



# Mechanical power normalized to aerated lung predicts noninvasive ventilation failure and death and contributes to the benefits of proning in COVID-19 hypoxemic respiratory failure

Giovanni Musso<sup>1</sup> · Claudio Taliano<sup>2</sup> · Marco De Iulii<sup>3</sup> · Elena Paschetta<sup>2</sup> · Caterina Fonti<sup>1</sup> · Andrea Ferraris<sup>3</sup> · Marta Druetta<sup>2</sup> · Ines Sarah Vianou<sup>2</sup> · Francesca Raghino<sup>2</sup> · Federica Riedo<sup>2</sup> · Davide Deangelis<sup>2</sup> · Gloria Tirabassi<sup>4</sup>

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## Abstract

**Background** Concern exists that noninvasive ventilation (NIV) may promote ventilation-induced lung injury (VILI) and worsen outcome in acute hypoxemic respiratory failure (AHRF). Different individual ventilatory variables have been proposed to predict clinical outcomes, with inconsistent results.

Mechanical power (MP), a measure of the energy transfer rate from the ventilator to the respiratory system during mechanical ventilation, might provide solutions for this issue in the framework of predictive, preventive and personalized medicine (PPPM). We explored (1) the impact of ventilator-delivered MP normalized to well-aerated lung ( $MP_{WAL}$ ) on physiological and clinical responses to NIV in COVID-19-related AHRF and (2) the effect of prone position (PP) on  $MP_{WAL}$ .

**Methods** We analyzed 216 noninvasively ventilated COVID-19 patients (108 patients receiving PP + NIV and 108 propensity score-matched patients receiving supine NIV) with moderate-to-severe ( $paO_2/FiO_2$  ratio < 200) AHRF enrolled in the PRO-NIV controlled non-randomized study (ISRCTN23016116).

Quantification of differentially aerated lung volumes by lung ultrasonography (LUS) was validated against CT scans. Respiratory parameters were hourly recorded, ABG were performed 1 h after each postural change. Time-weighted average values of ventilatory variables, including  $MP_{WAL}$ , and gas exchange parameters ( $paO_2/FiO_2$  ratio, dead space indices) were calculated for each ventilatory session. LUS and circulating biomarkers were assessed daily.

**Results** Compared with supine position, PP was associated with a 34%  $MP_{WAL}$  reduction, attributable largely to an absolute MP reduction and secondly to an enhanced lung re-aeration.

Patients receiving a high  $MP_{WAL}$  during the 1<sup>st</sup> 24 h of NIV [ $MP_{WAL}(\text{day 1})$ ] had higher 28-d NIV failure (HR = 4.33, 95% CI: 3.09–5.98) and death (HR = 5.17, 95% CI: 3.01–7.35) risks than those receiving a low  $MP_{WAL}(\text{day 1})$ . In Cox multivariate analyses,  $MP_{WAL}(\text{day 1})$  remained independently associated with 28-d NIV failure (HR = 1.68, 95% CI: 1.15–2.41) and death (HR = 1.69, 95% CI: 1.22–2.32).

$MP_{WAL}(\text{day 1})$  outperformed other power measures and ventilatory variables as predictor of 28-d NIV failure (AUROC = 0.89; 95% CI: 0.85–0.93) and death (AUROC = 0.89; 95% CI: 0.85–0.94).

$MP_{WAL}(\text{day 1})$  predicted also gas exchange, ultrasonographic and inflammatory biomarker responses, as markers of VILI, on linear multivariate analysis.

**Conclusions** In the framework of PPPM, early bedside  $MP_{WAL}$  calculation may provide added value to predict response to NIV and guide subsequent therapeutic choices i.e. prone position adoption during NIV or upgrading to invasive ventilation, to reduce hazardous  $MP_{WAL}$  delivery, prevent VILI progression and improve clinical outcomes in COVID-19-related AHRF.

**Keywords** Predictive preventive personalized medicine (PPPM / 3PM) · COVID-19 · Hypoxemic respiratory failure · Individual outcomes · Differentially aerated lung volume · Predictive model · Noninvasive ventilation · Therapeutic choice · Lung ultrasound · Mechanical power · Well-aerated lung · Prone position

## Introduction

### The unmet need for accurate early predictors of treatment failure and death during noninvasive ventilation (NIV)

NIV is being increasingly used as first-line ventilatory support in de novo (i.e., not due to exacerbation of chronic lung disease or cardiac failure) acute hypoxemic respiratory failure (AHRF). However, concern has been raised that mechanical ventilation may exacerbate lung injury (i.e., ventilation-induced lung injury, VILI) and worsen outcome in spontaneously breathing patients with AHRF [1]. Different ventilatory variables have been proposed to contribute to VILI progression, including high tidal volume [2], minute ventilation [3] and inspiratory effort [4]: these parameters have been separately addressed in clinical studies, but data in noninvasively ventilated patients are scarce, inconsistent and inconclusive, at least in part due to the difficulty in controlling and monitoring time-varying individual ventilatory parameters in spontaneously breathing patients.

### Potential contribution of Mechanical Power (MP) to clinical prediction in the framework of PPPM

Predictive, Preventive, and Personalized Medicine (PPPM) is an effective integrative approach, which has been promoted by the European Association for Predictive, Preventive and Personalized Medicine (EPMA, <http://www.epmanet.eu/>) [5]. It contains three aspects: individual predisposition prediction, targeted preventive measures and personalized treatment algorithms [6].

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In recent years, a unifying patho-physiological theory, based on thermodynamic principles, has been proposed to underlie VILI: this theory attributes lung injury to the energy transfer from the ventilator to the pulmonary parenchyma, with energy dissipation within the lungs leading to heat production, cell integrity and extracellular matrix disruption, and inflammatory cell recruitment [7–9]. Consistently, mechanical power (MP), a measure of the energy transfer rate from the ventilator to the respiratory system, predicted mortality in invasively ventilated ARDS patients, irrespective of the combination of each ventilatory component [10–13].

Whether the energy delivered to the respiratory system during noninvasive ventilation (NIV) affects clinical outcomes in AHRF is unexplored. During COVID-19 pandemic, NIV intensity and duration were linked to an increased mortality in COVID-19-related AHRF [14–16],

but no individual ventilatory parameter, including respiratory drive and inspiratory effort, was able to predict clinical outcomes [17–20]. Furthermore, clinical benefits from awake prone position (PP) during NIV have been reported by several, but not all studies, through still unclear mechanisms [21, 22].

### Working hypothesis

We hypothesized the energy delivered by noninvasive ventilatory assistance to the respiratory system could contribute to physio-anatomical and clinical responses to NIV in Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) pneumonia-related AHRF, and that the clinical benefits of awake PP in these patients could be at least in part mediated by a reduced MP delivery during prone NIV. We therefore investigated:

- 1) the effect of prone position (PP) on different measures of MP during NIV.
- 2) the contribution of MP measures delivered early during either supine or prone NIV to physio-anatomical and clinical outcomes in COVID-19 pneumonia

### Methods

In this secondary analysis of the non-randomized, controlled Prone position in NonInvasive Ventilation (PRO-NIV) study (study ID: ISRCTN23016116) [23], we studied 216 SARS-CoV-2 pneumonia patients with acute (i.e. symptom onset < 14 days of hospital admission) moderate-to-severe AHRF (paO<sub>2</sub>/FiO<sub>2</sub> ratio < 200 mmHg while on a FiO<sub>2</sub> 50% Venturi mask or a non-rebreather reservoir bag mask): 108 patients treated with NIV (CPAP or PSV) plus early PP and 108 matched controls treated with supine NIV) at HUMANITAS Gradenigo COVID Subintensive Care Unit between June 1st 2020 and June 30th 2021.

In both groups, NIV was initiated within 24 h of admission to Subintensive Care Unit and delivered continuously for ≥ 48 h or until discharge or death; full-face mask was the initial interface of choice. PP was initiated within 24 h of admission in the PP group. NIV and PP duration, equipment, settings, standard care, monitoring, treatment failure criteria were protocolized a priori before patients enrollment (see supplementary text, Supplementary Fig. 1, Supplementary Table 1) [23].

### Measurements

**Respiratory parameters** NIV duration, posture, ventilatory settings and parameters (spO<sub>2</sub>, RR, VTe, MV) were continuously monitored and recorded on an hourly basis on a predefined form.

ABGs were performed during NIV, every 24 h and  $\geq 1$  h after each postural change, after achievement of ventilatory stability (defined by a  $\leq 10\%$  variation in RR and VTe and air leaks  $< 10\%$  for  $\geq 30$  min).

The following gas exchange parameters were calculated from ABG:  $\text{paO}_2/\text{FiO}_2$  ratio and dead space indices (DSIs) [Ventilatory Ratio (VR) and corrected Minute Ventilation ( $\text{MV}_{\text{corr}}$ )].

The energy delivered by ventilatory assistance to respiratory system per time unit (mechanical power, MP) was estimated via Becher formula [24], which was already evaluated in noninvasively ventilated patients and was recommended to improve noninvasive ventilatory support monitoring in COVID-19 pneumonia [14, 25]. In this formula,  $\Delta\text{Pinsp}$  was replaced by  $\Delta\text{Paw}$  (airway pressure over PEEP) to reflect the energy imparted by ventilator during inspiration [1, 26].

Since NIV is a dynamic process, to reflect the power delivered during the entire ventilatory sessions, time weighted-average of hourly MP values during each NIV session (supine/prone) was calculated as the area under the parameter-versus-time plot (detailed in supplementary text) [27]. The same procedure was followed to calculate time weighted-average values of RR, VTe, and MV for each ventilator session and for each day.

For MV, we also planned to verify consistency between time-averaged values and those obtained at the time of ABGs, which were used to calculate DSIs.

The primary exposure variable of interest was MP normalized by the volume of well-aerated lung ( $\text{MP}_{\text{WAL}}$ ), to reflect the “intensity” of the power, i.e., the volume of well-aerated lung exposed to energy load during mechanical ventilation, during the 1<sup>st</sup> 24 h of NIV [ $\text{MP}_{\text{WAL}}$  (day 1)].

We also normalized MP by predicted body weight ( $\text{MP}_{\text{PBW}}$ ) to account for individual lung size variation.

**Lung imaging** All patients underwent a lung CT scan on admission: the nature and extent of parenchymal involvement were scored using a validated index [28] and the volume of well-aerated lung (WAL), of poorly aerated lung (PAL) and of non-aerated lung (NAL) were quantified on CT scans via a validated open-source software (3D Slicer ver.4.13.2) (see supplementary text) [29].

Lung ultrasound was performed daily from admission (day 0) to day 7 by three intensivists with expertise in lung and cardiac recording and interpretation (each operator having performed at least 50 supervised procedures and at least 200 non-supervised procedures) [30] using the same equipment (HM70A Samsung, Seoul, Korea), the same convex-array probe and the same setting.

The accuracy of ultrasound examinations in staging lung disease severity was preliminarily evaluated at baseline against the CT scan (double-blinded operators, LUS performed within 24 h of CT examination).

The severity and extent of parenchymal involvement of each of 6 lung regions (2 anterior, 2 lateral, 2 dorsal) were scored (range 0–3) [31] and recorded on a predefined form and the following indices were calculated (supplementary text):

- regional and global lung ultrasound score (LUS);
- regional and global LUS reaeration score, a validated index of lung recruitment (i.e., change from consolidated, non-aerated tissue to aerated tissue) [32, 33];
- additionally, using software-based lung parenchyma segmentation and analysis function [29], each lung was divided into six areas to mirror as much as possible the regions explored by ultrasound, and regional and global LUS-derived WAL volume (i.e. lung volume with LUS score 0–1), PAL (i.e. lung volume with LUS score 2) and NAL (i.e. lung volume with LUS score 3) were derived from admitting LUS scan examinations as previously described in ARDS [34]. Global LUS-derived WAL volume, a predictor of COVID-19 pneumonia outcome [24], was then calculated from daily LUS scans through day 0–7 (detailed in supplementary text).

The agreement between regional LUS score and regional CT classification was assessed with Cohen’s kappa coefficient, and the association between regional CT-derived gas/tissue content and regional LUS categories was assessed by simple linear regression and Spearman’s rank correlation ( $r_s$ ).

Details on full derivations are provided in supplementary text.

The PEEP at which each LUS examination was made was recorded.

- Circulating biomarkers: eighteen circulating inflammatory and procoagulative biomarkers were measured daily from admission to discharge or death [35].

## Definitions and timepoints

We adopted the following definitions:

- **day 0 (baseline)**: the time of NIV initiation;
- **day 1**: first 24 h after NIV initiation;
- **day 7**: day 7 after NIV initiation;
- **timepoint sp0**: supine position. In PP group, the session preceded the first PP session. ABG was performed  $\geq 1$  h after supine NIV initiation, after achieving ventilatory stability;
- **timepoint pp1**: first PP session in PP group. ABG was performed  $\geq 1$  h after prone NIV initiation, after achieving ventilatory stability;

- **timepoint sp1**: supine position; ABG was performed  $\geq 1$  h after resupination following the first PP session in the PP group and 24 h after NIV initiation in the supine group, after achieving ventilatory stability;

This schedule allowed comparing all groups in the supine position, after 24 h of NIV, while taking into account the effect of the first PP session (pp1) in the PP group.

Further definitions are provided in legends to Table 1 and in a study scheme (Supplementary Fig. 1).

## Outcomes

Primary outcomes were the occurrence of.

- NIV failure within 28 days of enrolment, defined as intubation OR death;
- death, censored at 28 days after enrollment.

Secondary outcomes were:

- endotracheal intubation (ETI) at 28 days (after excluding patients with a do-not-intubate, DNI, order);
- 60-day death
- O<sub>2</sub>-response:  $\text{paO}_2/\text{FiO}_2_{\text{sp1}} - \text{paO}_2/\text{FiO}_2_{\text{sp0}}$  (or  $\Delta\text{paO}_2/\text{FiO}_2_{\text{sp0-1}}$ ).
- CO<sub>2</sub>-response:  $\Delta\text{VR}_{\text{sp0-1}}$ ;
- C-reactive protein (CRP) response:  $\Delta\text{CRP}_{0-1}$ ;
- global LUS response at day 1:  $\Delta\text{global LUS}_{0-1}$ ;
- global reoxygenation score at day 1: global reoxygenation score<sub>1</sub>;
- change in LUS- assessed WAL (%) at day 1 ( $\Delta\text{WAL}_{0-1}$ )

## Statistical analyses

### Sample size calculation and propensity score (PS)-matching of PP and supine group.

Sample size calculation and PS-matching of PP and supine groups for relevant baseline covariates are detailed in supplementary text.

**Descriptive statistics** Data are given as median (IQR) or n (%) as appropriate.

We used chi-square test or Fisher's exact test for categorical variables, *T*-Test for normally distributed and Kruskal–Wallis test for non-normal continuous variables.

Time change in continuous variables was assessed by computing the AUC with the trapezoid method [36].

Repeated measures two-factor (within subject and between group) ANOVA was used to compare continuous variables assessed at multiple timepoints (i.e., respiratory and biochemical parameters), after log-transformation of non-normal variables.

To explore the effect of early  $\text{MP}_{\text{WAL}}$  delivery on clinical outcomes, the whole cohort was split into 2 groups according to median  $\text{MP}_{\text{WAL}}$  values at day 1. The probability of 28-day NIV failure, death and ETI in low vs high  $\text{MP}_{\text{WAL}}$  group at day 1 was compared using Kaplan–Meier procedure and log-rank test. Data were analyzed on an intention-to-treat basis.

Beside categorizing patients into low/high  $\text{MP}_{\text{WAL}}$ , we explored dose–response relationship between early power delivery and clinical outcomes by dividing the entire cohort into quartiles of power measures at day 1. Comparison between quartiles was made by ANOVA with post-hoc comparison from the first quartile performed using the Tukey test. We planned to assess also reciprocal relationship between  $\text{MP}$ ,  $\text{MP}_{\text{PBW}}$  and  $\text{MP}_{\text{WAL}}$  at day 1 by univariate analysis and Spearman correlation coefficient ( $r_s$ ).

Multivariable Cox proportional regression analysis adjusting for imbalanced covariates between groups was used to assess the effect of confounders on 28-d NIV failure, death and ETI in the whole cohort, with the maximum number of covariates allowed in each model set at (event rate  $\times N$ )/10, where *N* is the sample size [37]. The allocation assignment (PP or supine) was entered as a predefined covariate into the models. Calendar month of admission was forced into all models to account for unmeasured temporal disease trends during the pandemic.

Anticipating high collinearity between ventilatory variables, in all (Cox and linear) multivariable models we used a combination of backward procedure and exclusion of highly collinear variables through model-dependent Variance Inflation Factor (VIF) cut-off values to select covariates [38].

$\text{MP}$ ,  $\text{MP}_{\text{PBW}}$  and  $\text{MP}_{\text{WAL}}$  at day 1 were included into all backward multivariate models to assess relative robustness of the association of each power measure ( $\text{MP}$ ,  $\text{MP}_{\text{PBW}}$ ,  $\text{MP}_{\text{WAL}}$ ) with outcomes.

We also explored the predictive performance of each power measure and of other ventilatory variables at day 1 for 28-day NIV failure and death and the optimal cut-offs using the area under receiver operating characteristic curve (AUROC) analysis and Youden index.

Comparison between AUROC curves was made by DeLong's method.

In the physio-anatomical analysis, we explored dose–response relationship between the power delivered at day 1 by the ventilator to the respiratory system and gas exchange, ultrasonographic and circulating biomarker changes after the 1<sup>st</sup> 24 h of NIV by univariable and multivariable regression analysis, after log transformation of skewed parameters; the best fit among four predictive models (linear, exponential, logarithmic, binomial) was searched using  $R^2$  values.

Two-tailed *p* values  $< 0.05$  were considered statistically significant (MedCalc 19.7, Ostend, Belgium).

**Table 1** Baseline, treatment-related parameters and clinical outcomes of supine and PP group; within each treatment group, patients were divided according to median values of Mechanical Power<sub>WAL</sub> during the 1<sup>st</sup> 24 h of NIV (MP<sub>WAL</sub> ≥ 9.1 J/min/L or Low MP<sub>WAL</sub> (MP<sub>WAL</sub> < 9.1 J/min/L)(n = 216)

Parameter	Supine		PP		P high vs. low	High MP <sub>WAL</sub> (n = 41)	Low MP <sub>WAL</sub> (n = 67)	P high vs. low
	All (n = 108)	All (n = 108)	All (n = 108)	All (n = 108)				
Age(yr)	67(62, 75)	68(62, 75)	66(56, 73)	69(65, 75)	0.592	69(65, 75)	65(56, 73)	0.839
Male sex(n, %)	73(68%)	41(62%)	75(69%)	29(70%)	0.812	29(70%)	46(61%)	0.631
White, non-hispanic(n, %)	98(91%)	60(90%)	97(90%)	38(93%)	0.892	38(93%)	59(88%)	0.713
Time from symptom onset to hospital admission(d)*	7(5, 9)	6(5, 8)	7(5, 9)	7(5, 9)	0.899	7(5, 9)	7(5, 9)	0.638
Time from hospital admission to NIV (hrs)	20(7, 56)	20(7, 56)	20(7, 64)	20(6, 61)	0.802	20(6, 61)	20(7, 64)	0.739
BMI(kg/m <sup>2</sup> )	27.8 (25.9, 31.2)	27.7 (25.4, 30.2)	28.1 (26.3, 30.5)	27.9 (26.4, 30.1)	0.782	27.9 (26.4, 30.1)	28.2 (26.3, 30.5)	0.631
Obesity(BMI ≥ 30 kg/m <sup>2</sup> ) n(%)	36(33%)	22(33%)	38(35%)	13(32%)	0.639	13(32%)	25(37%)	0.412
Type 2 diabetes mellitus n(%)	26(24%)	15(23%)	28(26%)	13(31%)	0.713	13(31%)	15(22%)	0.492
Hypertension n(%)	60(56%)	37(56%)	56(52%)	22(54%)	0.639	22(54%)	34(51%)	0.579
Chronic lung disease								
COPD	12(11%)	7(10%)	10(10%)	4(10%)	0.824	4(10%)	6(9%)	0.902
Asthma	3(3%)	1(1%)	3(3%)	1(2%)	0.538	1(2%)	2(3%)	0.727
Coronary artery disease n(%)	3(5%)	2(5%)	4(6%)	2(7%)	0.902	2(7%)	2(6%)	0.859
Chronic atrial fibrillation n(%)	5(4%)	3(4%)	6(6%)	3(4%)	0.572	3(4%)	3(4%)	0.711
Chronic kidney disease n(%)	9(8%)	5(8%)	10(9%)	4(10%)	0.713	4(10%)	6(9%)	0.631
Immunocompromised state	1(1%)	1(1%)	1(0%)	0(0%)	0.782	0(0%)	1(0%)	0.972
Smoking status:								
former(%)	10(10%)	7(10%)	9(8%)	4(10%)	0.721	4(10%)	5(8%)	0.598
current(%)	10(10%)	7(10%)	6(6%)	2(5%)	0.386	2(5%)	4(6%)	0.383
Do-not-Intubate (DNI) n(%)	10(9%)	6(9%)	8(8%)	3(7%)	0.739	3(7%)	5(8%)	0.811
ISARIC 4 C mortality score	14(11, 17)	14(11, 17)	14(10, 18)	14(12, 18)	0.593	14(12, 18)	13(10, 15)	9.739
SAPS II score	36(32, 39)	36(31, 39)	35(30, 40)	36(32, 41)	0.538	36(32, 41)	34(30, 39)	0.513
Lung CT scan volumes								
WAL(L)	2.0(1.5, 2.5)	2.0(1.6, 2.4)	1.9(1.5, 2.4)	1.9(1.6, 2.3)	0.497	1.9(1.6, 2.3)	1.9(1.5, 2.4)	0.725
WAL(%)	49(43, 62)	49(44, 61)	49(45, 58)	50(39, 60)	0.672	50(39, 60)	49(45, 58)	0.539
-Normally aerated (%)	46(44, 55)	50(45, 55)	49(44, 55)	49(42, 55)	0.589	49(42, 55)	50(43, 54)	0.582
-Hyperinflated(%)	3(1, 4)	3(1, 4)	2(1, 4)	4(2, 4)	0.713	4(2, 4)	2(1, 4)	0.798
PAL(L)	1.9(1.6, 2.3)	1.9(1.6, 2.3)	1.2(1.0, 1.4)	1.7(1.1, 2.1)	0.639	1.7(1.1, 2.1)	1.2(1.0, 1.4)	0.607
PAL(%)	44(39, 50)	44(39, 50)	36(30, 41)	44(40, 48)	0.485	44(40, 48)	36(30, 41)	0.361
NAL(L)	0.4(0.3, 0.5)	0.4(0.3, 0.5)	0.5(0.4, 0.7)	0.4(0.4, 0.6)	0.738	0.4(0.4, 0.6)	0.5(0.4, 0.7)	0.811
NAL(%)	8(6, 10)	8(6, 10)	9(8, 13)	9(8, 12)	0.591	9(8, 12)	9(8, 13)	0.496
Lung global CT severity score	46(31, 63)	45(31, 63)	47(31, 62)	46(32, 65)	0.621	47(31, 62)	47(31, 62)	0.639
Lung global LUS severity score	25(22, 28)	25(22, 28)	25(22, 29)	25(23, 28)	0.838	25(23, 28)	25(22, 28)	0.729
C-reactive protein (mg/dL)	13.9(10.5, 18.5)	13.7(10.2, 18.9)	13.5(10.5, 19.2)	13.2(10.6, 18.9)	0.817	13.2(10.6, 18.9)	13.9(10.5, 19.2)	0.813

Table 1 (continued)

	36.6 (36.1, 36.9)	36.6 (36.1, 36.9)	36.5 (36.0, 36.9)	0.713	36.6 (36.2, 37.0)	36.5 (36.1, 36.9)	36.6 (36.2, 37.0)	0.712
Temperature(°C)								
Sys BP (mmHg)	130 (120, 141)	130 (120, 141)	130 (118, 140)	0.630	133 (119, 142)	130 (116, 140)	133 (119, 142)	0.767
Dia BP (mmHg)	75(65, 80)	75(65, 80)	75(68, 89)	0.784	75(68, 89)	75(68, 89)	75(68, 89)	0.784
Heart Rate (beats/min)	85(71, 96)	85(71, 96)	81(70, 99)	0.837	83(75, 98)	81(70, 99)	83(75, 98)	0.698
NRS (Dyspnoea)#	3(2.5)	3(2.5)	4(2.6)	0.528	4(2.6)	3(2.6)	4(2.6)	0.612
WOB scale#	3(2.3)	3(2.3)	3(2.3)	0.582	3(2.3)	3(2.3)	3(2.3)	0.812
RR(breaths/min)#	26(24, 30)	27(24, 30)	25(22, 30)	0.219	26(24, 30)	27(24, 30)	25(22, 30)	0.227
PaO <sub>2</sub> /FiO <sub>2</sub> ratio#	104(78, 137)	102(78, 137)	105(76, 140)	0.429	103(79, 136)	102(80, 139)	104(79, 136)	0.728
PaO <sub>2</sub> /FiO <sub>2</sub> ratio category n(%)#								
150–199	17(16%)	10(15%)	7(17%)	0.439	16(15%)	6(15%)	10(15%)	0.913
100–149	35(32%)	22(33%)	13(31%)	0.580	35(32%)	15(37%)	20(30%)	0.294
<100	56(52%)	35(53%)	21(50%)	0.479	57(53%)	21(51%)	36(54%)	0.683
paCO <sub>2</sub> (mmHg)#	34(31, 37)	34(31, 37)	35(32, 39)	0.713	36(31, 40)	35(31, 38)	36(31, 40)	0.602
paCO <sub>2</sub> >45 mmHg# n(%)	1(1%)	1(1%)	0(0%)	0.912	0(0%)	0(0%)	0(0%)	0.983
Arterial pH#	7.47 (7.45, 7.49)	7.47 (7.45, 7.49)	7.46 (7.44, 7.49)	0.734	7.45 (7.42, 7.49)	7.47 (7.44, 7.49)	7.45 (7.42, 7.49)	0.691
Adjuvant therapies								
Dexamethasone 6 mg/d	108 (100%)	66 (100%)	42(100%)	0.999	108(100%)	41(100%)	67(100%)	0.999
Antivirals								
Remdesivir	1(1%)	1(1%)	1	0.999	1	0	1(1%)	0.999
Lopinavir/ritonavir	0	0	0	0.999	0	0	0	0.999
Hydroxychloroquine	0	0	0	0.999	0	0	0	0.999
Tocilizumab	3(3%)	2(6%)	1(2%)	0.712	0	0	0	0.999
Convalescent plasma	1(1%)	1(1%)	0	0.999	0	0	0	0.999
Enoxaparin	104(96%)	63(96%)	40(96%)	0.631	104(96%)	39(96%)	64(96%)	0.731
Prophylactic dose	49(45%)	30(45%)	18(42%)	0.610	49(45%)	18(45%)	28(42%)	0.615
Intermediate dose#	13(12%)	8(12%)	8(19%)	0.583	13(12%)	5(12%)	13(19%)	0.592
Anticoagulant dose	42 (39%)	26 (39%)	16 (37%)	0.325	42 (39%)	16(39%)	25 (37%)	0.435
Warfarin/DOACs	4(4%)	2(3%)	2(5%)	0.531	4(4%)	1(2%)	3(4%)	0.612
SARS-CoV-2 vaccine	0(0%)	0(0%)	0(0%)	0.999	0(0%)	0(0%)	0(0%)	0.999
Panel B: treatment-related parameters								
Supine					PP			
All (n=108)	High MP <sub>wal</sub> (n=66)	High MP <sub>wal</sub> (n=66)	Low MP <sub>wal</sub> (n=42)	P high vs. low	Low MP <sub>wal</sub> (n=67)	High MP <sub>wal</sub> (n=41)	Low MP <sub>wal</sub> (n=67)	P high vs. low
Duration of the 1 <sup>st</sup> PP session (hrs)	–	–	–	–	11.8(10.1, 13.9)	12.1(10.1, 14.0)	11.8(10.1, 13.9)	0.571
Daily hours of PP therapy at 28 days	–	–	–	–	16.0(13.9, 18.1)	16.9(14.7, 18.9)	16.0(13.9, 18.1)	0.439
Days of PP therapy	–	–	–	–	5(4, 7)	5(4, 7)	5(4, 7)	0.312

**Table 1** (continued)

Patients completing $\geq 1$ PP session/ day for $\geq 2$ consecutive days (n, %)	–	–	–	108(100%)	41(100%)	67(100%)	0.999
Dexametomidine infusion during NIV (n, %)	38(35%)	24(36%)	14(33%)	0.712	32(78%)	50(75%)	0.813
Daily hours of NIV	24(24, 24) 21.2(20.0, 22.9)	24(24, 24) 21.6(20.4, 22.5)	24(24, 24) 19.7(18.4, 22.5)	0.999 0.513	24(24, 24) 21.5(20.4, 22.7)	24(24, 24) 20.2(18.6, 22.8)	0.999 0.495
Days of NIV	8(6, 11)	8(6, 11)	7(6, 10)	0.316	7(6, 10)	7(6, 10)	0.316
Ventilatory mode(%): CPAP/PSV							
Day 0	52%/48%	57%/43%	58%/42%	0.417	56%/44%	57%/43%	0.649
Day 1	52%/48%	57%/43%	58%/42%	0.417	56%/44%	57%/43%	0.649
Day 7	58%/42%	59%/41%	61%/39%	0.327	59%/41%	71%/40%	0.472
Interface(%): Full-face mask/helmet							
Day 0	100%/0%	100%/0%	100%/0%	0.999	100%/0%	100%/0%	0.999
Day 1	100%/0%	100%/0%	100%/0%	0.893	100%/0%	100%/0%	0.999
Day 7	96%/4%	94%/6%	98%/2%	0.831	93%/7%	97%/3%	0.749
PEEP (cmH2O)							
Day 0	8(8, 9)	8(8, 9)	8(7, 8)	0.813	8(7, 9)	7(6, 8)	0.612
Day 1	8(8, 9)	8(8, 9)	8(7, 8)	0.821	8(7, 9)	7(6, 8)	0.297
Day 0–7 <sup>s</sup>	8(7, 10)	9(8, 10)	8(7, 8)	0.192	8(7, 9)	7(6, 7)	0.103
Pressure Support(Ps) during PSV (mH2O)							
Day 0	4(3, 5)	4(3, 5)	3(3, 4)	0.649	4(3, 5)	3(3, 4)	0.492
Day 1	4(3, 5)	4(3, 5)	3(3, 4)	0.418	4(3, 5)	3(3, 4)	0.317
Day 0–7 <sup>s</sup>	4(3, 5)	4(3, 5)	3(3, 5)	0.214	4(3, 5)	3(3, 5)	0.118
NRS (Dyspnoea)							
Day 0	2(0, 3)	2(0, 3)	2(0, 3)	0.712	2(0, 3)	2(0, 3)	0.839
Day 1	2(0, 4)	2(0, 4)	2(0, 3)	0.429	2(0, 4)	2(0, 3)	0.736
Day 0–7 <sup>s</sup>	2(1, 3)	3(1, 4)	1(0, 2)	<b>0.034</b>	3(1, 4)	1(0, 2)	<b>0.021</b>
WOB scale							
Day 0	2(1, 3)	2(1, 3)	2(1, 3)	0.629	2(1, 3)	2(1, 3)	0.412
Day 1	2(1, 3)	2(1, 3)	2(1, 3)	0.582	2(1, 3)	2(1, 3)	0.493
Day 0–7 <sup>s</sup>	3(2, 4)	3(2, 4)	1(1, 2)	<b>0.035</b>	3(2, 4)	1(1, 2)	<b>0.022</b>
FiO2							
Day 0	0.50(0.45, 0.70)	0.50(0.45, 0.70)	0.50(0.45, 0.70)	0.783	0.50(0.50, 0.70)	0.50(0.45, 0.70)	0.712
Day 1	0.50(0.45, 0.70)	0.50(0.45, 0.70)	0.50(0.45, 0.70)	0.698	0.50(0.50, 0.70)	0.50(0.40, 0.70)	0.512
Day 0–7 <sup>s</sup>	0.50(0.40, 0.60)	0.60(0.50, 0.75)	0.40(0.35, 0.50)	<b>0.028</b>	0.50(0.50, 0.70)	0.40(0.35, 0.50)	<b>0.031</b>
VTe (ml/kg prBW)							
Day 0	7.6(7.1, 8.4)	8.0(7.6, 8.1)	7.3(6.5, 8.4)	0.412	7.7(6.9, 8.6)	7.4(6.5, 8.5)	0.595
Day 1	7.6(7.2, 8.8)	7.8(7.2, 8.8)	7.2(6.7, 8.6)	0.272	7.6(7.1, 8.4)	7.2(6.6, 8.4)	0.384
Day 0–7 <sup>s</sup>	7.7(7.3, 8.3)	8.0(7.2, 8.8)	7.4(6.8, 8.6)	0.231	7.9(7.1, 8.6)	7.6(6.8, 8.6)	0.611

**Table 1** (continued)

RR (breaths/min)		25(22, 30)	27(24, 30)	24(22, 28)	0.712	25(22, 30)	25(22, 30)	25(22, 30)	24(22, 26)	0.837
Day 0		24(22, 26)	26(22, 28)	22(20, 24)	0.39	24(20, 27)	26(22, 28)	26(22, 27)	22(20, 25)	0.391
Day 1		26(22, 28)	26(22, 28)	21(20, 25)	<b>0.018</b>	22(20, 25)	26(22, 27)	26(22, 27)	21(20, 25)	<b>0.021</b>
Day 0–7 <sup>§</sup>										
MV (L/min)		14.2(11.1, 16.1)	14.2(11.1, 16.1)	13.4(11.0, 16.9)	0.817	13.6(11.1, 16.7)	13.9(11.9, 15.6)	13.9(11.9, 15.6)	13.6(11.1, 16.7)	0.412
Day 0		13.6(12.6, 15.2)	13.9(12.6, 15.4)	13.1(10.6, 15.3)	0.534	13.3(10.9, 15.3)	13.8(11.9, 15.7)	13.8(11.9, 15.7)	13.1(10.6, 15.3)	0.239
Day 1		14.0(11.4, 16.1)	14.4(11.9, 16.1)	13.0(10.2, 15.6)	0.159	13.9(12.1, 15.9)	13.9(12.1, 15.9)	13.9(12.1, 15.9)	11.9(11.1, 15.9)	0.118
Day 0–7 <sup>§</sup>										
Time from NIV initiation to 1st PP session (hrs)		–	–	–	–	3(2, 4)	3(2, 4)	3(2, 4)	3(2, 4)	–
MPsp0 (J/min)		17.5(11.3, 20.0)	29.7(20.5, 28.7)	9.1(6.9, 13.4)	< <b>0.001</b>	18.3(15.4, 24.9)	29.9(25.5, 33.9)	29.9(25.5, 33.9)	13.1(10.1, 16.9)	< <b>0.001</b>
MP <sub>PBW</sub> sp0 (J/min/kg)		0.21(0.13, 0.26)	0.24(0.16, 0.28)	0.13(0.10, 0.27)	< <b>0.001</b>	0.20(0.16, 0.27)	0.25(0.17, 0.29)	0.25(0.17, 0.29)	0.17(0.11, 0.24)	< <b>0.001</b>
MP <sub>WAL</sub> sp0 (J/min/L)		9.9(8.0, 13.2)	15.8(10.9, 28.0)	6.1(4.4, 8.9)	< <b>0.001</b>	9.8(8.1, 13.1)	17.1(11.2, 21.7)	17.1(11.2, 21.7)	8.1(5.01, 11.9)	< <b>0.001</b>
MP (J/min)		16.7(10.5, 19.2)	27.8(24.5, 31.9)	8.7(6.3, 10.2) 8.8(6.6, 10.1)	< <b>0.001</b>	16.9(10.8, 19.3)	27.5(25.1, 31.9)	27.5(25.1, 31.9)	8.5(6.5, 9.2)	< <b>0.001</b>
Day 1		16.1(10.8, 19.8)	28.1(24.9, 32.2)	9.1(8.2, 10.4)	< <b>0.001</b>	17.2(10.4, 21.1)	27.8(25.0, 32.2)	27.8(25.0, 32.2)	8.9(6.8, 9.6)	< <b>0.001</b>
Day 2		16.6(10.1, 19.5)	27.6(24.1, 31.5)		< <b>0.001</b>	16.8(10.2, 20.4)	27.4(24.2, 33.1)	27.4(24.2, 33.1)	8.8(6.4, 9.4)	< <b>0.001</b>
Day 1–7										
MP <sub>PBW</sub> (J/min/kg)		0.19(0.10, 0.23)	0.23(0.17, 0.26)	0.12(0.10, 0.29)	< <b>0.001</b>	0.18(0.16, 0.22)	0.23(0.17, 0.27)	0.23(0.17, 0.27)	0.12(0.10, 0.29)	< <b>0.001</b>
Day 1		0.18(0.12, 0.23)	0.23(0.17, 0.26)	0.13(0.11, 0.29)	< <b>0.001</b>	0.19(0.15, 0.22)	0.22(0.16, 0.27)	0.22(0.16, 0.27)	0.12(0.12, 0.29)	< <b>0.001</b>
Day 2		0.19(0.10, 0.20)	0.23(0.12, 0.26)	0.13(0.11, 0.21)	< <b>0.001</b>	0.18(0.15, 0.24)	0.23(0.20, 0.29)	0.23(0.20, 0.29)	0.12(0.11, 0.22)	< <b>0.001</b>
Day 1–7										
MP <sub>WAL</sub> (J/min/L)		9.3(5.7, 21.2)	15.7(12.1, 27.1)	5.3(4.1, 7.4)	< <b>0.001</b>	8.9(5.5, 20.0)	16.2(13.8, 23.9)	16.2(13.8, 23.9)	4.9(4.2, 7.9)	< <b>0.001</b>
Day 1		9.0(5.1, 20.6)	15.6(12.1, 29.0)	5.1(3.7, 7.1)	< <b>0.001</b>	8.9(5.2, 19.4)	16.0(12.9, 22.1)	16.0(12.9, 22.1)	4.7(4.1, 7.9)	< <b>0.001</b>
Day 2		8.6(4.7, 18.9)	18.5(14.7, 22.9) ‡	4.6(3.6, 6.2) ‡	< <b>0.001</b>	9.9(6.7, 18.9)	20.6(16.1, 26.3) ‡	20.6(16.1, 26.3) ‡	4.5(3.6, 5.9)	< <b>0.001</b>
Day 1–7										
pH		7.48(7.45, 7.50)	7.47(7.45, 7.49)	7.47(7.42, 7.48)	0.471	7.47(7.45, 7.49)	7.46(7.42, 7.50)	7.46(7.42, 7.50)	7.47(7.44, 7.48)	0.498
Day 0		7.46(7.44, 7.48)	7.46(7.44, 7.47)	7.46(7.44, 7.49)	0.413	7.46(7.41, 7.47)	7.45(7.42, 7.48)	7.45(7.42, 7.48)	7.45(7.41, 7.47)	0.479
Day 1		7.46(7.43, 7.49)	7.46(7.43, 7.49)	7.43(7.40, 7.46)	0.394	7.45(7.43, 7.47)	7.44(7.40, 7.48)	7.44(7.40, 7.48)	7.42(7.40, 7.46)	0.309
Day 0–7 <sup>§</sup>										
paCO <sub>2</sub> mmHg		35(33, 39)	35(33, 39)	35(34, 40)	0.391	35(34, 40)	35(33, 39)	35(33, 39)	35(34, 40)	0.713
Dat 0		35(35, 40)	35(35, 40)	34(32, 39)	0.437	34(32, 39)	35(34, 40)	35(34, 40)	34(32, 39)	0.316
Day 1		36(35, 40)	36(35, 40)	35(32, 40)	0.562	35(32, 39)	35(34, 39)	35(34, 39)	37(32, 39)	0.513
Day 0–7 <sup>§</sup>										
PaO <sub>2</sub> /FiO <sub>2</sub> ratio		147(116, 218)	149(115, 220)	142(110, 205)	0.562	142(116, 192)	143(114, 192)	143(114, 192)	141(119, 193)	0.629
sp0		155(135, 219)	143(122, 193)	168(130, 233) ‡	<b>0.009</b>	181(139, 219) ‡	152(118, 180)	152(118, 180)	198(152, 232) ‡	<b>0.001</b>
sp1		178(142, 197) ‡	150(127, 199)	185(168, 221) ‡	<b>0.002</b>	198(159, 231) ‡	155(128, 192)	155(128, 192)	220(163, 273) ‡	< <b>0.001</b>
sp0–7 <sup>§</sup>										
O <sub>2</sub> responders n (%) (paO <sub>2</sub> /FiO <sub>2</sub> sp0–1 > 0)		42(39%)	16(34%)	26(62%)	<b>0.009</b>	71(66%) <sup>¶</sup>	17(41%)	17(41%)	54(81%)	<b>0.002</b>
VR <sup>#</sup>		1.9(1.5, 2.4)	1.9(1.6, 2.3)	2.0(1.4, 2.4)	0.735	1.9(1.5, 2.3)	1.9(1.5, 2.3)	1.9(1.5, 2.3)	1.9(1.6, 2.3)	0.512
sp0		1.9(1.6, 2.3)	2.2(1.9, 2.3) ‡	1.6(1.2, 2.3) ‡	<b>0.010</b>	1.6(1.4, 2.0) ‡	1.9(1.6, 2.3)	1.9(1.6, 2.3)	1.5(1.3, 2.0) ‡	<b>0.009</b>
sp1		1.9(1.5, 2.4)	2.3(1.8, 2.4) ‡	1.6(1.0–2.2) ‡	<b>0.008</b>	1.5(1.1–1.9) ‡	1.9(1.6, 2.3)	1.9(1.6, 2.3)	1.4(0.9, 1.7) ‡	< <b>0.001</b>
sp0–7 <sup>§</sup>										



**Table 1** (continued)

MV corr (L/min) <sup>‡</sup>						
sp0	12.1(10.1, 13.7)	12.2(10.1, 13.7)	11.9(10.1, 13.7)	11.9(10.1, 13.7)	12.3(11.4, 13.4)	11.9(10.1, 13.7)
sp1	12.5(10.2, 14.9)	12.7(10.2, 14.9) ‡	10.9(9.3, 12.6) ‡	11.0(9.8, 12.6) ‡	12.1(10.5, 13.5)	10.8(9.3, 12.6) ‡
sp0-7 <sup>§</sup>	12.5(10.2, 15.1)	13.2(11.2, 15.3) ‡	10.9(9.0, 12.3) ‡	11.1(9.9, 12.3) ‡	12.2(10.4, 14.0)	10.5(8.9, 12.3)
CO2 responders n(%) (VR sp0-1 < 0)	32(30%)	11(16%)	21(50%) †	47(66(71%) <sup>  </sup>	12(29%)	47(71%) †
Ventral LUS						
score	6(5, 9)	7(5, 9)	6(4, 8)	7(5, 8)	7(5, 8)	7(5, 8)
Day 0	6(5, 7)	7(5, 9)	5(5, 7)	7(5, 8)	7(5, 8)	7(5, 8)
Day 1	6(5, 7)	7(5, 9)	4(3, 7)	8(4, 7)	8(5, 7)	7(4, 7)
Day 0-7 <sup>§</sup>						
Lateral LUS						
score	8(7, 9)	8(7, 9)	8(7, 9)	8(7, 9)	8(7, 9)	8(7, 9)
Day 0	8(7, 9)	8(7, 9)	7(6, 8)	7(7, 8)	8(7, 9)	6(7, 8) ‡
Day 1	8(7, 10)	8(7, 10)	7(6, 8)	6(5, 7)	6(5, 10) ‡	6(5, 7) ‡
Day 0-7 <sup>§</sup>						
Dorsal LUS score						
Day 0	10(9, 11)	10(9, 11)	10(9, 11)	10(9, 11)	10(9, 11)	10(9, 11)
Day 1	10(9, 11)	11(9, 12)	10(7, 11)	8(7, 10) ‡	10(9, 11)	8(7, 10) ‡
Day 0-7 <sup>§</sup>	10(9, 12)	11(9, 13)	10(8, 12)	6(5, 8) ‡	8(6, 10) ‡	6(5, 8) ‡
Global LUS score						
Day 0	24(22, 28)	25(22, 27)	24(22, 28)	25(21, 28)	25(22, 28)	25(21, 28)
Day 1	24(20, 27)	26(21, 27)	22(18, 25) ‡	22(19, 26) ‡	25(22, 28)	21(18, 24) ‡
Day 0-7 <sup>§</sup>	24(20, 27)	26(21, 28)	21(18, 24) ‡	21(18, 24) ‡	22(20, 26) ‡	19(16, 22) ‡
Global LUS reiteration score						
Day 1	0(-4, 1)	0(-7, -2)	1(-1, 4)	4(3, 8)	2(-1, 5)	6(5, 10)
Day 1-7 <sup>§</sup>	-1(-5, 1)	-6(-9, -4)	5(2, 8)	8(4, 11)	5(2, 8)	10(6, 14) ‡
Global LUS reiteration score ≥ 8 (n, %)						
Day 1	9(8%)	0(0%)	9(21%)	26(24%)	1(2%)	25(37%)
Day 1-7 <sup>§</sup>	20(19%)	0(0%)	19(45%) ‡	59(55%) ‡	11(26%)	48(71%) ‡
WAL (%)						
Day 0	50(43, 59)	50(46, 61)	50(41, 61)	49(41, 59)	49(39, 60)	49(45, 59)
Day 1	48(41, 60)	46(41, 57)	50(42, 62)	55(46, 62) ‡	49(40, 60)	57(51, 64) ‡
Day 0-7 <sup>§</sup>	49(38, 62)	38(34, 56) ‡	59(49, 69) ‡	58(52, 64) ‡	51(42, 62)	64(55, 70) ‡
Blood lactate (mmol/L)						
day 0	1.0(0.9, 1.1)	1.0(0.9, 1.1)	1.0(0.9, 1.1)	1.0(0.9, 1.2)	1.0(0.9, 1.2)	1.0(0.9, 1.2)
day1	1.1(1.0, 1.2)	1.1(1.0, 1.2)	1.1(1.0, 1.2)	1.1(1.0, 1.2)	1.1(1.0, 1.2)	1.1(1.0, 1.2)
day 0-7 <sup>§</sup>	1.2(1.0, 1.3)	1.2(1.0, 1.3)	1.1(1.0, 1.2)	1.1(1.0, 1.2)	1.2(1.1, 1.3)	1.1(1.0, 1.2)
C-reactive protein (mg/dL)						
day 0	14.5(10.5, 19.0)	14.7(10.2, 18.9)	14.2(10.9, 19.0)	13.5(10.5, 19.2)	13.2(10.6, 18.9)	13.9(10.5, 19.2)
day1	13.4(9.9, 18.9)	15.2(10.5, 19.2)	11.5(7.5, 14.5) ‡	9.8(7.5, 12.5) ‡	12.1(8.8, 19.1)	8.4(4.6, 12.3) ‡
day 0-7 <sup>§</sup>	11.7(6.2, 14.1) ‡	13.9(10.2, 16.4)	7.4(2.1, 9.0) ‡	4.5(3.1, 8.0) ‡	9.8(7.3, 16.1)	1.5(3.1, 1.0) ‡
Procalcitonin (ng/mL) † ‡						
day 0	0.52(0.40, 0.62)	0.54(0.40, 0.62)	0.58(0.41, 0.67)	0.57(0.41, 0.67)	0.56(0.40, 0.65)	0.58(0.41, 0.67)
day1	0.41(0.31, 0.69)	0.51(0.41, 0.69)	0.35(0.15, 0.55) ‡	0.35(0.15, 0.55) ‡	0.49(0.42, 0.63)	0.15(0.05, 0.25) ‡
day 0-7 <sup>§</sup>	0.31(0.17, 0.45) ‡	0.51(0.17, 0.65)	0.10(0.02, 0.20) ‡	0.25(0.12, 0.37) ‡	0.46(0.39, 0.61)	0.05(0.02, 0.10) ‡

Table 1 (continued)

D-dimer (mg/L)		Supine		PP		P high vs. low		High MP <sub>wal</sub>		Low MP <sub>wal</sub>		P high vs. low	
day 0	day 1	All (n=108)	High MP <sub>wal</sub> (n=66)	Low MP <sub>wal</sub> (n=42)	All (n=108)	High MP <sub>wal</sub> (n=41)	Low MP <sub>wal</sub> (n=67)	High MP <sub>wal</sub> (n=41)	Low MP <sub>wal</sub> (n=67)	High MP <sub>wal</sub> (n=41)	Low MP <sub>wal</sub> (n=67)	High MP <sub>wal</sub> (n=41)	Low MP <sub>wal</sub> (n=67)
3.1(1.5, 3.9)	3.1(1.7, 3.9)	3.1(1.5, 3.9)	3.1(1.7, 3.9)	2.9(1.9, 3.8)	2.8(1.4, 3.4)	2.9(1.7, 3.8)	2.7(1.4, 3.4)	2.9(1.7, 3.8)	2.7(1.4, 3.4)	2.9(1.7, 3.8)	2.7(1.4, 3.4)	2.9(1.7, 3.8)	2.7(1.4, 3.4)
3.1(1.9, 4.0)	3.5(1.9, 4.1)	3.1(1.9, 4.0)	3.5(1.9, 4.1)	2.5(1.8, 3.2)	2.6(1.4, 3.2)	3.0(1.8, 3.9)	2.4(1.4, 3.2)	3.0(1.8, 3.9)	2.4(1.4, 3.2)	3.0(1.8, 3.9)	2.4(1.4, 3.2)	3.0(1.8, 3.9)	2.4(1.4, 3.2)
1.9(1.0, 4.9) ‡	3.9(2.0, 4.9)	1.9(1.0, 4.9) ‡	3.9(2.0, 4.9)	0.9(0.3, 1.4) ‡	1.0(0.3, 1.9) ‡‡	2.9(1.5, 3.9)	0.7(0.3, 0.9) ‡‡	2.9(1.5, 3.9)	0.7(0.3, 0.9) ‡‡	2.9(1.5, 3.9)	0.7(0.3, 0.9) ‡‡	2.9(1.5, 3.9)	0.7(0.3, 0.9) ‡‡
Panel C: Clinical outcomes													
NIV failure at 28 d	56 (52%)	47(70%)	9(21%) ≠	<0.001	20(19%) <sup>Π</sup>	17(42%)	3(4%) ≠	17(42%)	3(4%) ≠	17(42%)	3(4%) ≠	17(42%)	3(4%) ≠
Days to NIV failure	7(6, 7)	7(6, 7)	8(7, 8)	0.713	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)
Death at 28 d	52(48%)	45(67%)	7(17%)	<0.001	16(15%) <sup>Π</sup>	15(37%)	1(2%) ≠	15(37%)	1(2%) ≠	15(37%)	1(2%) ≠	15(37%)	1(2%) ≠
Days to death	12(9, 15)	12(9, 15)	15(14, 18)	0.213	15(14, 18)	13(11, 15)	15(14, 18)	13(11, 15)	15(14, 18)	13(11, 15)	15(14, 18)	13(11, 15)	15(14, 18)
ETI at 28 d	38/99 (38%)	34/62 (55%)	4/37(11%)	0.004	11/97 (11%)	9/36(25%)	2/61 (3%) <sup>**</sup>	9/36(25%)	2/61 (3%) <sup>**</sup>	9/36(25%)	2/61 (3%) <sup>**</sup>	9/36(25%)	2/61 (3%) <sup>**</sup>
Days to ETI	7(6, 7)	7(6, 7)	8(7, 8)	0.529	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)	7(6, 7)	8(7, 8)
Death at 60 d	52(48%)	45(67%)	7(17%)	<0.001	17(15%) <sup>Π</sup>	16(37%)	1(2%) ≠	16(37%)	1(2%) ≠	16(37%)	1(2%) ≠	16(37%)	1(2%) ≠
Days in ICU	9(2, 16)	9(2, 16)	6(2, 10)	0.129	6(2, 10)	8(2, 12)	6(2, 10)	8(2, 12)	6(2, 10)	8(2, 12)	6(2, 10)	8(2, 12)	6(2, 10)

For each parameter median (IQR) is indicated, unless otherwise specified

The *P* values refer to comparison between low MP<sub>wal</sub> and high MP<sub>wal</sub> group within supine and PP treatment groups (statistically significant *p*-values are written in bold characters). Data are expressed as median (IQR) or as n(%) values, unless otherwise specified

\* *P* < 0.05 vs. High MP<sub>wal</sub> (day 1), within the same treatment group (PP or supine)

\*\* *P* < 0.01 vs. High MP<sub>wal</sub> (day 1), within the same treatment group (PP or supine)

≠ *P* < 0.001 vs. High MP<sub>wal</sub> (day 1), within the same treatment group (PP or supine)

|| *P* < 0.05 vs. supine group

¶ *P* < 0.01 vs. supine group

Π *P* < 0.001 vs. supine group

† *P* < 0.01 vs. timepoint sp0

‡ *P* < 0.01 vs. day 0

\*\* *P* < 0.001 vs. day 0

# on admission, while on a FiO2 50% Venturi mask or a non-rebreather reservoir bag mask

## prophylactic dose twice daily

†† patients with documented infection (*n* = 4 within each group) were excluded from this analysis

Abbreviations: ABG: arterial blood gas analysis; DOAC: direct oral anticoagulants; ISARIC: International Severe Acute Respiratory Infection Consortium; MP: mechanical power; MP<sub>FBW</sub>: mechanical power corrected for predicted body weight; MP<sub>wal</sub>: mechanical power corrected for well-aerated lung volume; NAL: non-aerated lung volume; NIV: noninvasive ventilation; NRS: numeric rating scale; PAL: poorly aerated lung volume; PP: prone position; RR: respiratory rate; SAPS: Simplified acute physiology score; WAL: well-aerated lung volume; WOB (work of breathin scale, as determined by Apigo scale

For each parameter median (IQR) is indicated, unless otherwise specified

The *P* values value refer to comparison between groups at baseline, at the end of follow-up and to comparison in changes during the follow-up, respectively (statistically significant *p*-values are written in bold characters). Data are expressed as mean ± SEM

**Table 1** (continued)

## Definitions:

Baseline: day of enrollment, before NIV initiation

§Day 0: baseline, i.e. the time of NIV initiation in both treatment groups

§Day 1: the first 24 h of NIV in both (PP and supine) treatment groups

§Day 7: day 7 after NIV initiation in both (PP and supine) treatment groups

§Day 0–7: mean value through day 0–7. Between-group comparison was made with repeated measures two-factor (within subject and between group) ANOVA, after log-transformation of non-normal variables

sp0:  $\geq 1$  h since (supine) NIV initiation on day 0

sp1: 24 h after NIV initiation in both (PP and supine) treatment groups

O2 response: change in  $\text{paO}_2/\text{FIO}_2$  ratio during NIV in supine position at day 1 (timepoint sp1) as compared with timepoint sp0

A positive O2 response is defined by:  $\text{pO}_2/\text{FIO}_2\text{sp1} - \text{pO}_2/\text{FIO}_2\text{sp0} > 0$ , or  $\Delta\text{paO}_2/\text{FIO}_2\text{sp0-1} > 0$

CO2 response: an increase in CO2 clearance, defined by a reduction in dead space indices (VR and  $\text{MV}_{\text{corr}}$ , tested separately) at sp1 as compared with timepoint sp0

A positive CO2 response is defined by:  $\text{VRsp1} - \text{VRsp0} < 0$  (or  $\Delta\text{VRsp0-1} < 0$ ) and by  $\text{MV}_{\text{corr}}\text{sp1} - \text{MV}_{\text{corr}}\text{sp0} < 0$  (or  $\Delta\text{MV}_{\text{corr}}\text{sp0-1} < 0$ )

This schedule allowed comparing gas exchange responses among groups every day, in the same (supine) position, after taking into account the effect of the overnight PP session in the PP groups. For VTe, RR, MV, MP measures, time weighted-average of hourly values during each session are presented

For MV, we verified consistency between time-average MV values and values obtained at the time of ABG (which were used to calculate Dead Space Indices): the comparison confirmed a good agreement between the two values, with  $p\text{-value} > 0.6$  for comparison at all timepoints (not shown)

Ventral LUS (lung ultrasound) score: the score is the sum of individual scores for region L1, L2, R1, R2 (ranging 0–12)

Lateral LUS score: the score is the sum of individual scores for region L3, L4, R3, R4

Dorsal LUS score: the score is the sum of individual scores for region L5, L6, R5, R6

Global LUS score: the score is the sum of ventral, lateral and dorsal region scores (the sum of the 12 regions' score, ranging 0–36)

LUS re-aeration score, global: the sum of ventral, lateral and dorsal re-aeration scores, calculated according to the method proposed and validated by Bouhemad et al

WAL(%): well-aerated lung volume as % total lung volume, resulting from the sum of regional WAL volumes assessed by LUS and validated against CT scan (see online supplement)

## Results

### Characteristics at Inclusion

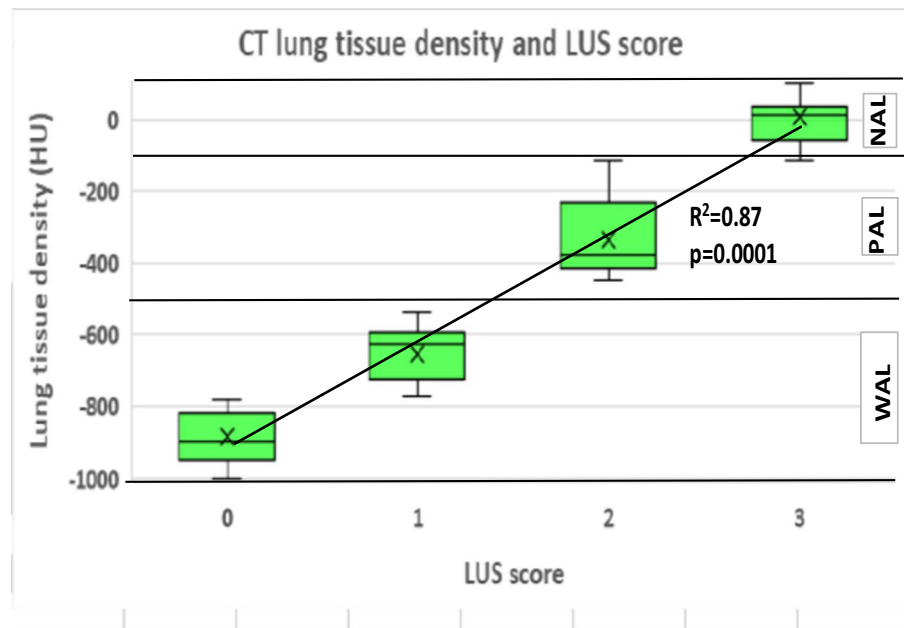
We analyzed 216 COVID-19 patients (108 treated with PP and 108 with supine NIV) (Table 1, Supplementary Fig. 2). Pre-post-matching SMDs, PS density and logit(PS) distribution plots revealed good balance between PP and

supine groups in selected covariates (Supplementary Fig. 3, Supplementary Table 2).

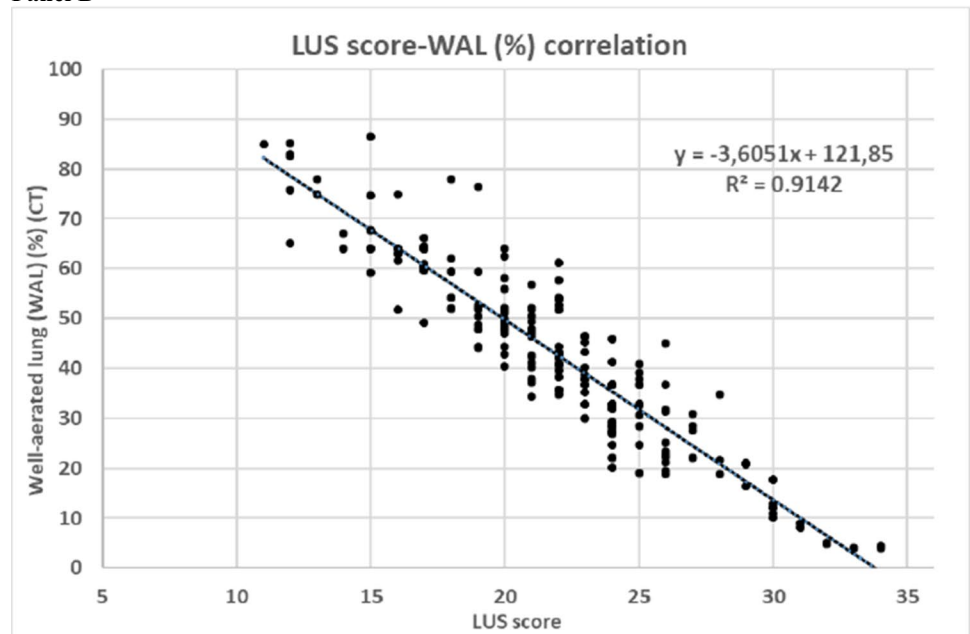
Baseline demographics, pharmacological therapies, clinical-radiological features, and respiratory parameters of patients treated with PP or supine NIV, subgrouped according to median  $MP_{WAL}$  at day 1, were similar across groups; NRS (dyspnea), WOB score [39] and RR showed no evidence for increased respiratory drive, while lung CT

**Fig. 1** Panel A: categorization of individual lung regions with different CT-assessed gas/tissue density in relation to their LUS score. Panel B: correlation between WAL(%) assessed by software-based analysis of CT scans and WAL(%) as estimated by global lung ultrasound (LUS) score in the 216 COVID-19 pneumonia patients included in the study. The Spearman correlation coefficient ( $r_s$ ) with its 95%CI and statistical significance are shown. Abbreviations: CT: computed tomography; HU: Hounsfield Units; LUS: lung ultrasound; NAL: non-aerated lung volume; PAL: poorly aerated lung volume; WAL: well-aerated lung volume

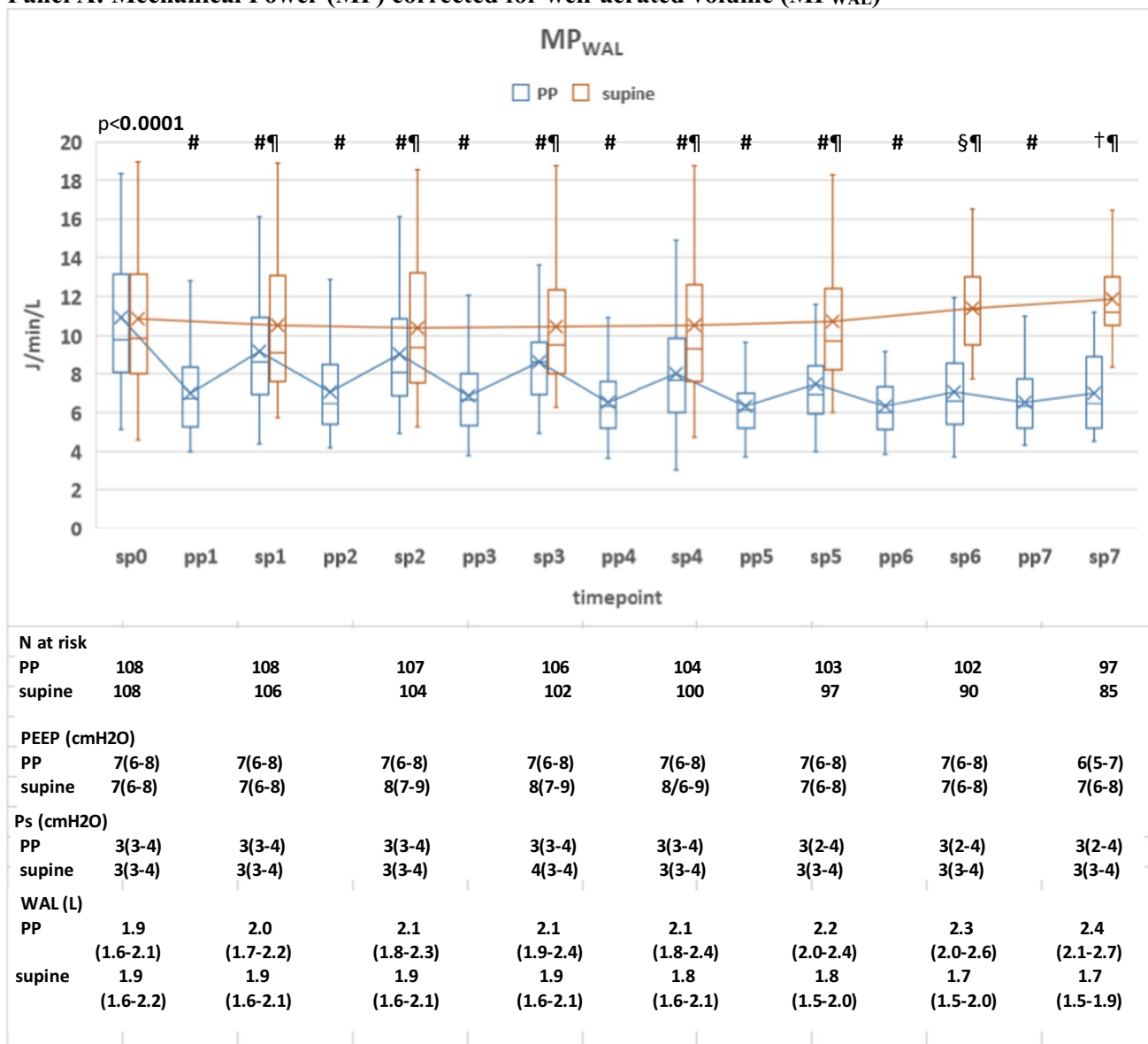
**Panel A**



**Panel B**



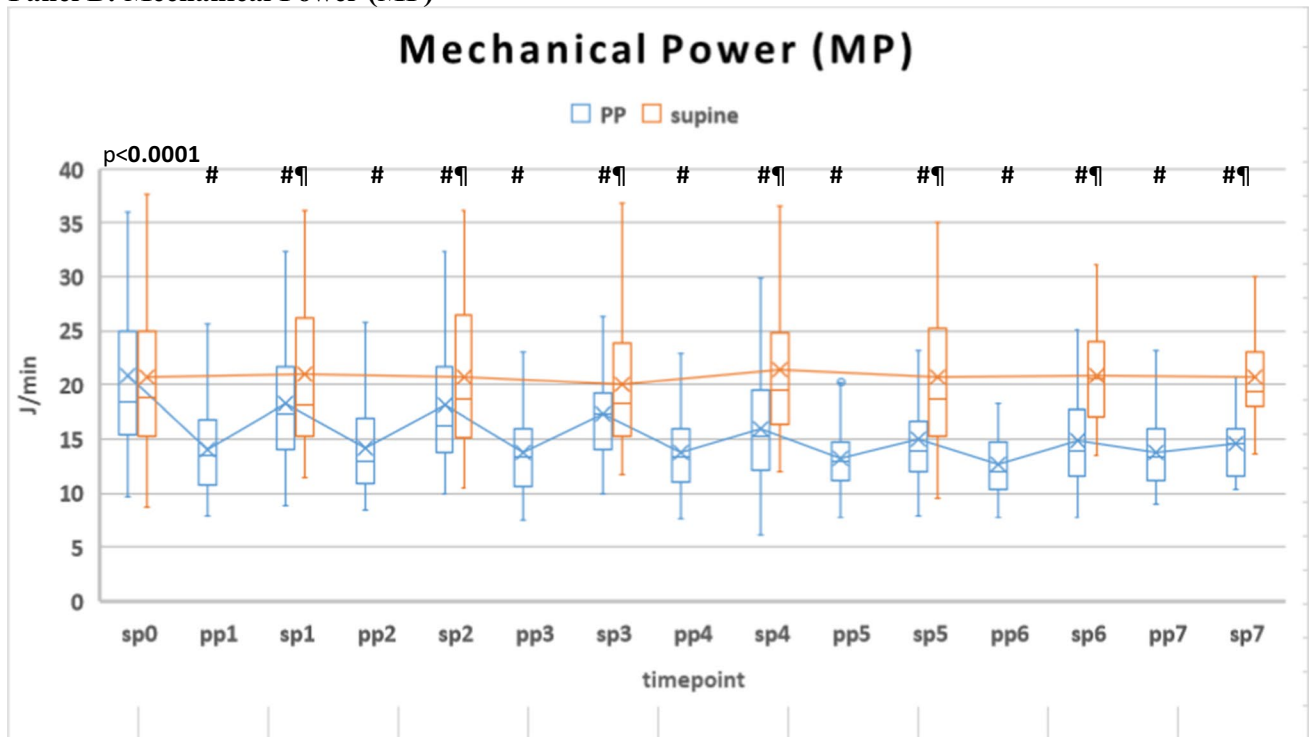
**Panel A: Mechanical Power (MP) corrected for well-aerated volume (MP<sub>WAL</sub>)**



**Fig. 2** Panel A–D: time course of MP<sub>WAL</sub>, MP and their components during the initial 7 days of NIV in the PP (*n*=108) and supine (*n*=108) group. N at risk and median (IQR) values of PEEP, Pressure support (Ps) and well-aerated lung volume (WAL) are shown at the bottom of panel A. # *P*<0.01 vs. baseline (same group); § *P*<0.01 vs. baseline (both groups) † *P*<0.001 vs. baseline (both groups) ‡ *P*<0.01 between PP and supine groups ¶ *P*<0.001 between PP and supine groups. In the box plots the middle line represents the median observed value, boxes represent the interquartile range (IQR), whiskers extend to the most extreme observed values with 1.5 times the interquartile range of the nearer quartile, and dots represent observed values outside that range. The connecting line connects the mean values within each box plot at different time points. For VT<sub>e</sub>, RR, MV, MP, MP<sub>WAL</sub> time weighted–average of hourly values during each session (supine/prone) of NIV are presented. For MV, we verified consistency between time-average MV values and values obtained at the time of ABG (which were used to calculate Dead Space Indices): the comparison confirmed a good agreement between the two values, with *p*-value>0.7 for comparison at all timepoints (not shown). The timepoints are indicated as follows: sp0: supine position timepoint 0 (baseline, after NIV initiation). In PP group, the session preceded the first PP session. ABGs were performed ≥1 h after supine NIV initiation, after achieving ventilatory stability; pp1: first PP session in PP

group. ABGs were performed ≥1 h after prone NIV initiation, after achieving ventilatory stability; sp1: supine position timepoint 1 (after the initial 24 h of NIV); in the PP group this corresponded to the respiration after the 1<sup>st</sup> PP session on day 1. pp2: during the 2<sup>nd</sup> PP session; sp2: supine position timepoint 2 (after the 2<sup>nd</sup> day of NIV, in the PP group this also corresponded to the respiration after the 2<sup>nd</sup> PP session on day 2; pp3 during the 3<sup>rd</sup> PP session; sp3 supine position timepoint 3 (after the 3<sup>rd</sup> day of NIV, in the PP group this also corresponded to the respiration after the 3<sup>rd</sup> PP session on day 3. pp4 during the 4<sup>th</sup> PP session; sp4 supine position timepoint 4 (after the 4<sup>th</sup> day of NIV, in the PP group this also corresponded to the respiration after the 4<sup>th</sup> PP session on day 4. pp5 during the 5<sup>th</sup> PP session; sp5 supine position timepoint 5 (after the 5<sup>th</sup> day of NIV, in the PP group this also corresponded to the 5<sup>th</sup> PP session on day 5. pp6 during the 6<sup>th</sup> PP session; sp6 supine position timepoint 6 (after the 6<sup>th</sup> day of NIV, in the PP group this also corresponded to the respiration after the 6<sup>th</sup> PP session on day 6. pp7 during the 7<sup>th</sup> PP session; sp7 supine position timepoint 7 (after the 7<sup>th</sup> day of NIV, in the PP group this also corresponded to the respiration after the 7<sup>th</sup> PP session on day 7. This schedule allowed comparing gas exchange responses among group at day 1, after 24 h of NIV, in the same (supine) position, after taking into account the effect of the first overnight PP session (timepoint pp1) in the PP groups

**Panel B: Mechanical Power (MP)**



**Panel C: expiratory tidal volume (VTe)**

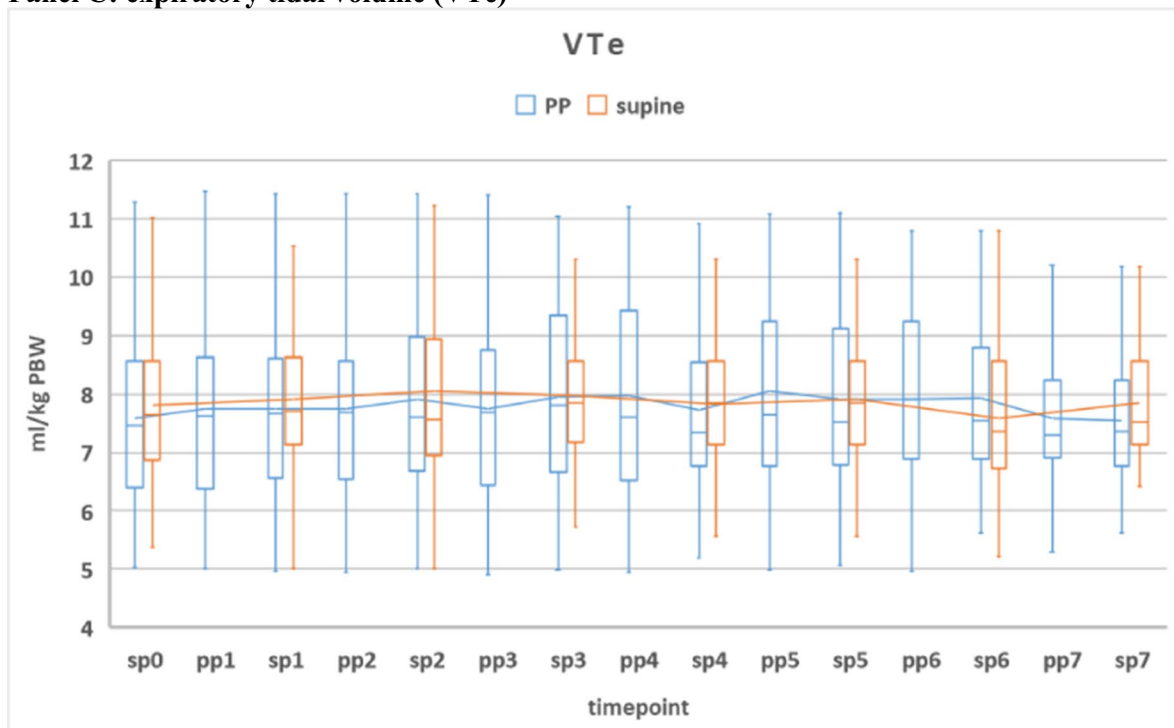


Fig. 2 (continued)

**Panel D: respiratory rate (RR)**

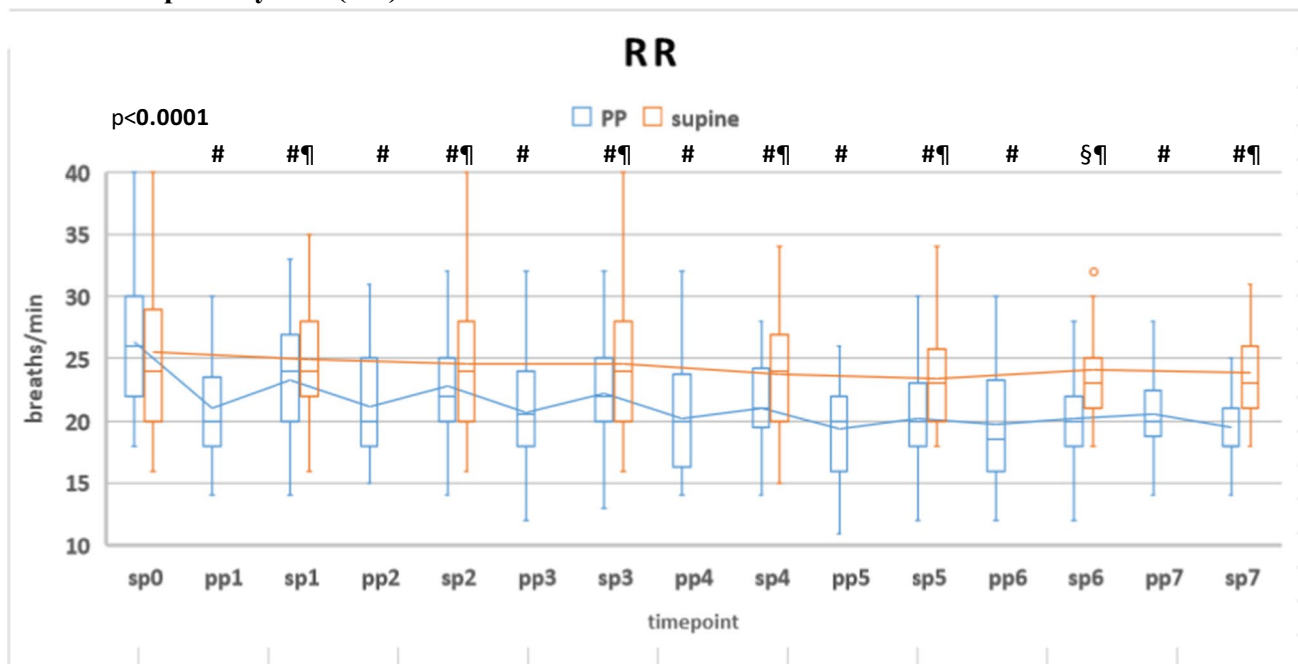


Fig. 2 (continued)

scans showed largely predominant ground-glass opacities (Table 1).

**LUS lung aeration assessment**

The median (IQR) global LUS severity score was 25 (21, 30), closely correlating with global CT severity score ( $r_s = 0.83$ ;  $p < 0.001$ ; Supplementary Fig. 4).

Regional LUS categorization closely correlated with CT-assessed gas/tissue density, with each step increase of LUS score being associated with a significant increase in lung tissue density (Fig. 1 panel A): CT-LUS agreement was almost complete for WAL ( $k = 0.91$ ; 95%CI: 0.85–0.97), substantial for PAL ( $k = 0.61$ ; 95%CI: 0.57–0.66) and moderate ( $k = 0.55$ ; 95%CI: 0.51–0.60) for NAL (Supplementary Table 3A–B), consistent with previous reports in ARDS [34].

Based on these findings, an equation was developed to predict WAL(%) from global LUS score (Fig. 1 panel B).

**Treatment-related parameters and outcomes**

No patient was lost to follow-up and there were no missing data for evaluated end-points.

Patients initiated NIV and PP within 24 h of admission to the Subintensive Care Unit. Over the initial 48 h of treatment, NIV was delivered continuously or until intubation

and only brief interruptions were allowed for eventual adjustments and nursing care, lasting no more than few minutes; subsequently, daily breaks, lasting no more than 2 h, were allowed for meals and nursing care, depending on patient clinical condition and tolerance.

In PP and supine groups, ventilatory settings were similar among groups at baseline and remained unchanged from timepoints sp0 to sp1 (Table 1).

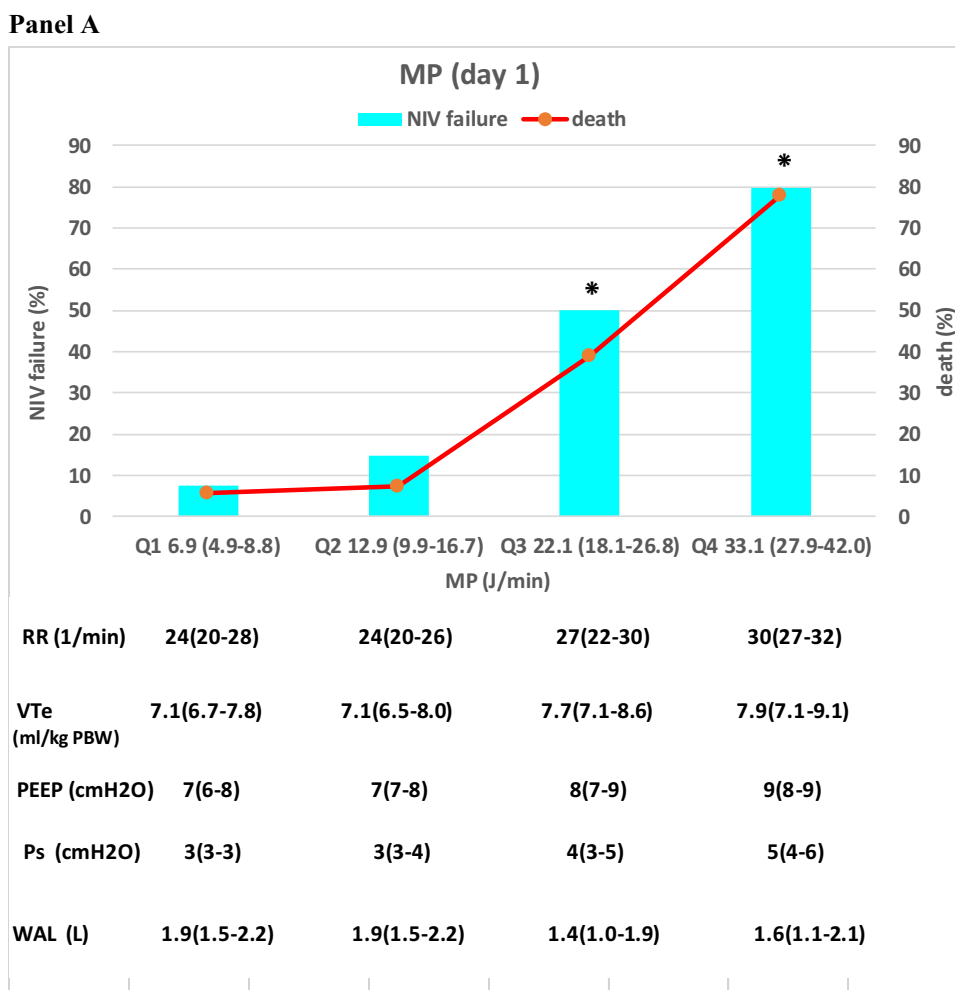
Daily hours of NIV and PP, the duration of the longest PP session, daily PP sessions and days of PP therapy are reported in Table 1.

Compared with supine group, PP therapy was associated with improved gas exchange and ultrasonographic parameters and clinical outcomes (Supplementary Fig. 5–6, Supplementary Table 4).

**Effect of PP therapy on  $MP_{WAL}$**

PP therapy was associated with a significant  $MP_{WAL}$  reduction:  $MP_{WAL}$  decreased by a median 34% (IQR: 30–38%) during the first PP session (timepoint pp1) as compared with pre-proning values (timepoint sp0) (Fig. 2 panel A–D).  $MP_{WAL}$  reduction during 1<sup>st</sup> PP session was driven mainly by a RR decrease and secondly by a modest (5%; 2–7%) WAL increase (Fig. 2A–D). The magnitude of WAL % increase during 1st PP session was consistent with recent reports [40–42].

**Fig. 3 Panel A–B:** relationship between MP, MP<sub>PBW</sub> and MP<sub>WAL</sub> during day 1 of NIV in the whole study population (*n* = 216). **Panel C–D:** quartiles of MP (Panel A), MP<sub>PBW</sub> (Panel B) and MP<sub>WAL</sub> (Panel C) and 28-d NIV failure and death (%) in the whole study population (*n* = 216). Median (range) of MP, of components of MP and of well aerated lung (WAL) volumes are displayed at the bottom of each graph. \**p* < 0.05 vs. other quartiles for NIV failure and death; †*p* < 0.001 vs other quartiles for NIV failure and death



Daily MP<sub>WAL</sub> swings between prone and supine position subsided after day 5(timepoint pp5)(P supine vs. prone > 0.05), suggesting no additional effect on MP<sub>WAL</sub> from further PP days (Fig. 2A).

**Relationship of early (day 1) power measures with clinical outcomes**

We first assessed the relationship between different power measures at day 1 and clinical outcomes (NIV failure, death) (Fig. 3A–C): we observed a progressive, linear, statistically significant increase in NIV failure and death rates across each MP<sub>WAL</sub> quartile, but not across MP and MP<sub>PBW</sub> quartiles, which rather showed a steep increase in the rate of clinical outcomes in the 3-4<sup>th</sup> quartile as compared with the lower 2 quartiles.

The investigation of mutual relationship between MP, MP<sub>PBW</sub> and MP<sub>WAL</sub> at day 1 disclosed a the weak correlation between MP<sub>WAL</sub> and the other power measures, indicating for any given value of MP delivered by NIV to the

respiratory system, the energy per unit volume of WAL varied widely (Fig. 3D–E).

**Early (day 1) MP<sub>WAL</sub> is independently associated with clinical outcomes**

We then categorized the whole study population based on median MP<sub>WAL</sub> delivered during the initial 24 h of NIV (day 1) into high MP<sub>WAL</sub> (i.e. MP<sub>WAL</sub> ≥ 9.1 J/min/L) or low MP<sub>WAL</sub> (i.e., MP<sub>WAL</sub> < 9.1 J/min/L); patients receiving a low MP<sub>WAL</sub>(day 1) showed lower 28-d NIV failure, intubation and death rates than those receiving a high MP<sub>WAL</sub>(day 1) (Table 1, Fig. 4).

In Cox proportional multivariable models, MP<sub>WAL</sub> (day 1) predicted 28-d NIV failure (HR 1.682; 95%CI: 1.147–2.412, *p* = 0.003), intubation (HR 1.521; 95%CI: 1.193–2.314, *p* = 0.009) and death (HR 1.697; 95%CI: 1.217–2.313, *p* = 0.002) independently of baseline illness and lung disease severity and of other ventilatory variables (Table 2).



Fig. 3 (continued)

Panel B



**Predictive performance of MP<sub>WAL</sub>(day 1) for clinical outcomes**

Each ventilatory variable at day 1 was regressed on NIV failure and mortality in the whole study population: MP<sub>WAL</sub>(day 1) showed the highest AUROC for predicting 28-d NIV failure (AUROC 0.89; 95%CI: 0.85–0.93, *p* < 0.001) and death (AUROC 0.89; 95%CI: 0.85–0.94, *p* < 0.001), outperforming all other ventilatory parameters and WAL (*p* < 0.011 for both comparisons by DeLong’s test) (Table 3, Fig. 5). Additionally, MP<sub>WAL</sub>(day 1) optimal thresholds for both NIV failure and death overlapped.

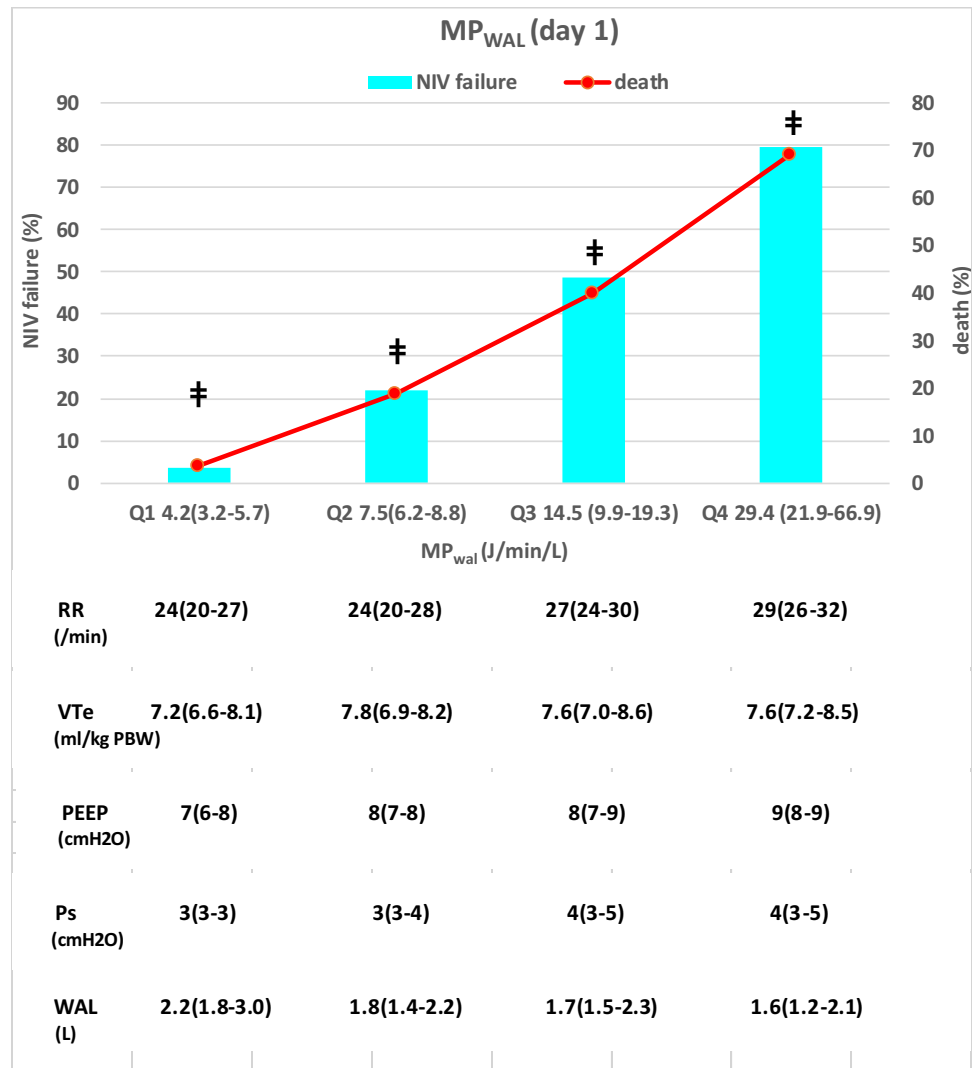
**Time course of ventilatory and other physio-anatomical variables during the initial 7 days of NIV**

Over the initial 7 days there were missing data in the physiological parameters due to the occurrence of NIV failure or success and subsequent Unit discharge. Because these data were not missing at random but due to the consequence of treatment effect, we did not perform multiple imputation and excluded missing values from analyses.

Figure 6 shows time course of different ventilatory, ultrasonographic and inflammatory parameters in PP and supine patients receiving either high or low MP<sub>WAL</sub>(day 1).

Fig. 3 (continued)

Panel C



Within each treatment group (PP or supine), median daily  $MP_{WAL}$  remained relatively constant during initial days of NIV (Fig. 6A–B); gas exchange parameters (paO<sub>2</sub>/FiO<sub>2</sub> ratio, VR, MVcorr), ultrasonographic parameters (global LUS score, global re-aeration score, WAL %) and inflammatory biomarkers (CRP, procalcitonin) improved significantly over the initial 24 h of NIV (day 1, timepoint sp0-1) only in patients receiving a low  $MP_{WAL}$ , but not in those receiving a high  $MP_{WAL}$  (Table 1, Fig. 6C–P). The differences between low and high  $MP_{WAL}$  group observed at day 1 were magnified during the initial 7 days of NIV (Table 1, Fig. 6).

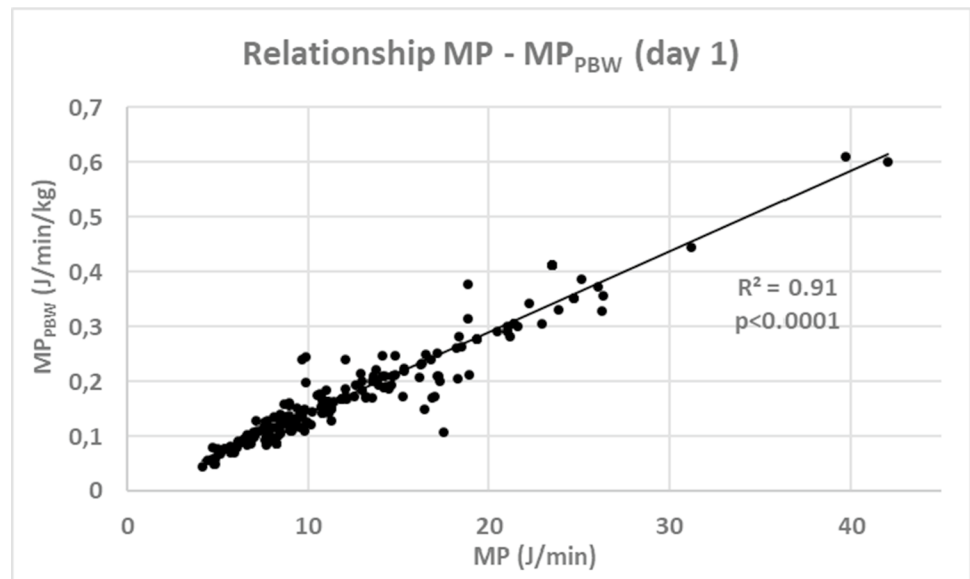
### Impact of early (day 1) $MP_{WAL}$ on physio-anatomical responses

We next explored potential mechanisms underlying the association of  $MP_{WAL}$ (day 1) with the observed clinical outcomes.

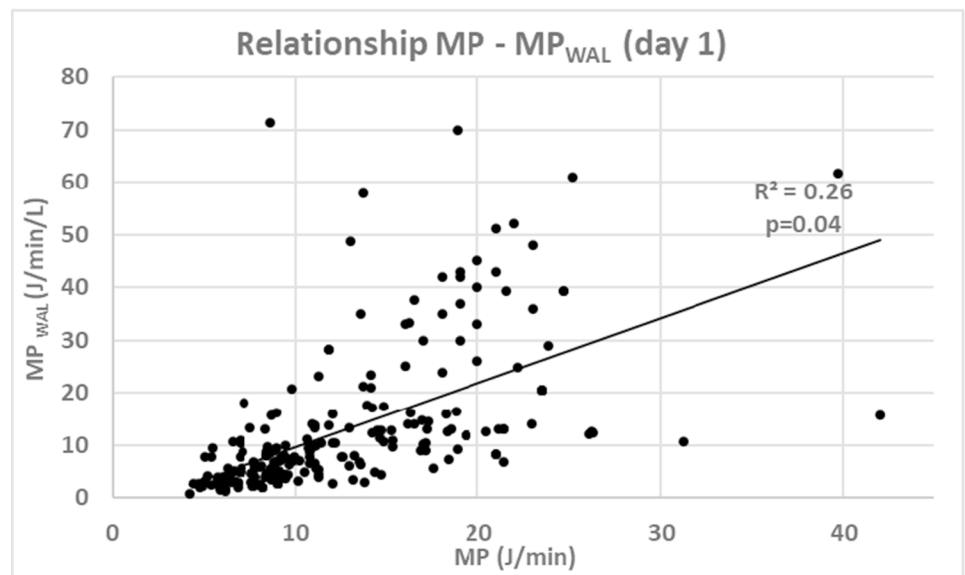
In the whole study population, early  $MP_{WAL}$ (day 1) correlated significantly with O<sub>2</sub> response, CO<sub>2</sub> response ultrasonographic responses and C-reactive protein changes at resupination (timepoint sp1) in univariate analysis (Fig. 7).

Fig. 3 (continued)

Panel D



Panel E



The observed associations were confirmed by multivariable analysis, where  $MP_{WAL}$ (day 1) independently predicted  $\Delta VR_{sp0-1}$  ( $\beta = 0.43$ ,  $p = 0.011$ ),  $\Delta global LUS_{sp0-1}$  ( $\beta = 0.41$ ,  $p = 0.018$ ), global reoxygenation score<sub>sp1</sub> ( $\beta = -0.49$ ,  $p = 0.009$ ),  $\Delta WAL_{sp0-1}$  ( $\beta = 0.41$ ,  $p = 0.018$ ) and  $\Delta C$ -reactive protein<sub>sp0-1</sub> ( $\beta = 0.38$ ,  $p = 0.029$ ) (Table 4).

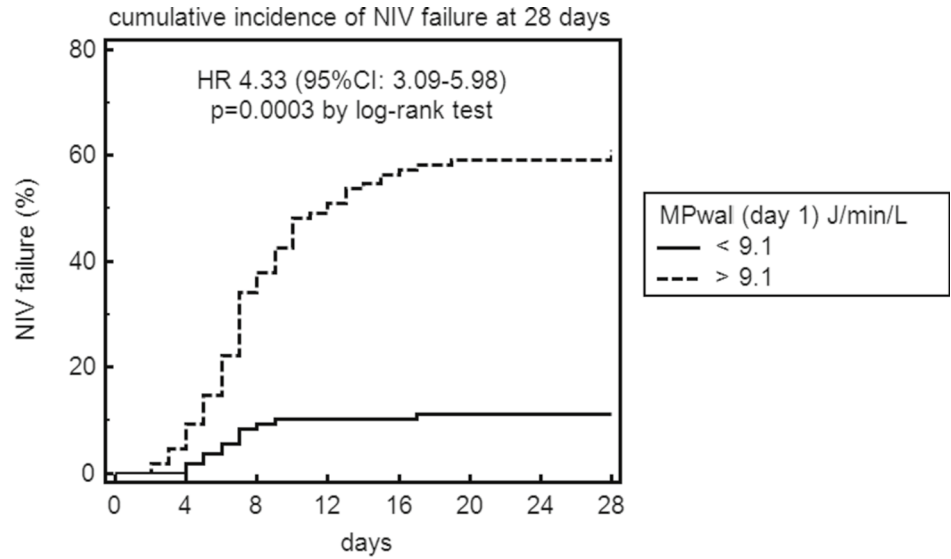
## Discussion

In the first report exploring  $MP_{WAL}$  in COVID-19 AHRF treated with prone or supine NIV, we found that.

- 1) PP was associated with a significant  $MP_{WAL}$  reduction, attributable mainly to an absolute MP reduction and secondly to a relief in the “intensity” of the power delivered to the aerated lung through enhanced lung reoxygenation (Fig. 2).
- 2)  $MP_{WAL}$  delivered during the first 24 h of NIV [ $MP_{WAL}$ (day 1)] outperformed other power measures and ventilatory variables in clinical and pathophysiological outcome prediction.
- 3)  $MP_{WAL}$ (day 1) independently predicted different markers of VILI, including gas exchange parameters, ultrasonographic and inflammatory biomarkers, in both supine and proning patients.

**Fig. 4** Cumulative incidence of Noninvasive Ventilation (NIV) failure (Panel A), death (Panel B) and endotracheal intubation (Panel C) at 28 days after enrollment in patients grouped according to high ( $\geq 9.1$  J/min/L) vs low ( $< 9.1$  J/min/L)  $MP_{WAL}$  at day 1. In the endotracheal intubation group, patients with a Do-Not-Intubate (DNI) disposition were excluded

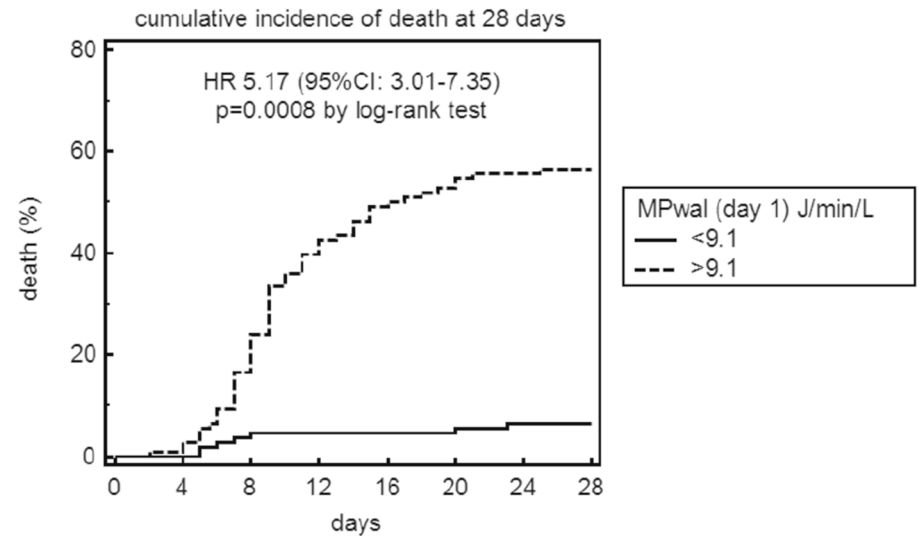
**Panel A: NIV failure**



Number at risk

Group: < 9.1	108	106	98	97	97	96	96	0
Group: > 9.1	108	98	67	53	46	44	44	0

**Panel B: death**

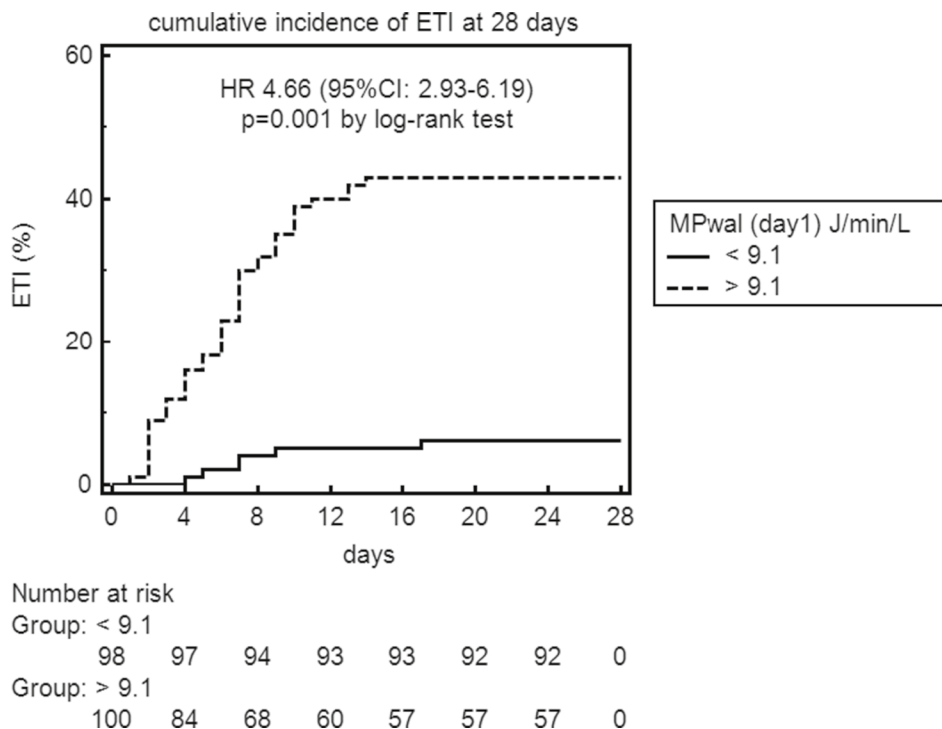


Number at risk

Group: < 9.1	108	108	103	103	102	101	100	0
Group: > 9.1	108	105	82	62	54	49	48	0

Fig. 4 (continued)

**Panel C: endotracheal intubation (ETI)**



Diferent mechanical ventilatory variables have been proposed to affect clinical outcomes and to contribute to VILI, all of which have been separately addressed in experimental or clinical studies [1-3]. The MP represents the energy delivered to the respiratory system by mechanical ventilation, which results from a combination of ventilatory variables. Therefore, MP might have a higher predictive value for patient-centered outcomes, as different combinations of its components may yield a similar damage to the lung [4-8]. The ability to combine the effect of time-varying ventilatory variables seems particularly attractive in spontaneously breathing patients.

Our findings suggest MP delivered early after NIV initiation predicts both NIV failure and mortality. However, the power should be normalized to the size of for the size of well-inflated lung to get an optimal cut-off that could be used in clinical practice, as VILI originates from the interaction between the MP delivered to the respiratory system by the ventilation and the anatomical and pathophysiological characteristics of the latter. Notably, we demonstrated that bedside LUS could be used to accurately estimates WAL size, consistent with data from nonCOVID-19 ARDS [29].

Lastly, we showed that early PP may reduce MP<sub>WAL</sub> while improving oxygenation and CO<sub>2</sub> clearance during NIV. Therefore, early PP therapy may be a more “energetically” advantageous strategy to relieve hypoxemia than PEEP uptitration, which may overdistend the lung and increase MP and lung injury when it does not recruit atelectatic lung tissue [8, 35]. The association of PEEP levels

and NIV duration with COVID-19 pneumonia severity and mortality is consistent with this view [11-13].

Our analysis may have several clinical implications for noninvasive AHRF management.

First, it suggests PP can effectively reduce MP delivery. Second, they suggest early MP<sub>WAL</sub> calculation may help define the trade-offs between the benefits and risks of noninvasive ventilatory support, helping to titrate NIV to the least possible energy to achieve oxygenation and enhancing prompt NIV up-grade to invasive mechanical ventilation (IMV) to prevent VILI progression. Both these issues warrant evaluation in future ad hoc trials enrolling different AHRF etiologies.

**Strengths and limitations**

Strengths of our report are the thorough patient assessment, the hourly ventilatory data collection, which reflect actual power delivery during each ventilatory session more accurately than once daily data, and the separate assessment of supine and prone ventilatory modality. Limitations of our analysis include its post hoc nature and the absence of randomization in the original study. Furthermore, we focused on ventilator-delivered energy and did not assess the energy transferred from respiratory muscles to the lung during inspiration. However, consistent with COVID-19 literature, our patients had no clinical-radiological evidence for increased inspiratory effort or reduced lung compliance [14-17], and Pes swings, an index of inspiratory effort, are unrelated to disease course

and unaffected by PP [43], while MPWAL predicted physio-anatomical and clinical outcomes in our patient population.

## Conclusions and expert recommendations

Concern has been raised that mechanical ventilation may promote VILI and worsen outcome in spontaneously breathing patients with AHRF. Different ventilatory variables have been proposed to contribute to VILI progression, but no effective predictive, preventive and patient-centered model has been developed [44–48].

Based on our findings we suggest early quantitation of well-aerated lung volume before NIV initiation in each patient with AHRF candidate to NIV, through CT scan analysis or at least through lung ultrasound, which in our series was at least as accurate for WAL quantitation as free open source software.

After NIV initiation, the value of MP delivered to the patient by NIV could be estimated from routine ventilatory parameters using available formulas and adjusted for individual WAL volume to estimate  $MP_{WAL}$ : if patient's  $MP_{WAL}$  exceeds suggested safety threshold (9.1 J/min/L), VILI could be prevented by implementing PP, which reduced  $MP_{WAL}$  by an average of 34% in our series.

If PP fails to reduce  $MP_{WAL}$  below safety threshold, NIV upgrade to invasive ventilation should be considered to achieve complete ventilatory control and reduce  $MP_{WAL}$  and the risk of VILI.

The added value of this approach in noninvasively ventilated AHRF patients is to provide an accurate tool for early prediction of the risk of VILI and adverse outcomes (i.e.,  $MP_{WAL}$  at day 1), an effective mean to prevent or reduce the risk of VILI (i.e., prone position adoption). Furthermore, this approach should be personalized, i.e. the MP delivered by the ventilator to patient's respiratory system should be adjusted for individual WAL size, which varies widely across AHRF patients and could be calculated by lung imaging techniques.

This integrated approach, which showed accuracy in our study, needs prospective validation in independent cohorts of patients with AHRF of diverse etiologies.

## Appendix

### PPPM Innovation highlights

#### Working hypothesis in the framework of PPPM

Concern has been raised that mechanical ventilation may promote lung injury (so called ventilation-induced lung injury, VILI) and worsen outcome in spontaneously breathing patients with acute hypoxemic respiratory failure (AHRF).

Different ventilatory variables have been proposed to contribute to VILI progression, but data in noninvasively

ventilated patients are scarce, inconsistent and inconclusive and no valuable outcome predictor currently exists.

Mechanical power (MP), a measure of the energy transfer rate from the ventilator to the respiratory system, predicted mortality in invasively ventilated ARDS patients, but its role in noninvasively ventilated AHRF is unexplored.

### Innovation towards the

#### 1. predictive approach,

Mechanical Power normalized to the volume of well-aerated lung ( $MP_{WAL}$ ) delivered during the initial 24 h of noninvasive ventilation (NIV) independently predicts NIV failure intubation and death and affects physio-anatomical

**Table 2** Cox multivariable analysis of predictors of 28-d NV failure, death and endotracheal intubation (ETI) ( $n=216$ )

28-d NIV failure			
SAPS II	1.027	0.983 to 1.272	0.293
PP therapy (1 = yes, 0 = No)	0.581	0.392 to 0.772	<b>0.009</b>
Baseline $pO_2/FiO_2^*$	0.982	0.734 to 1.696	0.128
Baseline WAL (L)	1.044	0.891 to 1.986	0.319
RR (day 1)	1.186	0.892 to 1.539	0.146
VTe(day 1) (ml/kgPBW)	1.017	0.749 to 2.013	0.318
PEEP(day 1)(mmHg)	1.179	0.874 to 1.528	0.412
$MP_{WAL}$ (day 1)(J/min/L)	1.682	1.147 to 2.412	<b>0.005</b>
28-d death			
Parameter	HR	95%CI	P
Age	1.088	1.0426 to 1.198	<b>0.028</b>
ISARIC 4C score	1.026	0.947 to 1.192	0.334
PP therapy	0.629	0.271 to 0.812	<b>0.010</b>
Baseline $paO_2/FiO_2^*$	0.999	0.894 to 1.166	0.296
Baseline WAL (L)	1.039	0.792 to 1.893	0.427
RR (day 1)	1.116	0.975 to 1.428	0.239
$MP_{WAL}$ (day 1)	1.697	1.217 to 2.316	<b>0.002</b>
28-d endotracheal intubation			
SAPS II	1.021	0.872 to 1.812	0.513
PP therapy (1 = yes, 0 = No)	0.598	0.283 to 0.781	0.007
Baseline $pO_2/FiO_2^*$	0.992	0.621 to 1.769	0.389
Baseline WAL (L)	1.028	0.891 to 1.986	0.319
RR (day 1)	1.112	0.783 to 1.702	0.192
VTe(day 1) (ml/kgPBW)	1.132	0.649 to 2.913	0.413
$MP_{WAL}$ (day 1)(J/min/L)	1.682	1.147 to 2.412	0.005

Statistically significant  $p$ -values are written in bold characters

ISARIC international severe acute respiratory infection consortium, NIV noninvasive ventilation, SAPS simplified acute physiology score, PEEP positive end-expiratory pressure,  $MP_{WAL}$ , mechanical power normalized to well-aerated lung volume, CI confidence interval, PBW predicted body weight

\*on admission, while on a  $FiO_2$  50% Venturi mask or a non-rebreather reservoir bag mask

**Table 3** Discrimination of ventilator parameters measured during the 1st 24 h of NIV (day 1) in predicting 28-d NIV failure and death in the whole study population ( $n = 216$ )

Parameter	NIV failure at 28 days				Death at 28 days			
	Cut-off	Se(%)	Sp(%)	AUROC (95%CI)	Cut-off	Se(%)	Sp(%)	AUROC (95%CI)
MP <sub>WAL</sub> (day 1) (J/min/L)	9.2	88	86	0.89 (0.85–0.93) *#	9.3	89	87	0.89 (0.85–0.94) *#
MP (day 1) (J/min)	16.7	78	77	0.80 (0.72–0.85) *	20.9	80	73	0.76 (0.72–0.83) *
MP <sub>PBW</sub> (day 1) (J/min/kg)	0.147	76	77	0.79 (0.72–0.85) *	0.169	84	76	0.79 (0.73–0.86) *
VTe(day 1) (ml/kg)	7.9	64	72	0.66 (0.58–0.73)	9.6	65	78	0.67 (0.59–0.74)
RR(day 1) (breaths/min)	28	75	61	0.65 (0.58–0.72)	31	69	60	0.64 (0.56–0.70)
PEEP(day 1) (cmH2O)	9	36	74	0.54 (0.47–0.61)	10	46	78	0.63 (0.55–0.70)
Ps(day 1) (cmH2O)	4	65	50	0.58 (0.47–0.68)	6	74	53	0.64 (0.53–0.74)
WAL(day 1) (L)	1.7	66	72	0.70 (0.62–0.78)	1.0	81	45	0.63 (0.55–0.71)

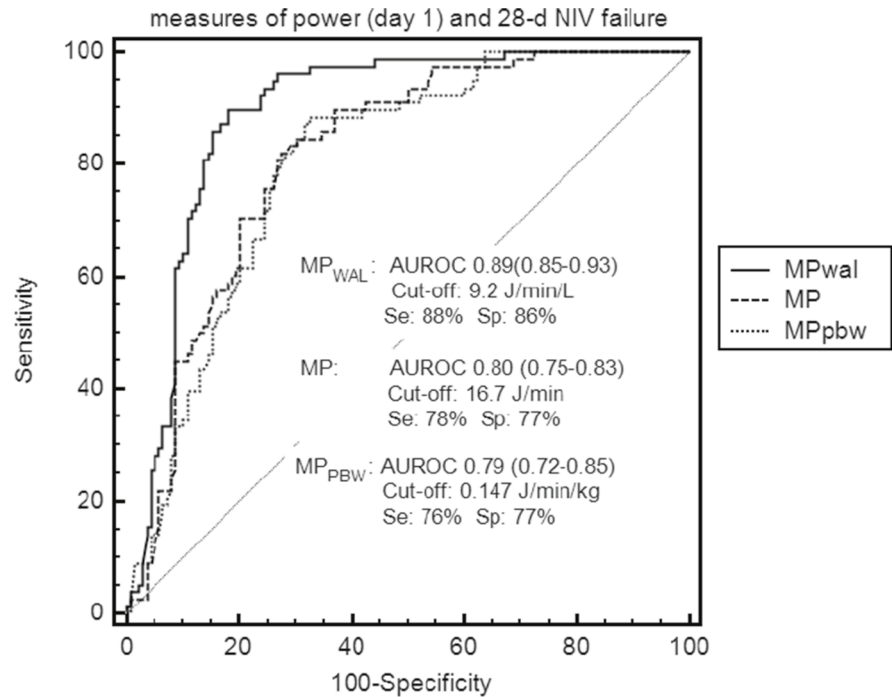
\*  $p < 0.001$  vs VTe, RR, PEEP, Ps, WAL at day 1 by DeLong test

#  $p < 0.01$  vs. MP or MP<sub>PBW</sub> at day 1 by DeLong test

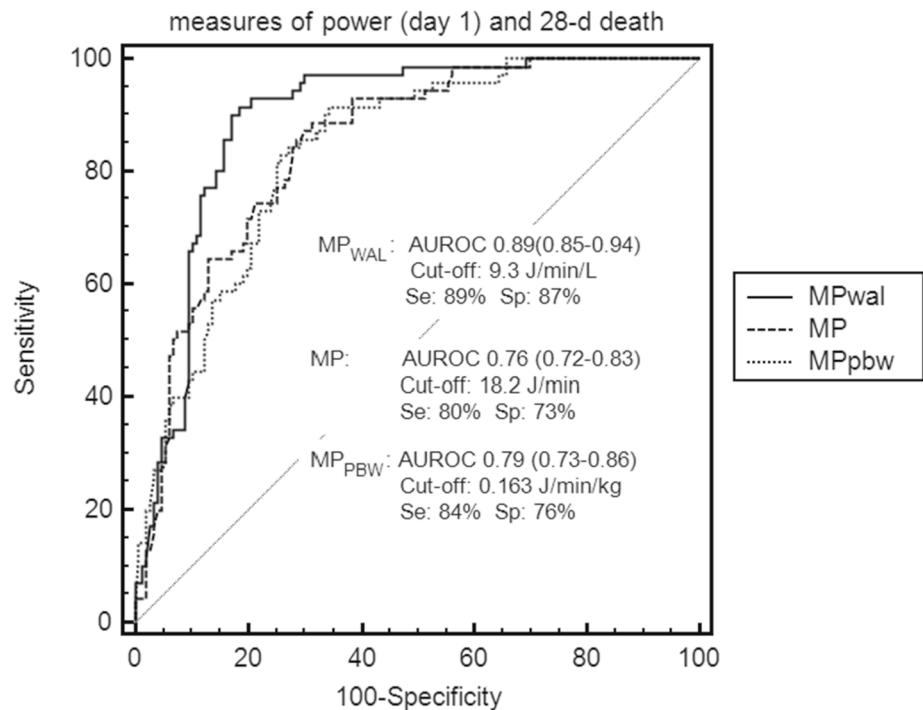
ISARIC international severe acute respiratory infection consortium, NIV noninvasive ventilation, SAPS simplified acute physiology score, PEEP positive end-expiratory pressure, MP<sub>WAL</sub> mechanical power normalized to well-aerated lung volume, MP mechanical power, AUROC area under receiver operating characteristic curve, CI confidence interval, PBW predicted body weight

**Fig. 5** Time-course of different ventilatory (Panel A-B), gas exchange (Panel C-F), ultrasonographic (Panel G-N) and inflammatory (Panel O-P) parameters during the initial 7 days of NIV in the PP and supine groups, grouped according to low  $MP_{WAL}$  or high  $MP_{WAL}$  during the 1st 24 h of NIV (day 1) ( $n=216$ ). \*  $P < 0.05$  vs baseline (same group) #  $P < 0.01$  vs. baseline (same group) §  $P < 0.01$  vs. baseline (both groups) †  $P < 0.001$  vs. baseline (both groups) ‡  $P < 0.001$  between groups ¶  $P < 0.001$  between groups #  $P < 0.001$  ‡

### Panel A: measures of power (day 1) and 28-d NIV failure



### Panel B: measures of power (day 1) and 28-d death





**Fig. 6** Dose–response relationship between Mechanical Power normalized to well-aerated lung volume during the 1<sup>st</sup> 24 h of NIV [MP<sub>WAL</sub> (day 1)] and physio-anatomical responses after the 1<sup>st</sup> 24 h of NIV ( $\Delta$ sp0-1) in the whole study population ( $n = 216$ ). PP patients are represented by black full dots, supine patients are represented by empty triangles. In the plots, the green area denotes a positive gas exchange (O<sub>2</sub> or CO<sub>2</sub>) response, the red area a negative gas exchange response. -O<sub>2</sub> response: an increase in paO<sub>2</sub>/FiO<sub>2</sub> ratio during NIV in supine position at day 1 (timepoint sp1) as compared with NIV supine at timepoint sp0: i.e.,  $pO_2/FiO_{2_{sp1}} - pO_2/FiO_{2_{sp0}} > 0$ , or  $\Delta pO_2/FiO_{2_{sp0-1}} > 0$ . -CO<sub>2</sub> response: an increase in CO<sub>2</sub> clearance, defined by a reduction in dead space indices (VR and MV<sub>corr</sub>, tested separately) at sp1 as compared with timepoint sp0 [ $VR_{sp1} - VR_{sp0} < 0$  (or  $\Delta VR_{sp0-1} < 0$ )]

**Panel A: MP<sub>WAL</sub> PP group**

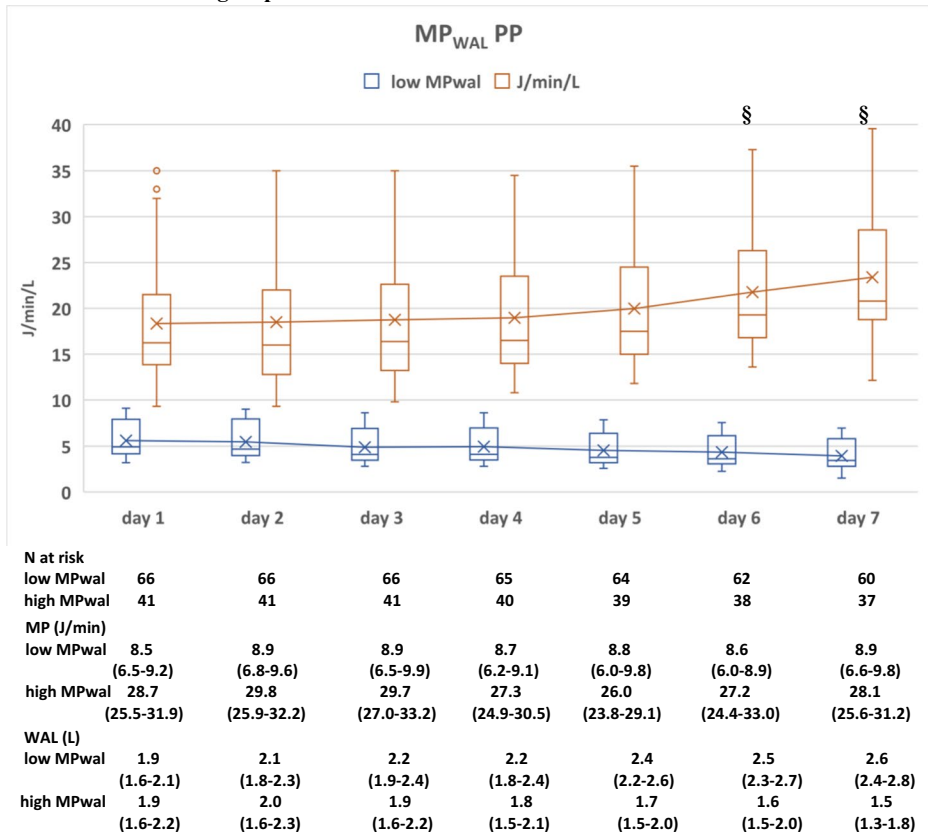
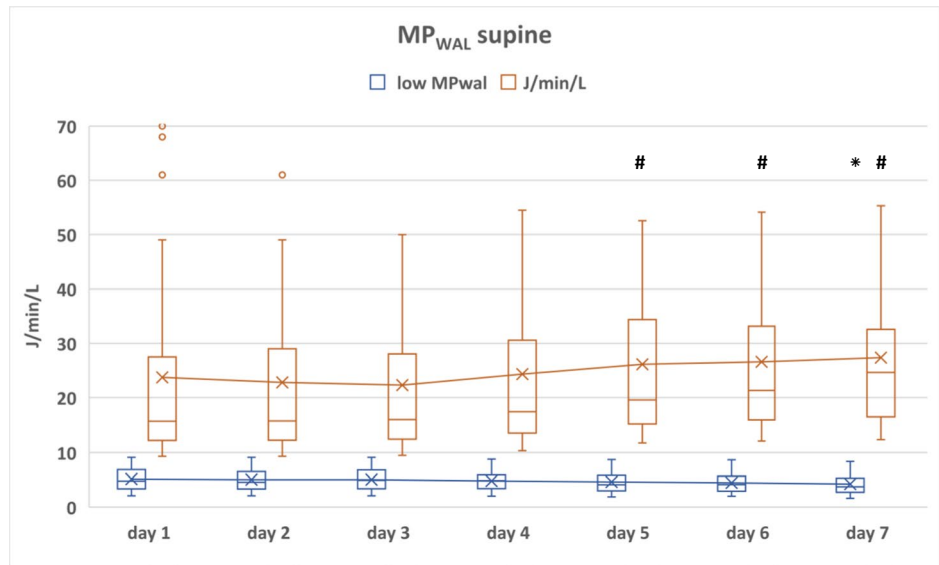


Fig. 6 (continued)

Panel B: MP<sub>WAL</sub> supine group

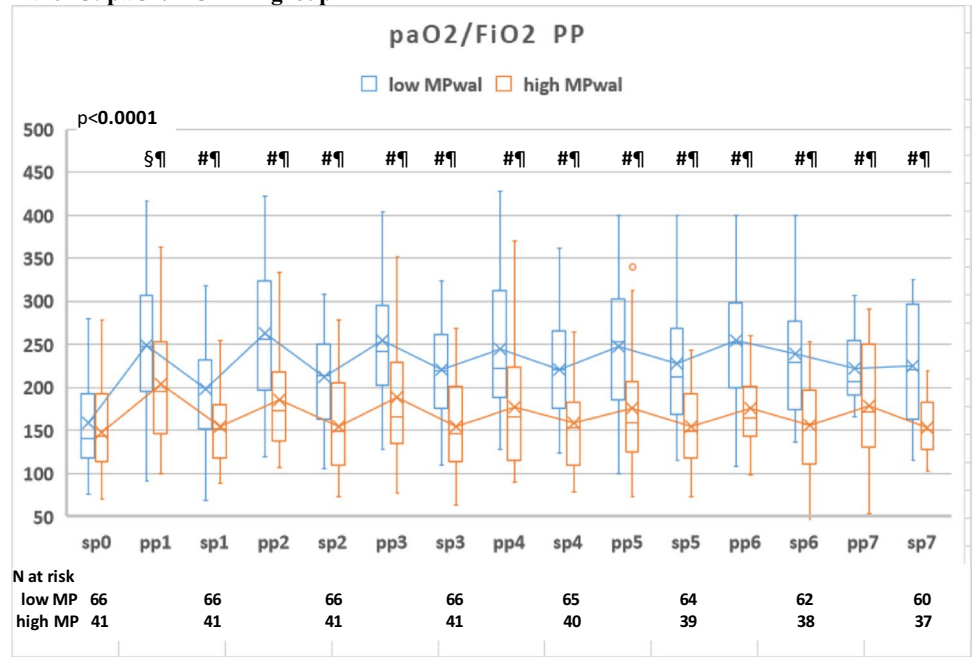


N at risk	day 1	day 2	day 3	day 4	day 5	day 6	day 7
low MP	42	42	42	42	41	41	40
high MP	67	65	63	61	57	54	47

MP (l/min)	day 1	day 2	day 3	day 4	day 5	day 6	day 7
low MPwal	8.7 (6.3-10.2)	8.8 (6.6-10.1)	8.9 (6.9-10.3)	8.7 (6.3-9.9)	9.1 (7.0-11.3)	9.4 (7.1-10.9)	9.5 (6.8-11.4)
high MPwal	27.8 (24.5-31.9)	28.1 (24.9-32.2)	27.6 (24.5-33.7)	28.1 (24.9-31.5)	27.5 (23.2-31.1)	26.0 (24.0-30.0)	25.8 (24.6-30.6)
WAL (L)	day 1	day 2	day 3	day 4	day 5	day 6	day 7
low MPwal	1.9 (1.7-2.1)	2.1 (1.8-2.3)	2.2 (2.0-2.4)	2.2 (1.9-2.4)	2.4 (2.1-2.7)	2.5 (2.2-2.8)	2.6 (2.4-2.9)
high MPwal	2.0 (1.7-2.3)	1.9 (1.8-2.2)	1.9 (1.6-2.12)	1.8 (1.5-2.1)	1.7 (1.5-2.0)	1.6 (1.5-2.0)	1.5 (1.3-1.8)

Fig. 6 (continued)

**Panel C: paO<sub>2</sub>/FiO<sub>2</sub> PP group**



**Panel D: paO<sub>2</sub>/FiO<sub>2</sub> supine group**

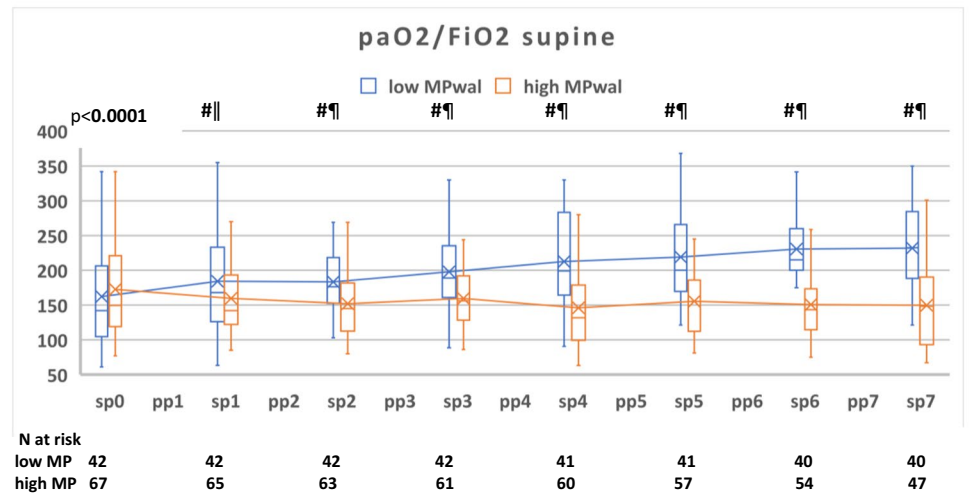
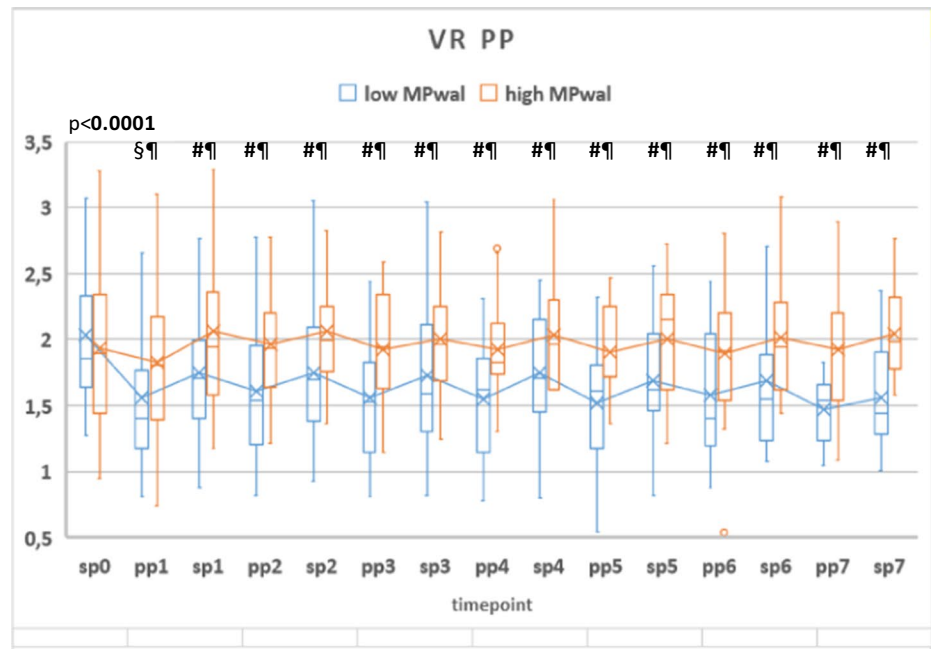


Fig. 6 (continued)

Panel E: Ventilatory Ratio (VR) PP group



Panel F: Ventilatory Ratio (VR) supine group

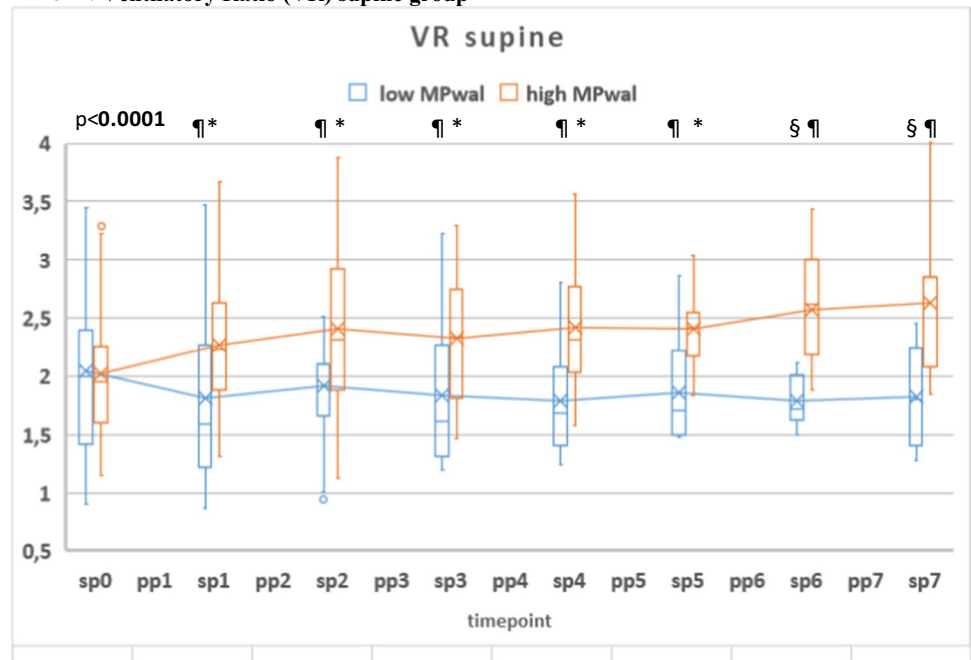
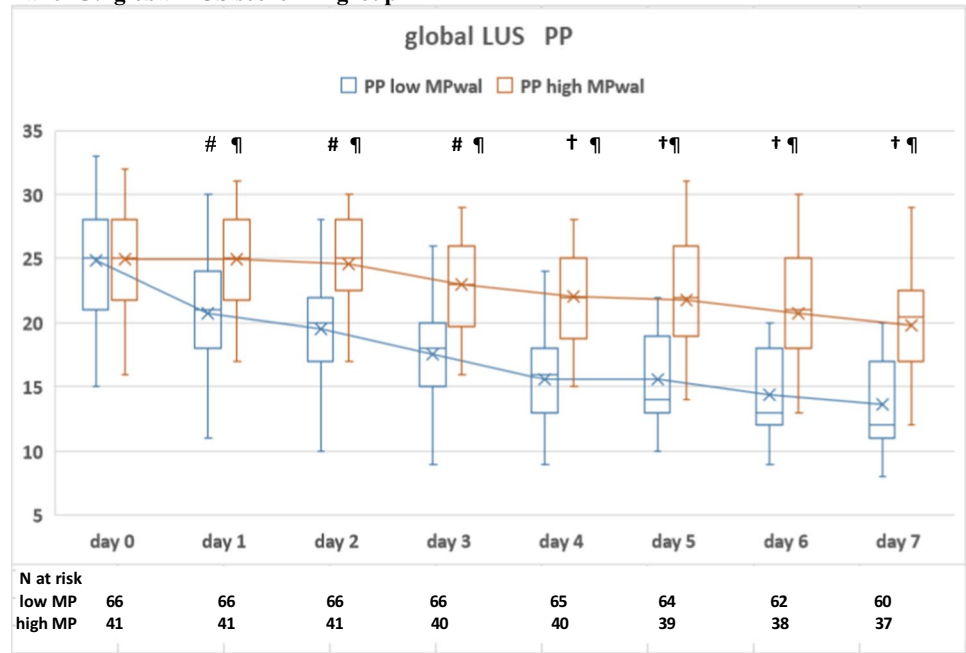


Fig. 6 (continued)

Panel G: global LUS score PP group



Panel H: global LUS score supine group

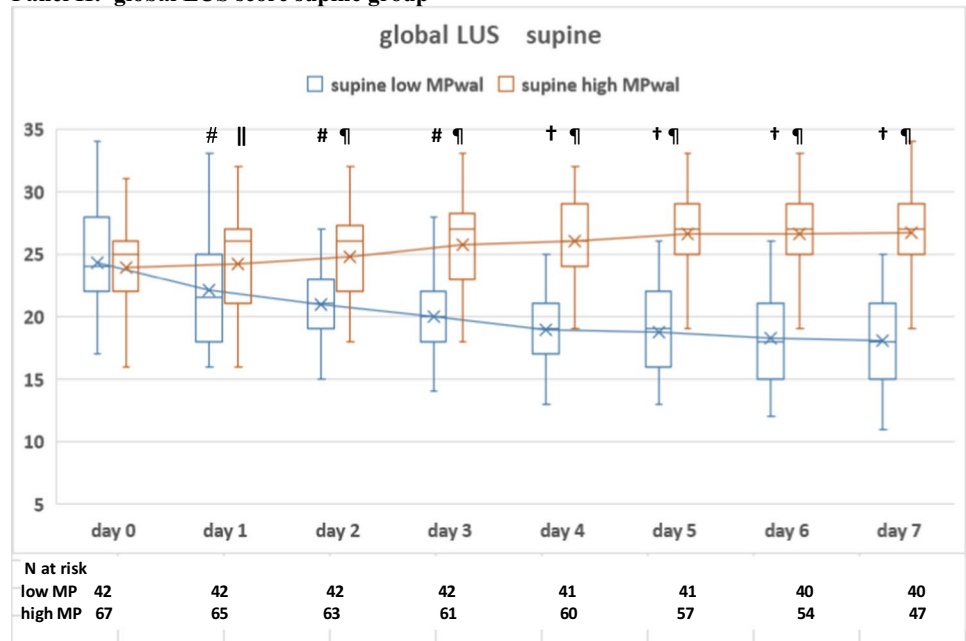
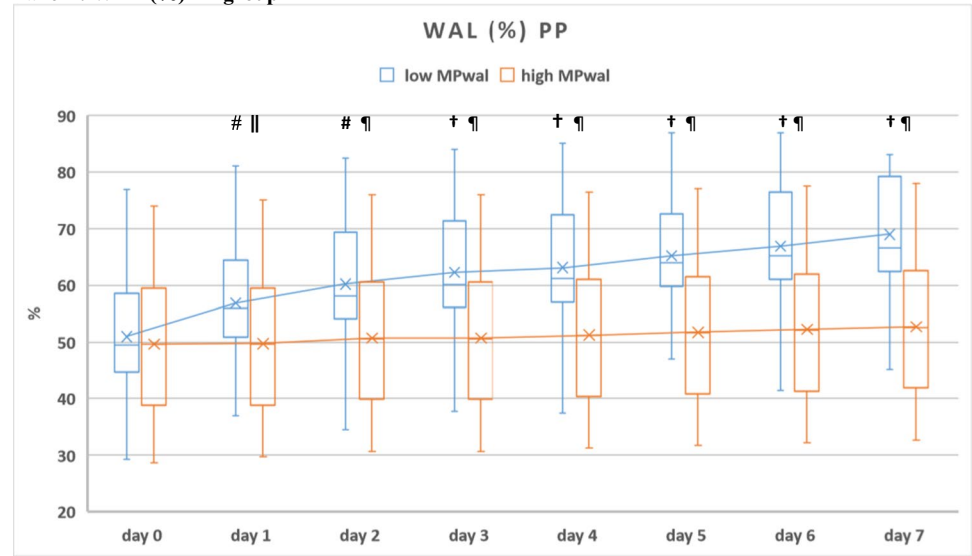


Fig. 6 (continued)

Panel I: WAL (%) PP group



Panel L: WAL (%) supine

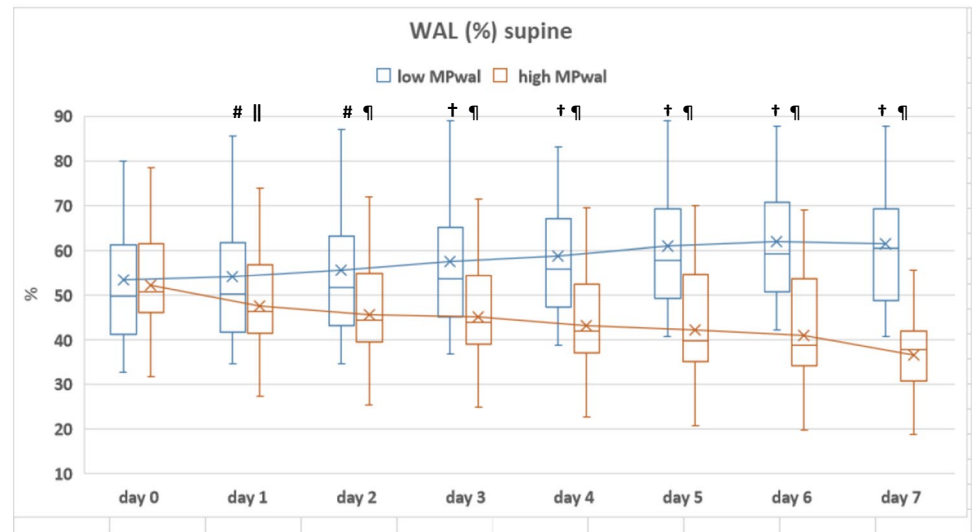
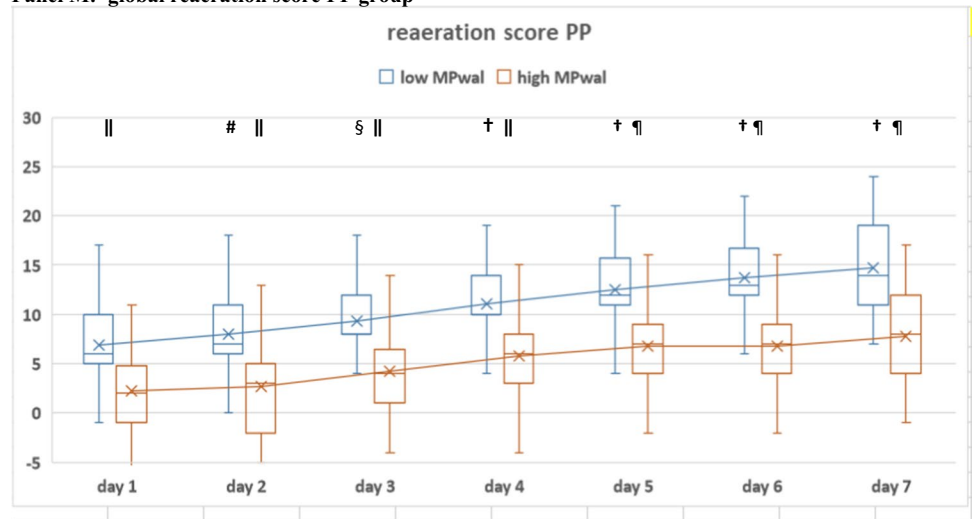


Fig. 6 (continued)

Panel M: global reactivation score PP group



Panel N: global reactivation score supine group

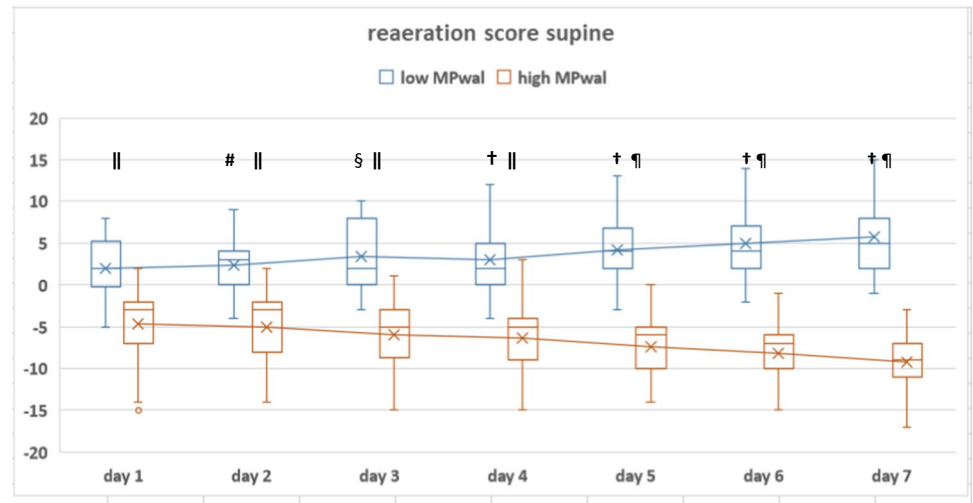
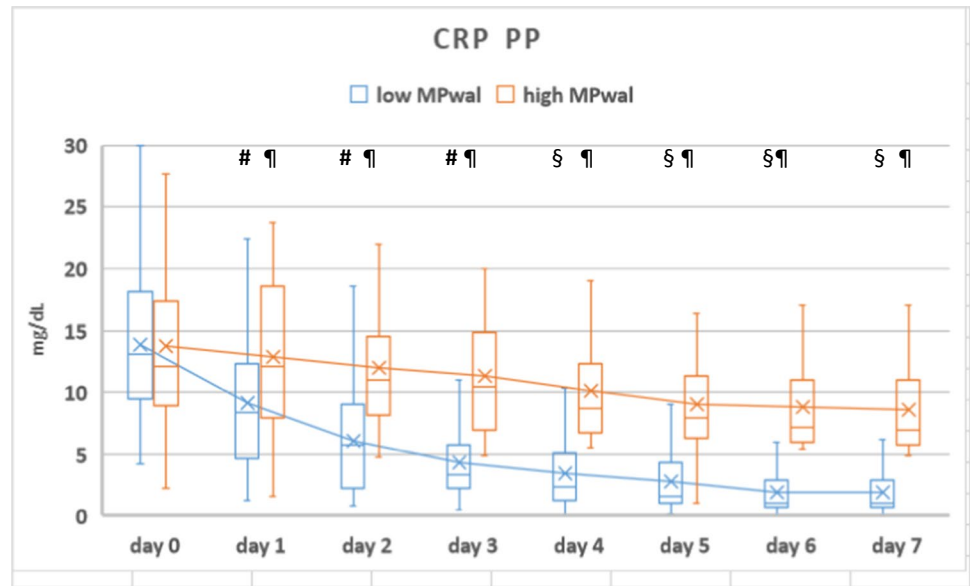
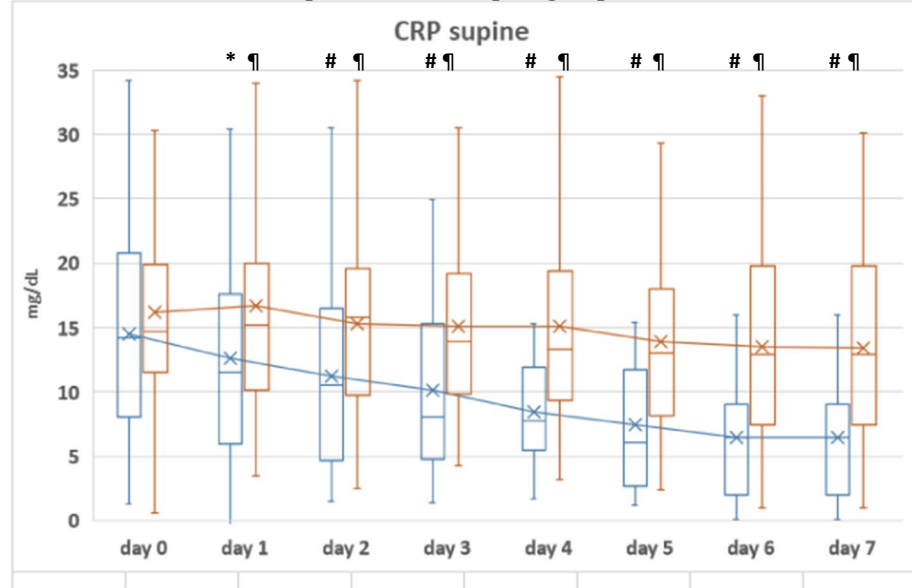


Fig. 6 (continued)

Panel O: serum C-reactive protein (CRP) PP group



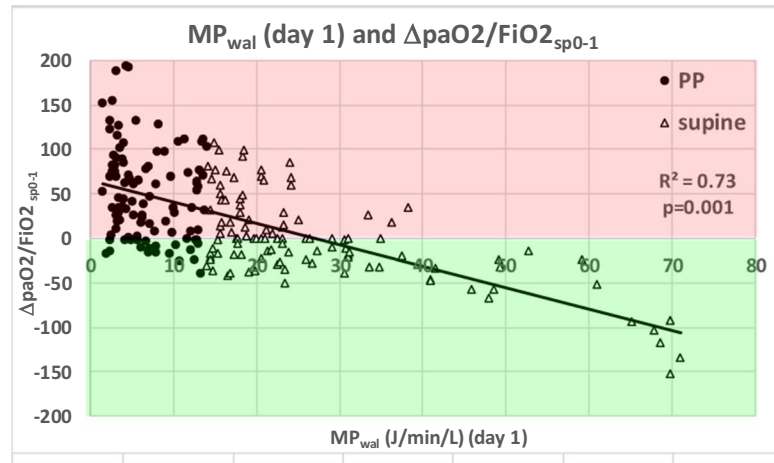
Panel P: serum C-reactive protein (CRP) supine group





**Fig. 7** Dose–response relationship between Mechanical Power normalized to well-aerated lung volume during the 1<sup>st</sup> 24 h of NIV [ $MP_{WAL}(\text{day 1})$ ] and physio-anatomical responses after the 1<sup>st</sup> 24 h of NIV ( $\Delta\text{spO}_2$ ) in the whole study population ( $n=216$ ). PP patients are represented by black full dots, supine patients are represented by empty triangles. Green area denotes a positive response, red area a negative one

**Panel A:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and O2 response ( $\Delta\text{paO}_2/\text{FiO}_2 \text{ ratio}_{\text{spO}_2-1}$ ) in the whole cohort ( $n=216$ ).



**Panel B:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and CO2 response ( $\Delta$ ventilatory ratio $_{\text{spO}_2-1}$ ) in the whole cohort ( $n=216$ ).

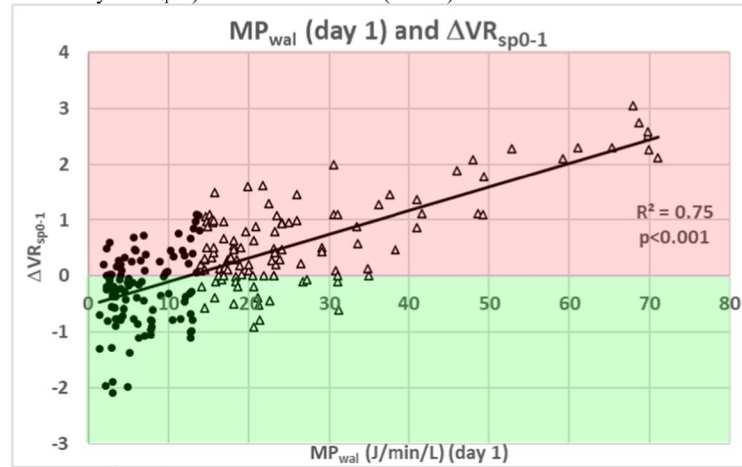
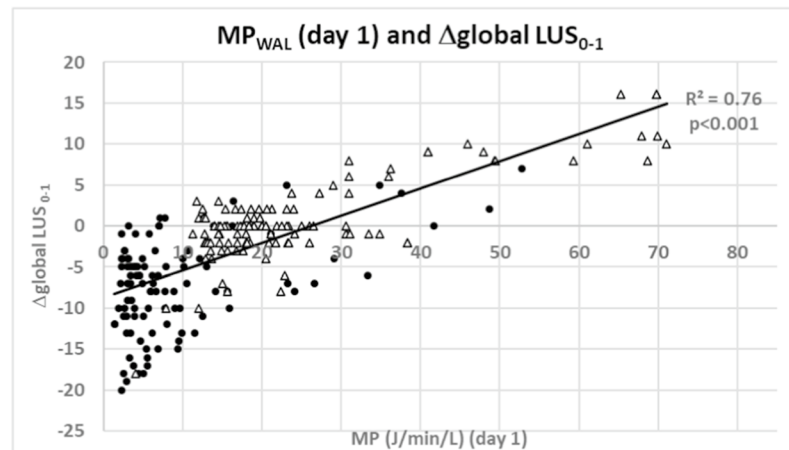


Fig. 7 (continued)

**Panel C:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and change in global lung ultrasonographic score at the end of day 1 ( $\Delta_{\text{global LUS}}_{0-1}$ ) in the whole cohort (n=216).



**Panel D:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and change in global well-aerated lung volume (WAL) (%) at the end of day 1 ( $\Delta_{\text{global WAL}}(\%)_{0-1}$ ) in the whole cohort (n=216).

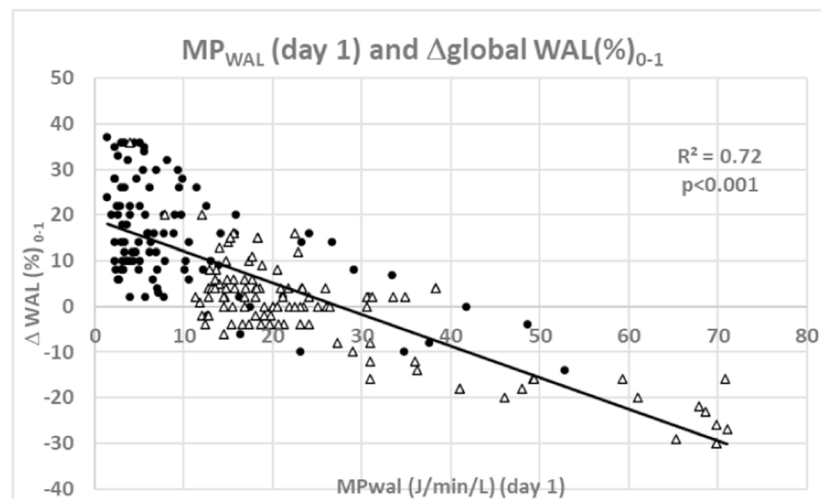
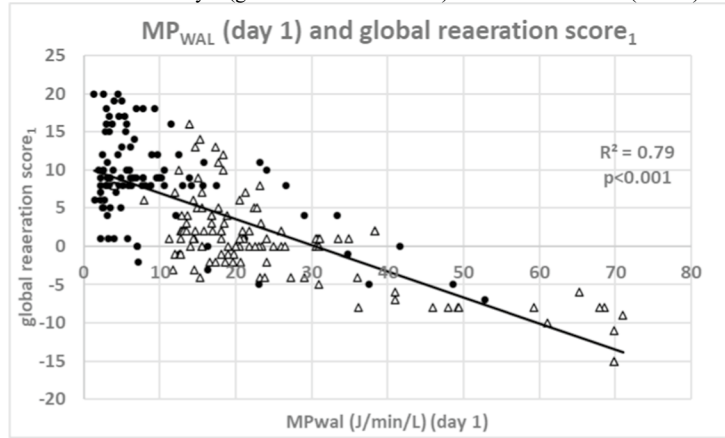
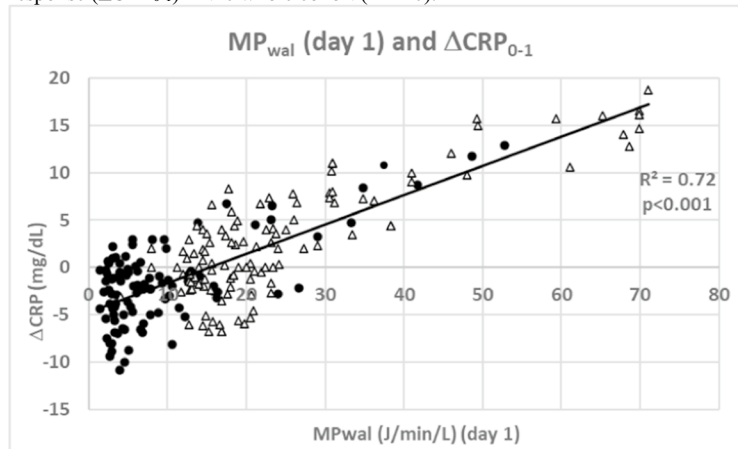


Fig. 7 (continued)

**Panel E:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and global reaeration score at the end of day 1 (global reaeration score<sub>1</sub>) in the whole cohort (n=216).



**Panel F:** Mechanical Power corrected for well-aerated lung volume ( $MP_{WAL}$ ) at day 1 and C-reactive protein response ( $\Delta CRP_{0-1}$ ) in the whole cohort (n=216).



**Table 4** Multivariable linear regression analysis of predictors of CO<sub>2</sub>-response (by ventilatory ratio, VR), ultrasonographic response and C-reactive protein responses in the whole study population ( $n = 216$ )

O <sub>2</sub> -response ( $\Delta\text{paO}_{2\text{sp0-1}}$ )						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
MP <sub>WAL</sub> (day 1)	0.46	0.006	<b>0.009</b>	1.51	0.66	0.62
Duration of 1 <sup>st</sup> PP session (hours)	0.42	0.010	<b>0.019</b>	1.49		
Not included in the model						
paO <sub>2</sub> /FiO <sub>2</sub> <sub>sp0</sub>	-0.29	0.312	0.312	1.47		
PEEP (day 1)	0.18	0.192	0.287	1.31		
VTe (day 1)	-0.27	0.216	0.312	1.21		
RR (day 1)	-0.15	0.189	0.193	1.77		
CO <sub>2</sub> -response ( $\Delta\text{VR}_{\text{sp0-1}}$ )						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
MP <sub>WAL</sub> (day 1)	0.44	0.011	<b>0.010</b>	1.59	0.69	0.61
Duration of 1 <sup>st</sup> PP session (hours)	-0.41	0.008	<b>0.028</b>	1.45		
Not included in the model						
VR <sub>sp0</sub>	-0.31	0.128	0.398	1.18		
PEEP (day 1)	-0.13	0.139	0.151	1.01		
RR(day 1)	0.29	0.146				
Global LUS response: $\Delta$ global LUS <sub>sp0-1</sub>						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
MP <sub>WAL</sub> (day 1)	0.41	0.009	<b>0.018</b>	0.06	0.68	0.63
global LUS <sub>sp0</sub>	-0.37	0.002	<b>0.009</b>	1.89		
Not included in the model						
RR (day 1)	-0.19	0.318	0.573	1.47		
PEEP (day 1)	-0.13	0.128	0.398	0.47		
Global reaeration score <sub>sp1</sub>						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
Duration of 1 <sup>st</sup> PP session (hours)	0.51	0.004	<b>0.012</b>	1.72	0.63	0.60
MP <sub>WAL</sub> (day 1)	-0.49	0.006	<b>0.009</b>	1.59		
Not included in the model						
global LUS <sub>sp0</sub>	0.29	0.612	0.138	1.29	<b>0.65</b>	<b>0.64</b>
PEEP (day 0)	0.16	0.316	0.479	1.13		
Well-aerated volume response: $\Delta\text{WAL}(\%)_{\text{sp0-1}}$						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
global LUS <sub>sp0</sub>	0.51	0.004	<b>0.012</b>	1.72	0.65	0.63
MP <sub>WAL</sub> (day 1)	-0.49	0.006	<b>0.010</b>	1.59		
Not included in the model						
WAL (day 0)	0.29	0.612	0.138	1.29		
PEEP (day 1)	0.16	0.316	0.479	1.13		
C-reactive protein response: $\Delta\text{CRP}_{\text{sp0-1}}$						
Parameter	$\beta$	SE	P	VIF	R <sup>2</sup>	R <sup>2</sup> <sub>adj</sub>
CRP <sub>sp0</sub>	-0.59	0.009	<b>0.011</b>	1.71	0.62	0.57
MP <sub>WAL</sub> (day 1)	0.38	0.005	<b>0.029</b>	1.12		
Not included in the model						
Obesity	0.31	0.269	0.513	1.19		
PEEP (day 0)	0.28	0.214	0.395	1.12		

Statistically significant  $p$ -values are written in bold characters

markers of VILI (i.e., gas exchange, lung re-aeration by lung ultrasound, and inflammatory biomarkers), outperforming all other ventilatory variables in outcome prediction.

#### 4. targeted prevention

We found prone position during noninvasive ventilation is an effective tool to reduce mechanical power delivered during NIV.

#### 5. personalization of medical services

Bedside MP<sub>WAL</sub> calculation during the 1<sup>st</sup> day of NIV may guide NIV delivery, help define the tradeoffs between the benefits of noninvasive support and the risks of VILI, and enhance prompt escalation to invasive mechanical ventilation to minimize lung injury progression.

#### How does the presented innovation go beyond

Early bedside MP<sub>WAL</sub> calculation is a useful parameter that can predict NIV outcome, suggest the need to adopt prone position to reduce MP delivery during NIV, and help decide when to stop NIV and upgrade treatment to invasive ventilation to more effectively prevent VILI progression.

**Abbreviations** ABG: Arterial blood gas; AHRF: Acute hypoxemic respiratory failure; CPAP: Continuous positive airway pressure; DSI: Dead space index; ETI: Endotracheal intubation; ISARIC: International Severe Acute Respiratory Infection Consortium; LUS: Lung ultrasound score; MV: Minute ventilation; MV<sub>corr</sub>: Corrected MV; NAL: Non-aerated lung volume; NIV: Noninvasive ventilation; NRS: Numeric rating scale; PBW: Predicted body weight; PEEP: Positive end-expiratory pressure; PP: Prone position; PRO-NIV: Prone position in Noninvasive Ventilation; Ps: Pressure support; PS: Propensity score; PSV: Pressure support ventilation; RR: Respiratory rate; SAPS: Simplified acute physiology score; MP: Mechanical power; MP<sub>WAL</sub>: Mechanical power normalized to well-aerated lung; PAL: Poorly aerated lung volume; SMD: Standardized mean difference; VILI: Ventilation-induced lung injury; VR: Ventilatory ratio; VTe: Expiratory tidal volume; WAL: Well-aerated lung volume; WOB: Work of breathing

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s13167-023-00325-5>.

**Authors' contributions** Giovanni Musso: conceived and designed the study, analyzed the results, drafted the article, gave final approval.

Claudio Taliano: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Marco De Iulii: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Elena Paschetta: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Caterina Fonti: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Andrea Ferraris: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Marta Druetta: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Ines Sarah Vianou: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Francesca Ranghino: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Federica Riedo: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Davide Deangelis: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

Gloria Tirabassi: acquired data, critically analyzed the results, contributed to the draft of the article, gave final approval.

**Data availability** Individual, de-identified participant data will be shared upon request to the corresponding author by email till up to 2 years after publication of the article.

#### Declarations

**Ethics approval** Ethics approval was granted by the Comitato Etico Interaziendale A.O.U. Città della Salute e della Scienza di Torino (prot. N. 0046392) on Dec 15th, 2020 as an ancillary study to the PRO-NIV study (ISRCTN23016116) and this study was performed in accordance with Helsinki declaration. All patients gave informed consent to participate.

**Consent for publication** All authors gave their consent for publication.

**Competing interests** no author has any present or past conflict of interest or financial and/or non-financial competing interest to disclose

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## Authors and Affiliations

Giovanni Musso<sup>1</sup>  · Claudio Taliano<sup>2</sup> · Marco De Iulii<sup>3</sup> · Elena Paschetta<sup>2</sup> · Caterina Fonti<sup>1</sup> · Andrea Ferraris<sup>3</sup> · Marta Druetta<sup>2</sup> · Ines Sarah Vianou<sup>2</sup> · Francesca Ranghino<sup>2</sup> · Federica Riedo<sup>2</sup> · Davide Deangelis<sup>2</sup> · Gloria Tirabassi<sup>4</sup>

✉ Giovanni Musso  
giovanni\_musso@yahoo.it

<sup>1</sup> Emergency Medicine Department, San Luigi Gonzaga Hospital, Regione Gonzole 10, Orbassano, 10043 Turin, TO, Italy

<sup>2</sup> Emergency Medicine Department, HUMANITAS Gradenigo, Turin, Italy

<sup>3</sup> Radiology Department, HUMANITAS Gradenigo, Turin, Italy

<sup>4</sup> Department of Biomedical Sciences, HUMANITAS University, Via Rita Levi Montalcini 4, 20072 Milan, Pieve Emanuele, Italy