 (17; 25)	24 (17; 32)	21 (18; 25)	18 (15; 20)	0.365
Resp rate NAVA level 2.0	20 (16; 27)	21,5 (18; 28)	20 (17; 27)	18 (14; 22)	0.441
Resp rate NAVA level 2.5	18 (15; 23)	22 (18; 27)	18 (17; 23)	15 (14; 20)	0.287
Resp rate NAVA level 3.0	18 (14; 23)	22 (17; 28)	20 (17; 23)	15 (12; 20)	0.251
EAdi peak, *µV*					
EAdi peak NAVA level 0.5	10.0 (5.3; 15.0)	9.0 (4.0; 15.0)	8.0 (3.8; 14.0)	11.0 (7.5; 18.0)	0.273
EAdi peak NAVA level 1.0	9.0 (5.0; 12.0)	6.8 (4.0; 12.0)	6.8 (4.0; 11.5)	9.0 (6.4; 14.0)	0.618

EAdi peak NAVA level 1.5	6.0 (4.0; 11.0)	5.3 (3.0; 11.0)	6.5 (4.0; 10.0)	7.0 (5.0; 14.0)	0.736
EAdi peak NAVA level 2.0	5.0 (3.8; 10.0)	4.4 (3.0; 9.5)	4.1 (3.3; 7.0)	7.3 (4.4; 12.0)	0.081
EAdi peak NAVA level 2.5	4.8 (3.0; 9.0)	4.1 (2.9; 9.0)	4.3 (3.0; 6.6)	7.0 (4.2; 10.0)	0.058
EAdi peak NAVA level 3.0	5.4 (3.5; 9.0)	4.0 (3.4; 7.5)	4.5 (3.0; 7.4)	7.2 (5.0; 11.0)	**0.029**
NME, *cmH₂ O/μV*					
NME NAVA level 0.5	0.93 (0.57; 1.57)	1.14 (0.88; 2.25)	0.82 (0.44; 1.18)	0.88 (0.60; 1.40)	0.641
NME NAVA level 1.0	1.20 (0.63; 1.53)	1.30 (1.02; 1.50)	1.13 (0.50; 1.50)	1.13 (0.63; 1.44)	0.823
NME NAVA level 1.5	1.00 (0.58; 1.57)	1.00 (0.57; 2.33)	1.24 (0.57; 1.75)	1.00 (0.57; 1.25)	0.912
NME NAVA level 2.0	1.00 (0.60; 1.67)	1.00 (0.64; 2.33)	1.03 (0.45; 1.50)	0.94 (0.53; 1.32)	0.887
NME NAVA level 2.5	1.00 (0.65; 1.45)	1.00 (0.70; 1.45)	1.00 (0.56; 1.28)	1.06 (0.65; 1.45)	0.954
NME NAVA level 3.0	1.00 (0.60; 1.40)	0.85 (0.54; 1.40)	1.13 (0.67; 1.50)	1.00 (0.52; 2.30)	0.731
ΔPocc, *cmH₂O*					
ΔPocc NAVA level 0.5	-9.0 (-12.3; -7.3)	-9.0 (-12.0; -7.0)	-8.0 (-11.0; -5.0)	-10.0 (-15.0; -7.0)	0.342
ΔPocc NAVA level 1.0	-9.5 (-12.0; -7.0)	-9.5 (-12.0; -7.0)	-7.0 (-9.0; -5.0)	-9.5 (-11.0; -6.0)	**0.018**
ΔPocc NAVA level 1.5	-7.0 (-10.0; -5.0)	-7.0 (-10.0; -5.0)	-7.0 (-10.0; -5.0)	-8.5 (-11.0; -5.0)	0.065
ΔPocc NAVA level 2.0	-6.5 (-10.5; -5.0)	-6.5 (-10.5; -5.0)	-6.0 (-9.0; -4.5)	-7.5 (-10.0; -5.0)	0.095
ΔPocc NAVA level 2.5	-5.5 (-7.5; -4.0)	-5.5 (-7.5; -3.5)	-5.0 (-7.0; -3.0)	-7.5 (-12.0; -6.0)	0.052
ΔPocc NAVA level 3.0	-5.0 (-7.0; -4.0)	-4.5 (-7.0; -3.5)	-5.0 (-7.0; -3.5)	-7.0 (-11.0; -4.0)	**0.047**
Pmus, *cmH₂O*					
Pmus NAVA level 0.5	7.5 (5.3; 10.5)	7.1 (5.3; 9.0)	6.0 (3.8; 8.3)	7.5 (5.3; 11.3)	0.442
Pmus NAVA level 1.0	7.1 (5.3; 9.0)	6.8 (5.3; 9.0)	5.3 (3.8; 6.8)	7.1 (4.5; 8.5)	**0.019**
Pmus NAVA level 1.5	6.0 (3.8; 8.3)	5.3 (3.5; 7.5)	5.3 (3.8; 7.5)	6.0 (3.8; 8.3)	0.545

Pmus NAVA level 2.0	5.3 (3.8; 7.5)	4.9 (3.8; 7.5)	4.5 (3.5; 6.8)	5.3 (3.8; 7.5)	0.105
Pmus NAVA level 2.5	5.3 (3.8; 7.5)	4.1 (2.8; 5.5)	3.8 (2.3; 5.3)	5.6 (4.5; 9.0)	0.050
Pmus NAVA level 3.0	3.8 (3.0; 5.3)	3.4 (2.8; 5.3)	3.8 (2.8; 5.3)	5.3 (3.0; 8.3)	**0.047**
DP static, *cmH₂O*					
DP NAVA level 0.5	9.0 (7.0; 11.0)	9.0 (7.0; 11.0)	8.0 (6.0; 11.0)	8.0 (6.0; 11.0)	0.823
DP NAVA level 1.0	9.0 (7.0; 12.5)	9.0 (7.0; 12.5)	8.0 (6.0; 11.0)	11.0 (9.0; 13.0)	0.051
DP NAVA level 1.5	10.0 (7.0; 11.5)	9.0 (7.0; 11.0)	9.0 (7.0; 11.0)	11.5 (8.0; 13.0)	0.074
DP NAVA level 2.0	10.0 (7.0; 12.5)	9.0 (7.0; 11.0)	9.0 (7.0; 11.0)	12.0 (7.0; 14.0)	0.060
DP NAVA level 2.5	10.0 (7.0; 14.0)	9.0 (7.0; 12.0)	9.0 (7.0; 12.0)	14.0 (8.0; 16.0)	**0.044**
DP NAVA level 3.0	10.0 (8.0; 13.0)	9.0 (7.0; 12.0)	9.0 (7.0; 12.0)	14.0 (8.0; 16.0)	**0.040**
ΔPL dynamic, *cmH₂O*					
ΔPL NAVA level 0.5	11.7 (8.1; 18.4)	8.8 (7.8; 19.6)	10.3 (6.1; 13.7)	14.1 (9.0; 20.6)	0.214
ΔPL NAVA level 1.0	12.7 (9.9; 21.4)	10.9 (9.9; 26.4)	10.5 (7.2; 14.9)	17.1 (10.1; 23.7)	0.132
ΔPL NAVA level 1.5	13.4 (9.7; 24.5)	11.5 (9.1; 20.7)	13.0 (9.4; 18.7)	21.9 (12.7; 31.4)	0.058
ΔPL NAVA level 2.0	13.4 (10.3; 27.8)	13.2 (10.1; 23.9)	12.6 (10.3; 18.7)	21.9 (12.2; 30.7)	**0.046**
ΔPL NAVA level 2.5	14.6 (11.3; 30.5)	12.2 (10.6; 25.8)	13.7 (10.5; 23.8)	22.6 (12.2; 30.7)	**0.041**
ΔPL NAVA level 3.0	19.5 (12.8; 33.4)	14.6 (11.3; 25.2)	13.7 (10.5; 26.9)	25.6 (16.4; 36.7)	**0.044**

Abbreviations. Vt/IBW, tidal volume normalized to ideal body weight. NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm. NME, neuromechanical efficiency. ΔPocc, airway pressure deflection generated by the patient's respiratory effort against the occluded airway. Pmus, pressure generated by the respiratory muscles during inspiration. DP, quasi static driving pressure. ΔPL, dynamic transpulmonary driving pressure.

Table 3

Table 3. Arterial blood gas parameters.

Data are expressed as median (interquartile range).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
pH					
pH NAVA level 0.5	7.45 (7.41; 7.49)	7.46 (7.41; 7.49)	7.45 (7.44; 7.48)	7.45 (7.41; 7.49)	0.962
pH NAVA level 2.0	7.46 (7.43; 7.49)	7.46 (7.44; 7.48)	7.46 (7.44; 7.48)	7.46 (7.43; 7.49)	0.978
pH NAVA level 3.0	7.47 (7.44; 7.50)	7.46 (7.44; 7.48)	7.47 (7.45; 7.51)	7.47 (7.43; 7.50)	0.944
$PaCO_2$, *mmHg*					
$PaCO_2$ NAVA level 0.5	41.7 (35.5; 44.7)	44.3 (40.2; 50.4)	41.4 (36.7; 47.0)	39.9 (34.0; 43.9)	0.273
$PaCO_2$ NAVA level 2.0	40.6 (35.2; 43.4)	41.8 (40.4; 45.2)	39.8 (36.6; 42.8)	37.4 (34.4; 43.4)	0.618
$PaCO_2$ NAVA level 3.0	39.9 (34.9; 43.2)	42.9 (38.5; 48.0)	38.6 (35.7; 41.3)	36.9 (33.9; 41.3)	0.736
PaO_2/FiO_2, *mmHg*					
PaO_2/FiO_2 NAVA level 0.5	288.0 (232.5; 343.5)	302.5 (274.0; 330.3)	265.0 (206.8; 345.3)	263.0 (232.5; 336.4)	0.273
PaO_2/FiO_2 NAVA level 2.0	282.0 (226.8; 342.0)	268.3 (219.7; 301.3)	336.8 (250.0; 369.3)	268.3 (212.5; 324.8)	0.520
PaO_2/FiO_2 NAVA level 3.0	285.0 (227.7; 345.0)	300.5 (287.7; 330.3)	272.8 (188.5; 370.0)	285.0 (227.0; 345.0)	0.618

Abbreviations. $PaCO_2$, arterial partial pressure of carbon dioxide. PaO_2 /FiO_2 , ratio of arterial partial pressure of oxygen to fractional inspired oxygen.

Table 4

Table 3. Clinical outcomes.

Data are expressed as mean (standard deviation), number (percentage), or median (interquartile range).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
IMV length, *days*	14 (5; 21)	6 (4; 11)	19 (16; 30)	12 (5; 19)	**0.015**
Successful extubation, *n (%)*	20 (43)	7 (70)	4 (25)	9 (43)	0.085
Reintubation, *n (%)*	7 (15)	2 (20)	2 (13)	3 (14)	0.884
TS, *n (%)*	19 (40)	3 (30)	7 (44)	9 (43)	0.803
NIV, *n (%)*	16 (34)	5 (50)	4 (25)	7 (33)	0.397
HFOT, *n (%)*	26 (55)	6 (60)	6 (38)	14 (67)	0.234
ICU LOS, *days*	17 (7; 28)	8 (6; 15)	23 (17; 34)	15 (6; 25)	**0.029**
ICU survival, *n (%)*	40 (85)	10 (100)	13 (81)	17 (81)	0.330
Hospital LOS, *days*	42 (23)	44 (22)	48 (27)	37 (20)	0.386
Hospital survival, *n (%)*	37 (80)	10 (100)	12 (75)	15 (75)	0.170

Abbreviations. IMV, invasive mechanical ventilation. TS, tracheostomy. NIV, post-extubation non-invasive ventilation. HFOT, post-extubation high-flow oxygen therapy. ICU LOS, ICU length of stay. Hospital LOS, hospital length of stay.

Figure 1

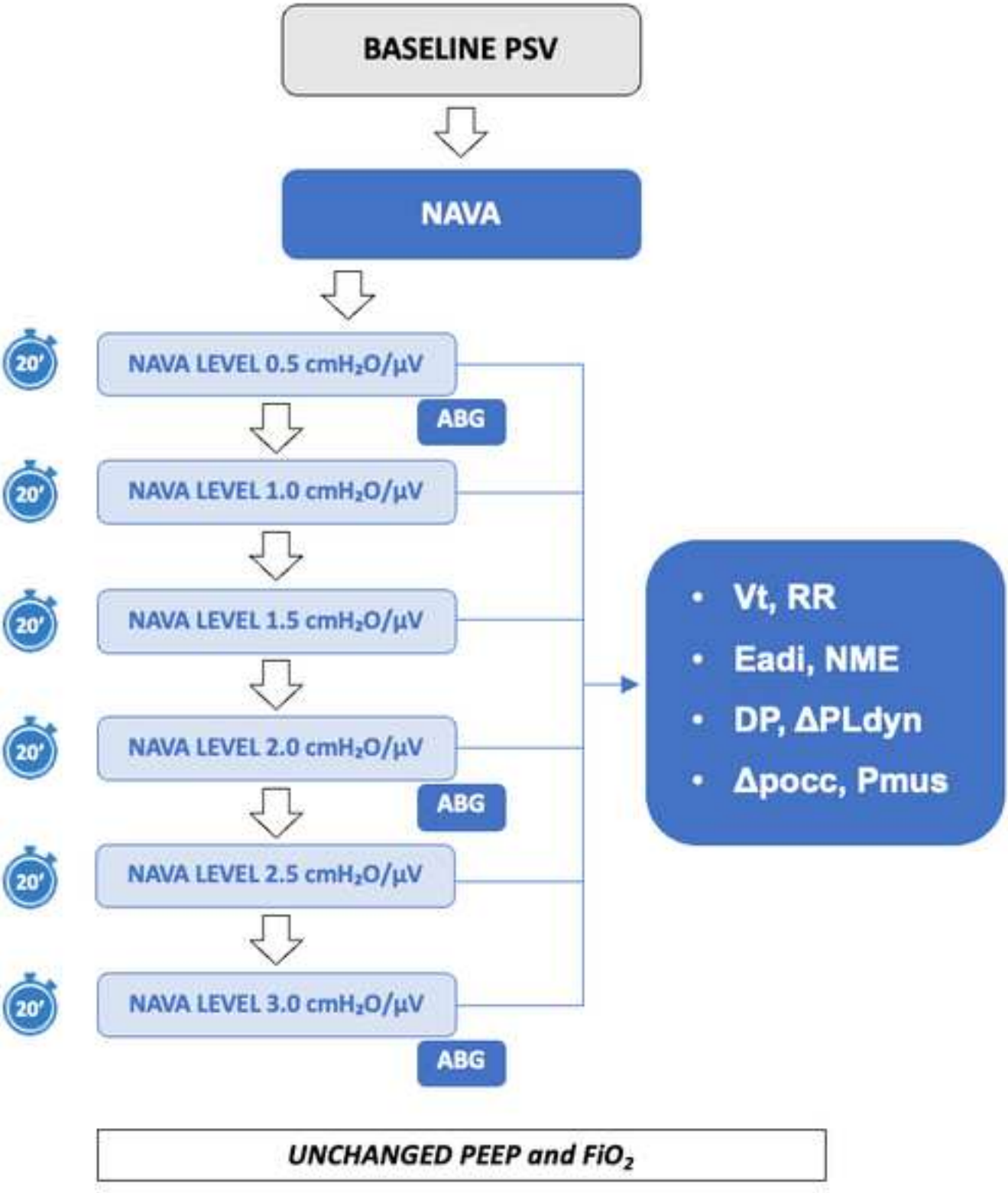


Figure 2A

Click here to access/download;Figure(s);Fig 2A.tiff

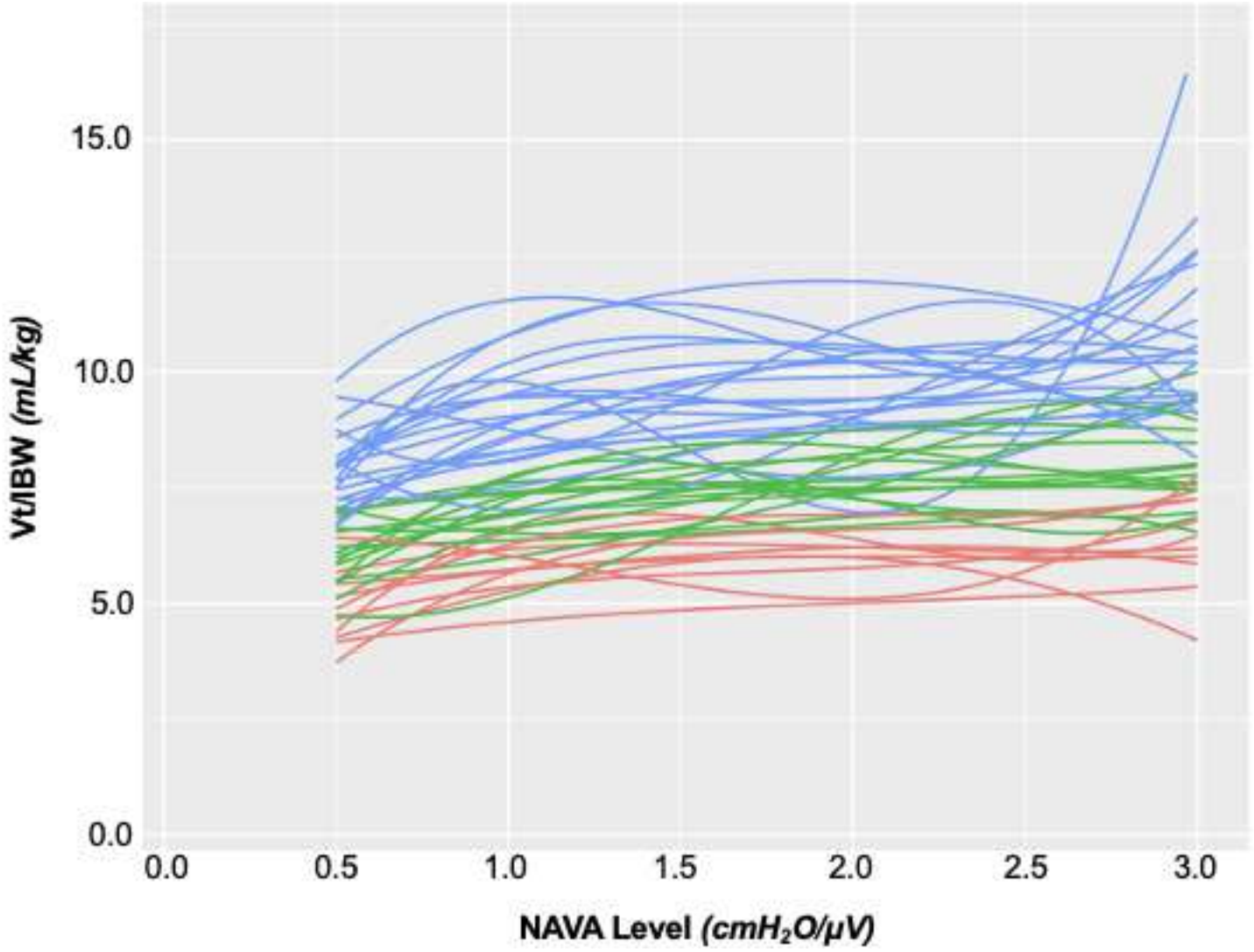


Figure 2B

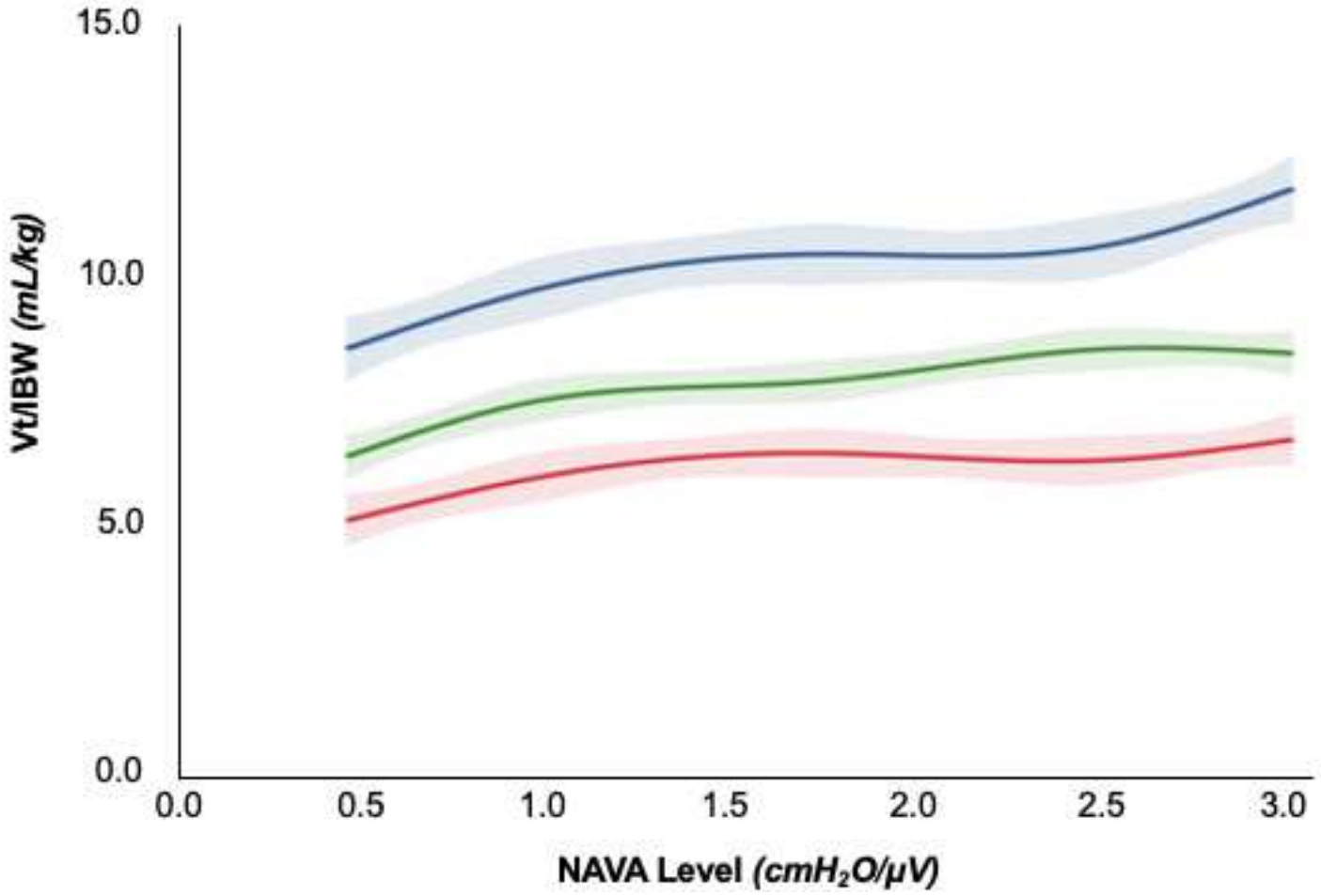


Figure 3A

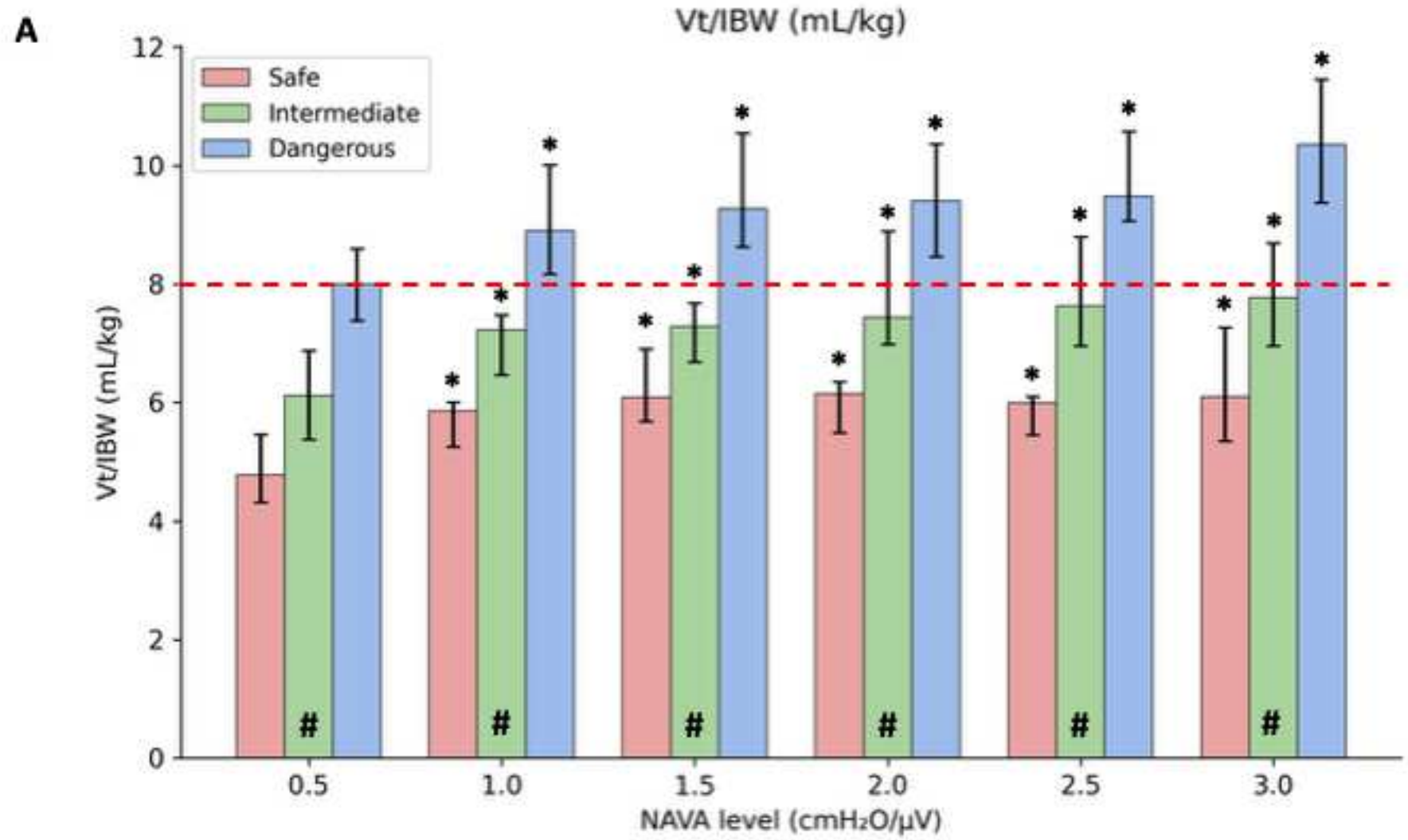


Figure 3B

Click here to access/download;Figure(s);Fig 3B.tiff

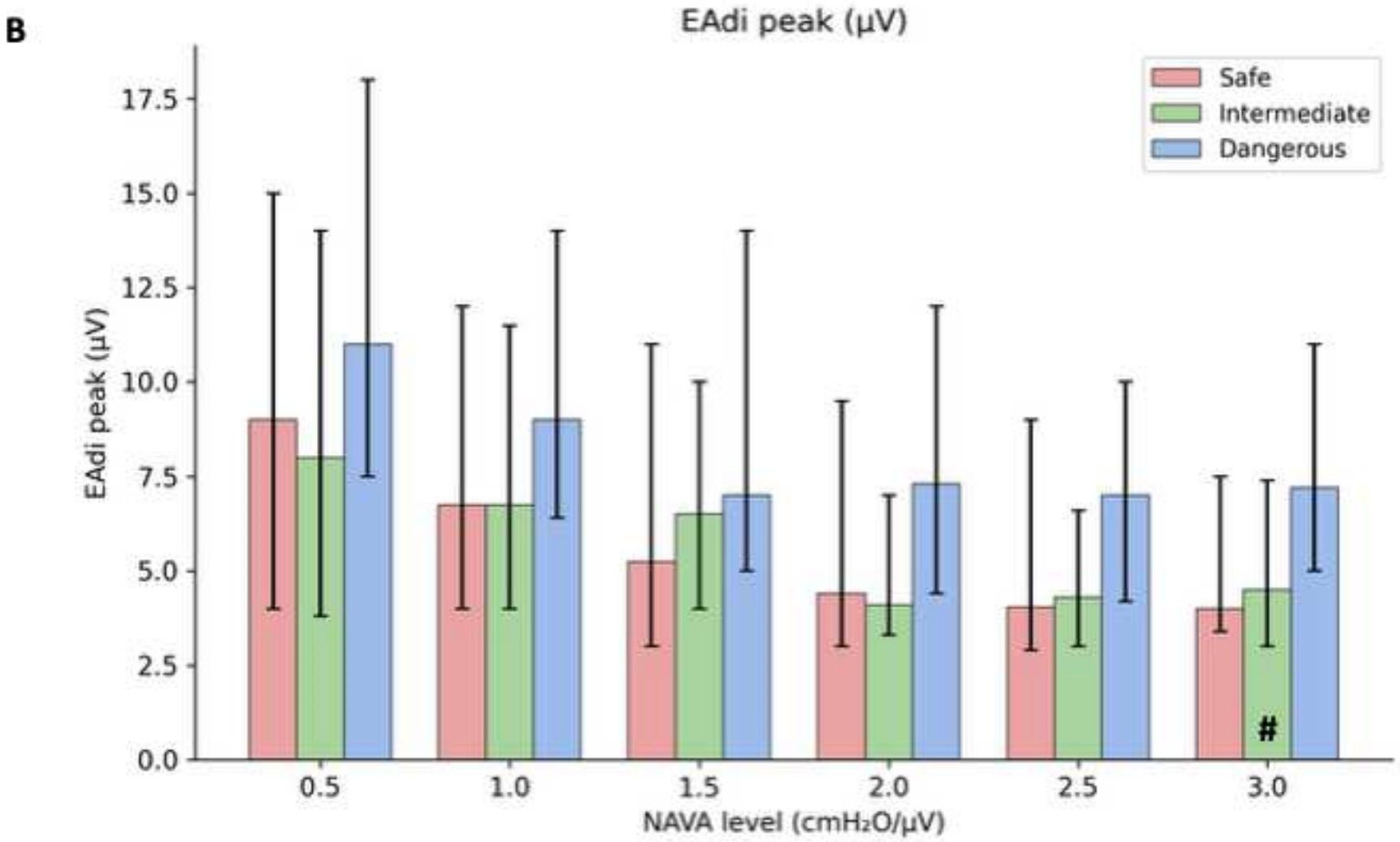


Figure 3C

Click here to access/download;Figure(s);Fig 3C.tiff

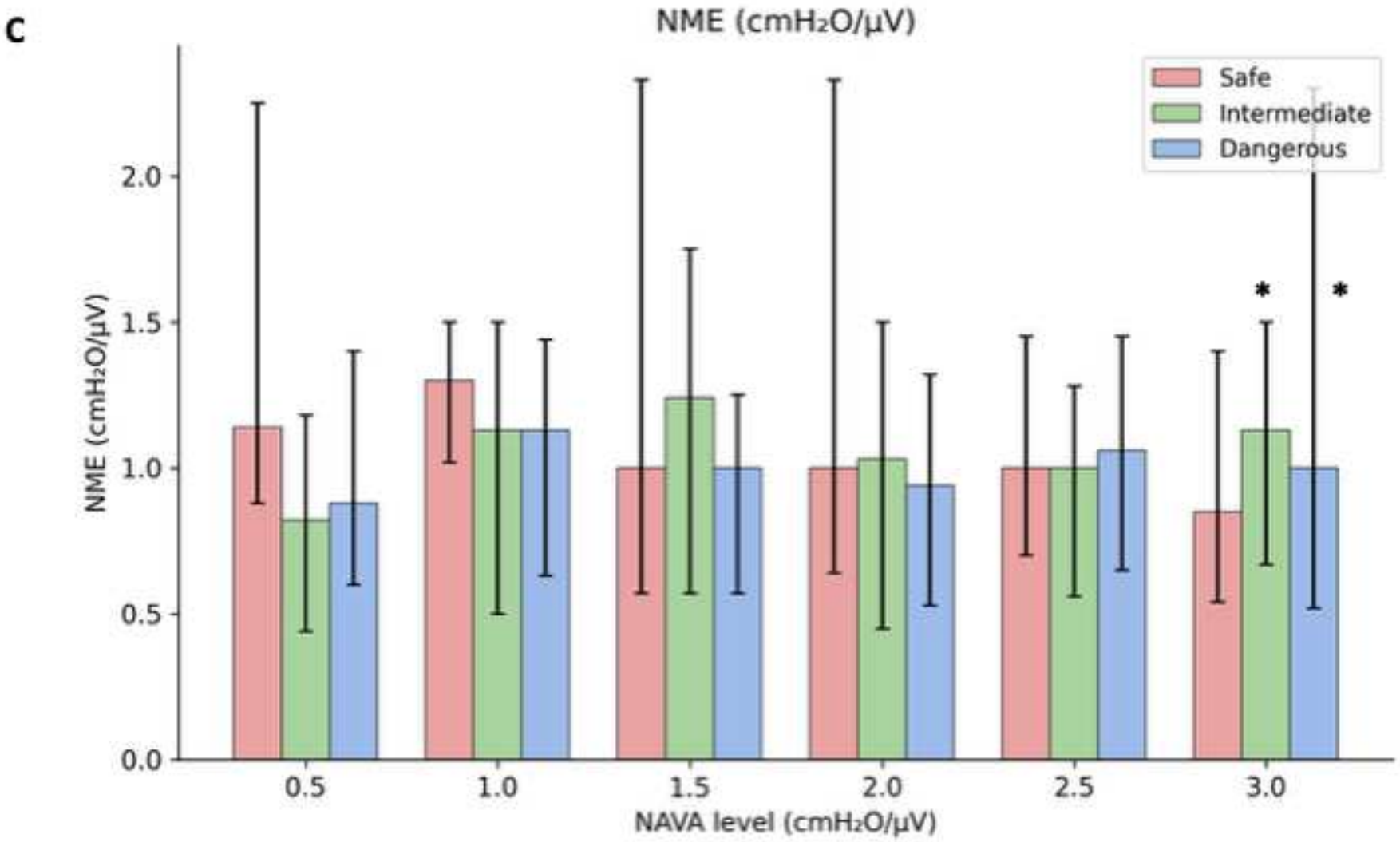


Figure 3D

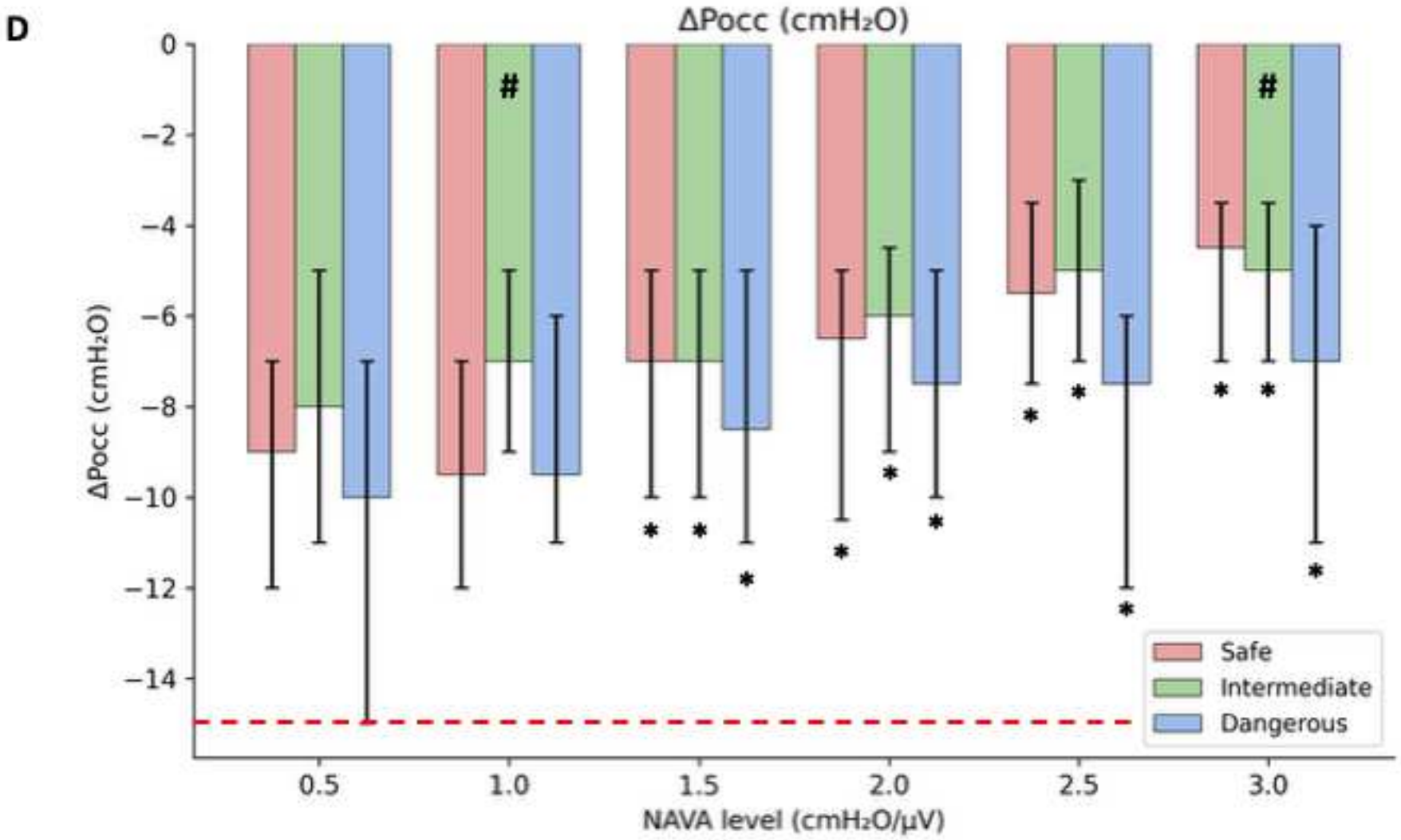


Figure 3E

Click here to access/download;Figure(s);Fig 3E.tiff

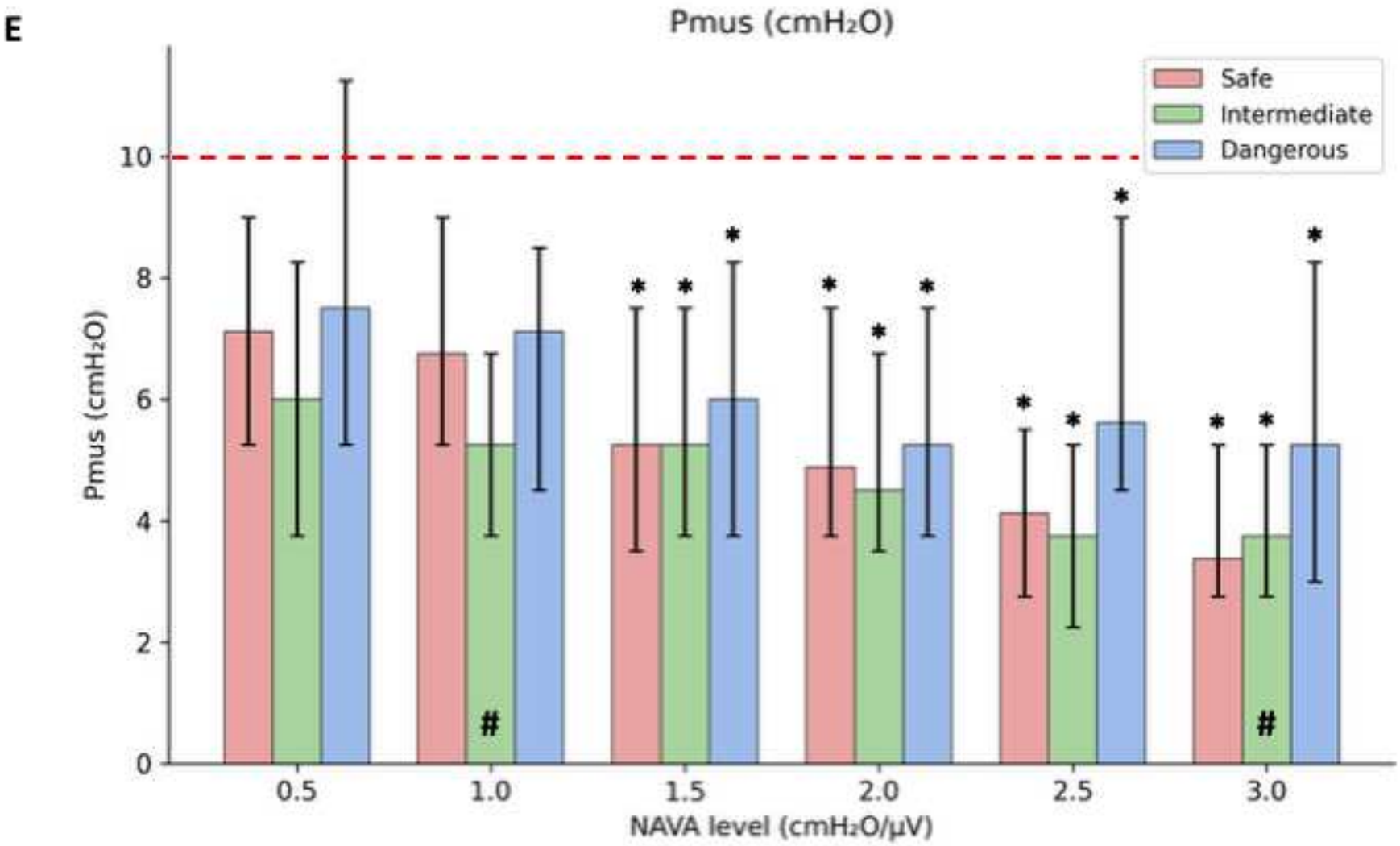


Figure 3F

Click here to access/download;Figure(s);Fig 3F.tiff

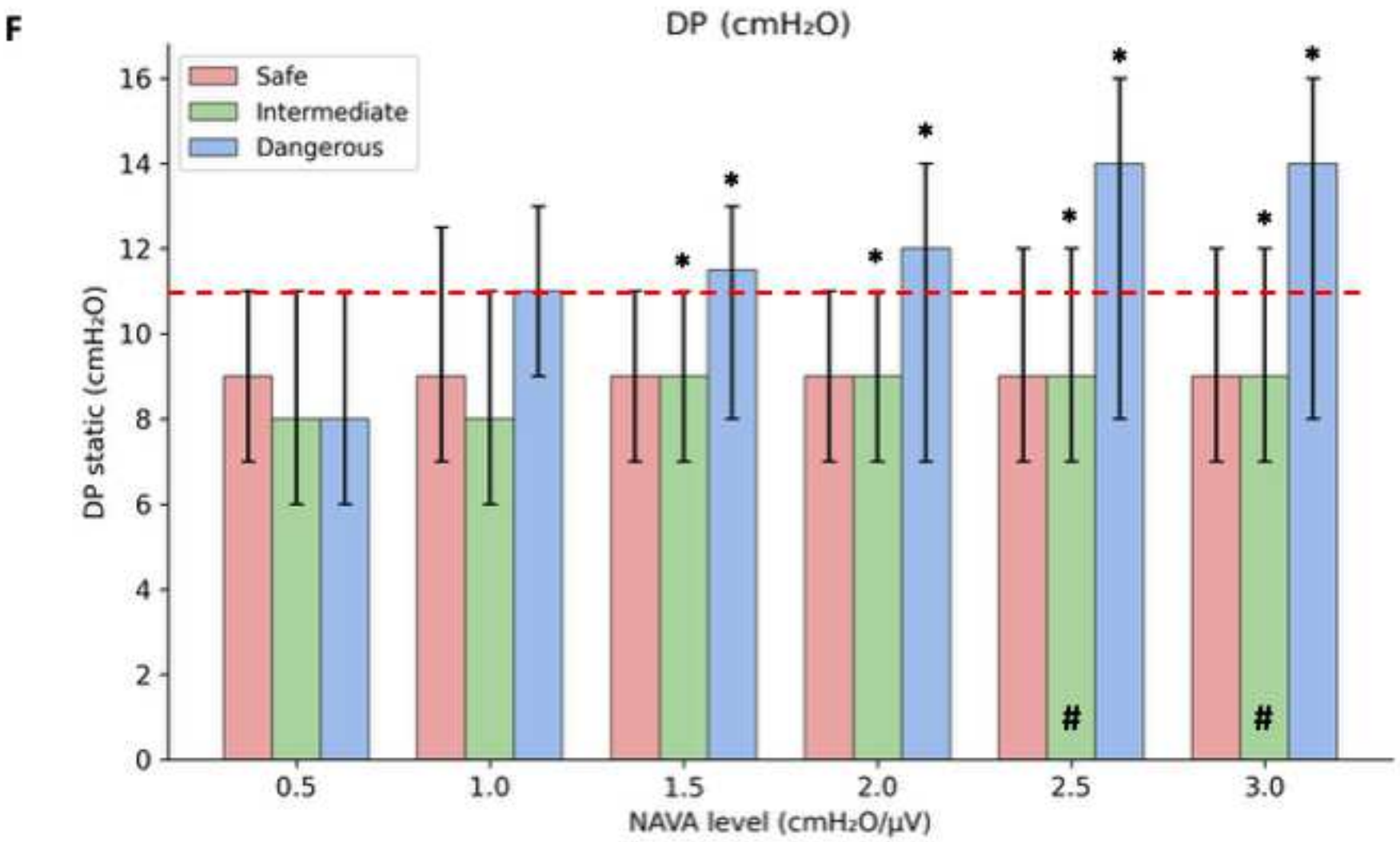
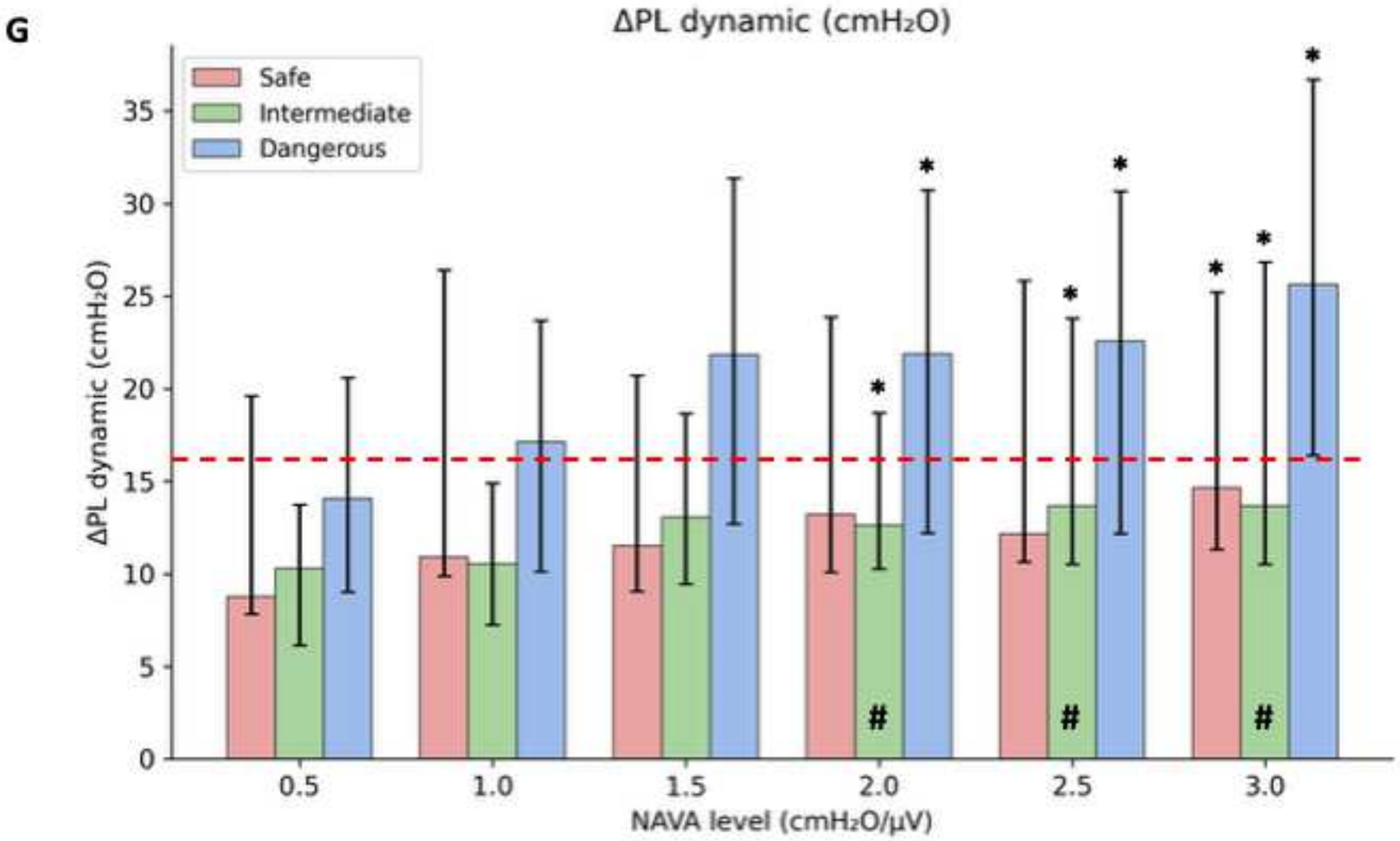


Figure 3G

Click here to access/download;Figure(s);Fig 3G.tiff



Tidal volume response to incremental NAVA levels identifies distinct ventilatory phenotypes associated with potential risk of patient self-inflicted lung injury

SUPPLEMENTARY MATERIAL

Supplementary Table 1. AIC values for model comparison across patients.

Supplementary Table 2. Markers of respiratory drive and effort, and ventilatory and lung injury–related parameters: p-values for difference with the reference value at NAVA level 0.5 $cmH_2O/\mu V$.

Supplementary Table 3. Differences among NAVA level steps of markers of respiratory drive and effort, and ventilatory and lung injury–related parameters.

Supplementary Table 4. Quasi static compliance of the respiratory system.

Supplementary Table 5. Diagnostic performance of tidal volume (Vt/IBW) at increasing NAVA levels for cluster discrimination.

Supplementary Table 1. AIC values for model comparison across patients.

Data are expressed as AIC scores.

	Linear	Quadratic	Cubic	B splines	Exponential	Logarithmic
ID						
1	21,478	18,648	10,892	14,844	15,611	23,944
2	3,850	-0,628	-0,419	-9,172	7,082	-0,410
3	17,764	14,356	16,168	-3,352	19,456	15,675
4	1,710	3,677	-5,646	-22,073	5,461	4,531
5	19,134	1,419	1,969	-21,689	18,596	18,733
6	20,999	20,256	17,189	13,493	21,747	19,802
7	4,750	3,838	3,63	-17,456	5,649	3,570
8	17,774	19,239	17,568	17,426	17,918	17,423
9	35,302	32,777	21,520	23,775	32,174	36,402
10	18,869	18,606	19,769	10,762	20,864	16,822
11	26,875	23,309	21,626	22,388	26,993	26,158
12	5,581	7,398	-3,410	-17,625	5,605	5,2168
13	12,585	9,530	10,958	13,085	9,591	18,274
14	20,025	18,148	20,135	14,250	23,614	17,715
15	5,387	-5,991	-5,128	-7,563	12,883	-5,293
16	4,230	5,794	6,806	-21,477	6,382	3,063
17	5,329	-0,601	-0,165	-13,511	7,444	3,403
18	25,916	27,732	27,351	17,230	26,676	25,463
19	11,858	13,756	15,338	8,023	13,120	11,989
20	2,216	4,182	5,802	7,921	5,570	3,498
21	13,897	14,442	14,734	15,530	13,565	14,108

22	8,243	6,168	6,133	8,752	12,521	3,637
23	22,056	15,003	14,727	-3,226	21,029	22,078
24	23,790	20,657	21,138	22,837	20,353	27,069
25	14,812	14,103	5,783	9,250	19,251	9,879
26	8,983	8,520	10,496	6,259	11,684	16,152
27	-2,085	-1,913	-0,0743	1,420	-2,853	2,392
28	29,601	31,599	32,285	33,533	29,556	29,567
29	-3,237	-4,712	-7,010	-48,417	0,0926	-7,465
30	-5,670	-8,956	-11,859	-11,339	3,347	-14,278
31	15,830	13,911	10,316	-5,695	20,254	10,027
32	16,930	16,467	18,443	14,207	20,089	15,128
33	17,310	5,297	5,872	6,248	22,078	10,392
34	18,364	9,726	-0,236	-12,869	20,683	14,944
35	12,0612	11,843	13,501	15,174	15,242	9,905
36	11,820	6,365	-8,173	-22,245	16,115	5,272
37	10,442	11,989	11,566	-6,828	15,383	12,299
38	23,207	22,268	20,325	15,788	23,320	22,622
39	19,865	18,597	14,012	4,623	14,915	22,424
40	25,171	25,874	21,412	20,467	26,244	24,864
41	19,513	21,013	20,227	13,172	24,101	20,397
42	21,025	20,091	21,874	-3,378	22,881	19,105
43	23,151	20,920	22,510	21,614	23,948	22,068
44	21,383	12,269	11,678	6,540	21,528	20,646
45	21,648	11,583	13,296	9,387	23,225	19,519
46	21,204	13,930	9,931	13,143	19,332	21,679

47	19,379	19,629	18,824	12,934	22,659	16,219
mean AIC	15,113	12,598	10,930	**3,535**	16,659	13,971
Best model for patient, ***n (%)***	1 (2)	3 (6)	5 (11)	**30 (64)**	4 (9)	4 (9)

Abbreviations. AIC, Akaike Information Criterion.

Supplementary Table 2. Markers of respiratory drive and effort, and ventilatory and lung injury–related parameters: p-values for difference with the reference value at NAVA level 0.5 $cmH_2O/\mu V$.

Data are expressed as p-values.

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*
Vt/IBW				
NAVA level 0.5 $cmH_2O/\mu V$	ref	ref	ref	ref
NAVA level 1.0 $cmH_2O/\mu V$	**<0.001**	**0.010**	**0.002**	**0.002**
NAVA level 1.5 $cmH_2O/\mu V$	**<0.001**	**0.027**	**<0.001**	**<0.001**
NAVA level 2.0 $cmH_2O/\mu V$	**<0.001**	**0.016**	**<0.001**	**0.002**
NAVA level 2.5 $cmH_2O/\mu V$	**<0.001**	**0.010**	**<0.001**	**<0.001**
NAVA level 3.0 $cmH_2O/\mu V$	**<0.001**	**0.004**	**<0.001**	**<0.001**
Respiratory rate				
NAVA level 0.5 $cmH_2O/\mu V$	ref	ref	ref	ref
NAVA level 1.0$cmH_2O/\mu V$	0.158	0.098	0.636	0.176
NAVA level 1.5 $cmH_2O/\mu V$	**0.004**	0.594	0.074	**0.025**
NAVA level 2.0 $cmH_2O/\mu V$	**0.011**	0.250	0.057	0.182
NAVA level 2.5 $cmH_2O/\mu V$	**<0.001**	0.105	**0.002**	**0.007**
NAVA level 3.0 $cmH_2O/\mu V$	**<0.001**	**0.039**	**0.018**	**0.009**
EAdi peak				
NAVA level 0.5 $cmH_2O/\mu V$	ref	ref	ref	ref

NAVA level 1.0cmH_2 O/µV	0.273	0.218	0.317	0.401
NAVA level 1.5 cmH_2 O/µV	0.395	0.343	0.289	0.512
NAVA level 2.0 cmH_2 O/µV	0.295	0.260	0.301	0.447
NAVA level 2.5 cmH_2 O/µV	0.693	0.621	0.588	0.742
NAVA level 3.0 cmH_2 O/µV	0.996	0.903	0.851	0.978
NME				
NAVA level 0.5 cmH_2 O/µV	ref	ref	ref	ref
NAVA level 1.0cmH_2 O/µV	0.412	0.508	0.361	0.447
NAVA level 1.5 cmH_2 O/µV	0.221	0.305	0.198	0.276
NAVA level 2.0 cmH_2 O/µV	0.118	0.182	0.104	0.159
NAVA level 2.5 cmH_2 O/µV	0.064	0.055	0.055	0.083
NAVA level 3.0 cmH_2 O/µV	**0.041**	0.072	**0.038**	**0.049**
ΔPocc				
NAVA level 0.5 cmH_2 O/µV	ref	ref	ref	ref
NAVA level 1.0cmH_2 O/µV	0.089	0.131	0.074	0.102
NAVA level 1.5 cmH_2 O/µV	**0.018**	**0.047**	**0.021**	**0.033**
NAVA level 2.0 cmH_2 O/µV	**0.006**	**0.021**	**0.008**	**0.012**
NAVA level 2.5 cmH_2 O/µV	**<0.001**	**0.009**	**0.002**	**0.004**
NAVA level 3.0 cmH_2 O/µV	**<0.001**	**0.004**	**<0.001**	**0.001**
Pmus				
NAVA level 0.5 cmH_2 O/µV	ref	ref	ref	ref
NAVA level 1.0cmH_2 O/µV	0.072	0.131	0.064	0.089

NAVA level 1.5 $cmH_2O/\mu V$	**0.009**	**0.047**	**0.012**	**0.018**
NAVA level 2.0 $cmH_2O/\mu V$	**0.003**	**0.021**	**0.005**	**0.009**
NAVA level 2.5 $cmH_2O/\mu V$	**<0.001**	**0.009**	**0.002**	**0.004**
NAVA level 3.0 $cmH_2O/\mu V$	**<0.001**	**0.004**	**<0.001**	**0.001**
DP static				
NAVA level 0.5 $cmH_2O/\mu V$	ref	ref	ref	ref
NAVA level 1.0$cmH_2O/\mu V$	0.188	0.273	0.159	0.221
NAVA level 1.5 $cmH_2O/\mu V$	**0.042**	0.098	**0.031**	**0.045**
NAVA level 2.0 $cmH_2O/\mu V$	**0.018**	0.074	**0.012**	**0.027**
NAVA level 2.5 $cmH_2O/\mu V$	**0.006**	0.401	**0.004**	**0.009**
NAVA level 3.0 $cmH_2O/\mu V$	**0.002**	0.180	**0.001**	**0.004**
ΔPL dynamic				
NAVA level 0.5 $cmH_2O/\mu V$	ref	ref	ref	ref
NAVA level 1.0$cmH_2O/\mu V$	0.301	0.412	0.276	0.338
NAVA level 1.5 $cmH_2O/\mu V$	0.089	0.159	0.072	0.104
NAVA level 2.0 $cmH_2O/\mu V$	**0.031**	0.098	**0.027**	**0.041**
NAVA level 2.5 $cmH_2O/\mu V$	**0.009**	0.055	**0.006**	**0.012**
NAVA level 3.0 $cmH_2O/\mu V$	**0.003**	**0.021**	**0.002**	**0.006**

Abbreviations. Vt/IBW, tidal volume normalized to ideal body weight. NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm. NME, neuromechanical efficiency. ΔPocc, airway pressure deflection generated by the patient's respiratory effort against the occluded airway. Pmus, pressure generated by the respiratory muscles during inspiration. DP, static driving pressure. ΔPL, dynamic transpulmonary driving pressure. Crs, respiratory system compliance.

Supplementary Table 3. Differences between NAVA level steps of markers of respiratory drive and effort, and ventilatory and lung injury–related parameters.

Data are expressed as median (interquartile range).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
Respiratory rate, *bpm*					
Difference Resp rate 0.5-1	0.0 (-2.0; 1.0)	-1.5 (-3; 0.75)	0.0 (-1.0; 2.0)	-1.1 (-2.0; 0.0)	0.252
Difference Resp rate 1-1.5	-2.0 (-3.0; 1.0)	0.5 (-1.75; 2.75)	-3.0 (-3.25; 0.0)	-1.1 (-3.1; 1.1)	**0.040**
Difference Resp rate 1.5-2	0.0 (-2.0; 2.0)	0 (-1.5; 0.75)	-1.1 (-2.25; 1.25)	0.0(-2.0; 2.0)	0.707
Difference Resp rate 2-2.5	-1.0 (-3.0; 0.0)	-1.5 (-2; -0.25)	-1.5 (-4.25; 1)	-1.0 (-2.0; 0.0)	0.649
Difference Resp rate 2.5-3	0.0 (-1.5; 2.0)	0 (-1; 0.75)	1.5 (-1; 3.25)	-1.0 (-3.0; 1.0)	0.157
Difference Resp rate mean	-0.6 (-0.9; 0.0)	-0.6 (-0.8; -0.1)	-0.7 (-1.45; 0.05)	-0.6 (-0.8; -0.2)	0.893
Difference Resp rate 0.5-3	-3.0 (-4.5; 0.0)	-3.0 (-4.0; -0.5)	-3.5 (-7.25; 0.25)	-3.0 (-4.0; -1.0)	0.893
EAdi peak, *µV*					
Difference EAdi peak 0.5-1	-2.0 (-3.5; -0.4)	-2.0 (-3.5; -0.4)	-1.0 (-2.5; 0.1)	-2.9 (-5.3; -1.0)	0.452
Difference EAdi peak 1-1.5	-1.0 (-2.0; 0.0)	-1.0 (-2.0; -0.5)	-0.1 (-2.0; 0.3)	-1.5 (-3.0; 0.9)	0.395
Difference EAdi peak 1.5-2	-1.0 (-2.0; 0.0)	-1.0 (-1.5; 0.0)	-1.1 (-2.0; 0.1)	-1.0 (-3.0; 0.0)	0.295
Difference EAdi peak 2-2.5	-0.5 (-1.1; 0.4)	-0.1 (-0.9; 0.2)	-0.5 (-1.0; 0.2)	-0.7 (-2.0; 0.6)	0.693
Difference EAdi peak 2.5-3	0.0 (-1.0; 1.0)	-0.1 (-0.7; 1.1)	0.0 (-1.2; 0.8)	0.0 (-1.0; 1.0)	0.996
Difference EAdi mean	-0.9 (-1.6; -0.2)	-1.0 (-1.6; -0.4)	-0.5 (-1.3; 0.0)	-1.0 (-2.2; -0.7)	0.305
Difference EAdi 0.5-3	-4.5 (-8.0; -0.9)	-4.8 (-7.8; -1.8)	-2.5 (-6.8; 0.2)	-5.0 (-10.8; -3.4)	0.305

NME, *cmH_2O / μV*					
Difference NME 0.5-1	0.05 (-0.16; 0.34)	0.05 (-0.05; 0.25)	0.09 (-0.04; 0.49)	0.01 (-0.17; 0.28)	0.752
Difference NME 1-1.5	0.00 (-0.36; 0.29)	-0.31 (-0.42; 0.01)	0.27 (-0.11; 0.87)	-0.01 (-0.35; 0.11)	0.066
Difference NME 1.5-2	0.00 (-0.20; 0.42)	0.21 (0.00; 0.54)	-0.14 (-0.67; 0.00)	0.04 (-0.20; 0.43)	**0.009**
Difference NME 2-2.5	-0.02 (-0.26; 0.17)	-0.15 (-0.26; 0.00)	-0.04 (-0.28; 0.22)	0.00 (-0.22; 0.28)	0.378
Difference NME 2.5-3	0.02 (-0.20; 0.40)	0.03 (-0.38; 0.40)	0.00 (-0.13; 0.14)	0.04 (-0.19; 0.79)	0.668
Difference NME mean	0.02 (-0.05; 0.08)	-0.01 (-0.15; 0.03)	0.03 (-0.06; 0.07)	0.02 (-0.02; 0.21)	0.439
Difference NME 0.5-3	0.09 (-0.25; 0.41)	-0.05 (-0.75; 0.15)	0.15 (-0.32; 0.34)	0.08 (-0.12; 1.03)	0.439
ΔPocc, *cmH2O*					
Difference ΔPocc 0.5-1	1.0 (0.0; 3.0)	0.5 (-1.0; 2.0)	2.0 (0.5; 3.5)	1.0 (-0.3; 2.0)	0.273
Difference ΔPocc 1-1.5	1.0 (-1.0; 3.0)	2.0 (1.0; 5.0)	0.0 (-1.6; 1.0)	1.0 (0.0; 3.0)	**0.028**
Difference ΔPocc 1.5-2	1.0 (-0.8; 2.0)	0.0 (-2.0; 0.6)	1.0 (-1.0; 2.5)	1.0 (0.0; 2.0)	0.315
Difference ΔPocc 2-2.5	0.0 (-1.0; 1.0)	1.5 (0.1; 4.0)	0.0 (-0.5; 0.2)	-1.0 (-3.0; 0.0)	**0.002**
Difference ΔPocc 2.5-3	0.0 (-1.0; 2.0)	-0.7 (-2.0; 1.0)	0.0 (0.0; 1.0)	1.0 (-1.0; 2.0)	0.322
Difference ΔPocc mean	0.8 (0.2; 1.4)	0.7 (0.5; 1.4)	0.7 (0.1; 1.4)	0.8 (0.2; 1.4)	0.787
Difference ΔPocc 0.5-3	4.0 (1.0; 7.0)	3.5 (2.5; 7.0)	3.5 (0.8; 7.0)	4.0 (1.0; 7.0)	0.787
Pmus, *cmH2O*					
Difference Pmus 0.5-1	-0.75 (-2.25; 0.75)	-0.75 (-2.25; 0.75)	-1.50 (-2.25; -0.75)	-0.75 (-1.50; 0.75)	0.273
Difference Pmus 1-1.5	-0.75 (-2.25; 0.75)	-0.75 (-2.25; 0.75)	0.00 (-0.75; 1.50)	-0.75 (-2.25; 0.00)	**0.028**
Difference Pmus 1.5-2	-0.75 (-1.50; 0.75)	-0.75 (-1.50; 0.75)	-0.75 (-1.50; 0.75)	-0.75 (-1.50; 0.00)	0.315
Difference Pmus 2-2.5	0.00 (-0.75; 0.75)	-1.50 (-3.00; 0.00)	0.00 (-0.75; 0.00)	0.75 (0.00; 2.25)	**0.002**
Difference Pmus 2.5-3	0.00 (-1.50; 0.75)	0.75 (-0.75; 1.50)	0.00 (-0.75; 0.00)	-0.75 (-1.50; 0.75)	0.322
Difference Pmus mean	-0.60 (-1.05; -0.15)	-0.52 (-0.98; -0.39)	-0.52 (-1.05; -0.13)	-0.60 (-1.05; -0.15)	0.815

Difference Pmus 0.5-3	-3.00 (-5.25; -0.75)	-2.62 (-4.88; -1.97)	-2.62 (-5.25; -0.66)	-3.00 (-5.25; -0.75)	0.815
DP static, *cmH2O*					
Difference DP 0.5-1	0.0 (-2.0; 2.0)	0.0 (-1.0; 2.0)	-0.5 (-2.0; 1.0)	1.0 (0.0; 2.0)	0.180
Difference DP 1-1.5	0.0 (-1.0; 1.5)	1.0 (0.0; 3.0)	0.0 (-1.0; 0.5)	-1.0 (-2.0; 1.5)	0.188
Difference DP 1.5-2	0.0 (-1.0; 2.0)	0.0 (-2.0; 1.0)	1.5 (0.0; 2.5)	0.0 (-2.0; 2.0)	0.106
Difference DP 2-2.5	0.0 (-2.0; 1,0)	0.0 (-2.0; 0.0)	-0.5 (-1.5; 2.5)	0.0 (-2.0; 2.0)	0.757
Difference DP 2.5-3	0.0 (-1.0; 3.0)	0.7 (-2.0; 4.0)	0.0 (-2.0; 3.5)	0.0 (-1.0; 3.0)	0.718
Difference DP mean	0.2 (0.0; 0.6)	0.2 (0.0; 0.6)	0.0 (-0.3; 0.4)	0.4 (0.0; 0.6)	0.616
Difference DP 0.5-3	1.0 (0.0; 3.0)	1.0 (0.0; 3.0)	0.0 (-1.5; 2.0)	2.0 (0.0; 3.0)	0.616
ΔPL dynamic, *cmH2O*					
Difference ΔPL 0.5-1	1.28 (0.32; 2.87)	1.91 (0.25; 3.17)	1.19 (0.11; 2.46)	2.99 (1.09; 5.01)	0.118
Difference ΔPL 1-1.5	1.42 (0.12; 3.96)	-0.45 (-1.75; 1.89)	2.10 (1.01; 4.83)	3.05 (-0.90; 5.49)	0.119
Difference ΔPL 1.5-2	1.15 (0.00; 2.74)	1.17 (0.35; 3.47)	0.18 (-0.81; 2.12)	1.17 (-3.63; 3.42)	0.612
Difference ΔPL 2-2.5	1.31 (0.14; 3.61)	1.40 (0.30; 3.90)	1.10 (0.00; 3.20)	1.80 (0.20; 4.80)	0.487
Difference ΔPL 2.5-3	2.18 (0.34; 5.92)	2.10 (1.15; 4.66)	2.08 (-0.27; 5.32)	7.63 (-2.50; 13.14)	0.824
Difference ΔPL mean	2.02 (1.14; 3.47)	1.91 (1.05; 3.01)	1.83 (0.98; 2.94)	2.88 (1.67; 4.92)	0.193
Difference ΔPL 0.5-3	5.96 (2.85; 12.58)	5.33 (3.14; 12.66)	5.08 (3.35; 9.39)	7.69 (4.37; 20.88)	0.278

Abbreviations. Vt/IBW, tidal volume normalized to ideal body weight. NAVA, neurally adjusted ventilatory assist. EAdi, electrical activity of the diaphragm. NME, neuromechanical efficiency. ΔPocc, airway pressure deflection generated by the patient's respiratory effort against the occluded airway. Pmus, pressure generated by the respiratory muscles during inspiration. DP, static driving pressure. ΔPL, dynamic transpulmonary driving pressure.

Supplementary Table 4. Quasi static compliance of the respiratory system at increasing NAVA levels.

Data are presented as median (interquartile range), or p-values. Quasi static compliance of the respiratory system was calculated with a stable positive end-expiratory pressure and zero-flow at end inspiration as the ratio of tidal volume to quasi static driving pressure (i.e., the difference between plateau pressure at end-inspiratory pause and total positive end expiratory pressure).

	Overall Population *(n = 47)*	**Safe Response** *(n = 10)*	**Intermediate Response** *(n = 16)*	**Dangerous Response** *(n = 21)*	p-value
Crs, mL/cmH_2 O					
Crs NAVA level 0.5	44.2 (34.3; 60.0)	50.0 (40.0; 95.7)	42.3 (33.7; 56.9)	35.6 (28.2; 44.8)	**0.041**
Crs NAVA level 1.0	50.9 (39.5; 64.4)	55.1 (40.4; 73.1)	52.7 (44.3; 66.5)	39.5 (31.5; 60.7)	0.263
Crs NAVA level 1.5	55.0 (40.1; 75.8)	61.1 (50.0; 80.0)	56.5 (46.2; 78.3)	36.2 (31.7; 59.8)	0.081
Crs NAVA level 2.0	53.3 (33.9; 79.5)	68.0 (42.7; 88.6)	53.7 (41.0; 66.4)	36.1 (31.5; 41.8)	0.082
Crs NAVA level 2.5	58.3 (38.3; 79.7)	63.3 (45.0; 85.0)	62.3 (36.1; 68.7)	39.4 (36.7; 71.29	0.382
Crs NAVA level 3.0	55.0 (37.1; 70.29	64.7 (48.0; 88.5)	55.2 (43.3; 71.0)	37.1 (32.5; 38.3)	**0.037**
p-values for difference with the reference value at NAVA level 0.5 cmH_2 O/µV					
NAVA level 0.5 cmH_2 O/µV	ref	ref	ref	ref	\
NAVA level 1.0cmH_2 O/µV	**0.049**	**0.010**	**0.023**	0.708	\
NAVA level 1.5 cmH_2 O/µV	**0.011**	0.322	**0.016**	0.279	\
NAVA level 2.0 cmH_2 O/µV	0.567	0.432	0.144	0.562	\
NAVA level 2.5 cmH_2 O/µV	**0.026**	0.160	0.083	0.562	\
NAVA level 3.0 cmH_2 O/µV	0.070	0.160	0.052	0.865	\
Differences between NAVA level steps					
mL/cmH_2 O					

Difference Crs 0.5-1	4.0 (−3.0; 18.4)	5.8 (4.3; 14.9)	6.9 (−0.4; 15.8)	−2.1 (−14.3; 19.1)	0.126
Difference Crs 1-1.5	1.0 (−5.0; 12.2)	−1.2 (−16.5; 0.7)	1.0 (−3.7; 8.1)	4.4 (−5.8; 13.6)	0.340
Difference Crs 1.5-2	−1.0 (−13.6; 5.8)	1.4 (−1.8; 4.7)	−5.5 (−10.4; 2.5)	−0.8 (−15.3; 7.0)	0.475
Difference Crs 2-2.5	2.8 (−3.7; 14.8)	2.1 (−0.3; 22.0)	2.7 (−12.5; 9.6)	2.8 (−9.4; 15.5)	0.678
Difference Crs 2.5-3	0.0 (−13.2; 10.4)	−3.0 (−33.9; 4.4)	−1.0 (−4.4; 12.5)	3.3 (−16.3; 9.6)	0.450
Difference Crs mean	5.8 (4.5; 7.4)	4.6 (3.7; 5.0)	5.7 (4.7; 7.9)	6.4 (4.4; 7.0)	0.076
Difference Crs 0.5-3	5.0 (−5.2; 20.9)	2.3 (0.1; 7.5)	10.2 (−4.7; 22.8)	4.2 (−12.7; 21.1)	0.656

Abbreviations. Crs, quasi static respiratory system compliance. NAVA, neurally adjusted ventilatory assist.

Supplementary Table 5. Diagnostic performance of tidal volume (Vt/IBW) at increasing NAVA levels for cluster discrimination.

Data are presented as areas under the receiver operating characteristic curve (AUC) (95% confidence intervals), calculated using bootstrap resampling. AUC values reflect the ability of Vt/IBW at each NAVA level to discriminate each cluster using a one-versus-rest approach. Ordinal AUC represents the mean pairwise discrimination across ordered clusters (low to high risk).

NAVA level	Cluster	AUC ROC curve	Sensitivity	Specificity
0.5 $cmH_2O/\mu V$	Safe Response	0.930 (0.830–0.988)	0.9	0.87
	Intermediate Response	0.710 (0.527–0.837)	1.0	0.61
	Dangerous Response	0.982 (0.944–1.000)	0.91	1.0
	Ordinal	0.936 (0.863–0.991)	/	/
1.0 $cmH_2O/\mu V$	Safe Response	0.978 (0.926–1.000)	1.0	0.95
	Intermediate Response	0.637 (0.474–0.796)	0.94	0.55
	Dangerous Response	0.949 (0.875–0.990)	0.91	0.89
	Ordinal	0.956 (0.885–0.997)	/	/
1.5 $cmH_2O/\mu V$	Safe Response	0.949 (0.863–1.000)	0.9	0.89
	Intermediate Response	0.696 (0.527–0.853)	1.0	0.61
	Dangerous Response	0.982 (0.938–1.000)	0.95	0.96
	Ordinal	0.952 (0.860–1.000)	/	/
2.0 $cmH_2O/\mu V$	Safe Response	0.995 (0.976–1.000)	1.0	0.95
	Intermediate Response	0.617 (0.458–0.778)	0.81	0.61
	Dangerous Response	0.941 (0.869–0.988)	0.91	0.89
	Ordinal	0.964 (0.917–0.992)	/	/

2.5 $cmH_2O/\mu V$	Safe Response	0.984 (0.940–1.000)	0.9	0.97
	Intermediate Response	0.633 (0.494–0.802)	0.88	0.58
	Dangerous Response	0.949 (0.873–0.994)	0.86	0.92
	Ordinal	0.960 (0.889–0.994)	/	/
3.0 $cmH_2O/\mu V$	Safe Response	0.946 (0.862–0.996)	1.0	0.78
	Intermediate Response	0.688 (0.531–0.821)	0.88	0.65
	Dangerous Response	0.973 (0.925–1.000)	0.95	0.92
	Ordinal	0.943 (0.857–0.996)	/	/

Abbreviations. NAVA, neurally adjusted ventilatory assist. AUC, area under the curve. ROC, receiver operating characteristic.