Physiological effects of the awake prone position combined with high-flow nasal oxygen on gas exchange and work of breathing in patients with severe COVID-19 pneumonia: A randomized crossover trial.

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METHODS

Exclusion criteria

The exclusion criteria were one or more of the following: contraindication to APP (lack of mobility, agitation or risk of inhalation) or to esophageal balloon insertion; the immediate need for intubation or the presence of hypercapnia with an indication for noninvasive ventilation ($PaCO_2$ >50 mmHg), hemodynamic instability (systolic blood pressure < 90 mm Hg or mean arterial pressure <65 mm Hg) and/or shock; a Glasgow Coma Scale score < 13; pregnancy or breastfeeding; and patients deprived of liberty or without health insurance.

High-flow nasal oxygen settings

Following the recommendation of the national institutional review board (Comité de Protection des Personnes Nord Ouest, ID 20.05.26.63610), the gas flow of the high-flow nasal oxygen device (Airvo 2, Fisher & Paykel Healthcare) had to be set initially at 30 L/min regardless of the fraction of inspired oxygen (F_IO_2). In case of poor tolerance by the patient, the committee consented to the investigators progressively incrementing the gas flow as clinically appropriate. F_IO_2 was titrated to maintain peripheral oxygen saturation (SpO_2) within the range of 92-97%.

Study protocol

The measurement at inclusion was obtained after a stabilization period of 10 minutes in the semirecumbent positionSRP. Patients were then randomized to receive in a crossover order the prone position (PP) and the semirecumbent position (SRP) in a crossover order. Patients randomized to the first sequence (Arm A) received the PP first and then the SRP, whereas patients randomized to the second sequence (Arm B) received the SRP first and then the PP. MeasurementMeasurements were obtained prior to (Baselinebaseline) and at the end of each

period, both lasting 120 minutes. To prevent carryover, Aa 2-hour period of washout separated the first from the second study period to prevent carryover. The baseline of the first study period was obtained in the semirecumbent positionSRP after 10 minutes of stabilization following the measurement at inclusion. The baseline of the second study period was obtained in the semirecumbent positionSRP after 10 minutes of stabilization following the washout period.

Prone and semirecumbent positioning

The interventions were standardized: 1) In SRP, the patients were placed in a semirecumbent position with an angle of 30-45° between the trunk and legs; 2) In PP, the patients were laid horizontally without bed inclination and were encouraged to feel comfortable using pillows under their head and chest if necessary. The changes from one position to another were performed with the assistance of the medical staff to minimize the patient's effort. During the washout period the position was not standardized and was left at the discretion of the patient.

CT-based lung extension severity scale

To further characterize the extent of pneumonia, a radiologist blindly reviewed all of the available chest CT scans by using a 5-level semiquantitative scale based on the average percentage of the typical findings (ground-glass opacity and consolidation) in each of the five lobes: <10%; 10-25%; 25-50%; 50-75%; > 75% of involvement.

Esophageal pressure measurement and related parameters

Prior to randomization, a 5 French 95-mm length esophageal balloon catheter (Cooper Surgical, Trumbull, CT, USA) was inserted through one nostril at a depth of 38-42 cm and was inflated

with 1 ml of air to measure the esophageal pressure (P_{ES}) (1, 2). To ensure reproducibility, the balloon was completely deflated before all of the measurements were taken by applying negative pressure, and then it was reinflated with 1 ml of air. The esophageal catheter was connected to the esophageal pressure port of an S1 ventilator (Hamilton Medical AG, Bonaduz, Suisse), which continuously displayed the P_{ES} waveform and allowed for the adjustment of the catheter's position if needed.

The P_{ES} signal was digitalized at 50 Hz and exported from the S1 ventilator to a laptop computer for delayed analysis using Acqknowledge 5.0 software (Biopac, Goleta, CA). All breaths were analyzed, and the results were averaged for each study step. We defined the start of inspiration at the instant of the P_{ES} initial decay and the end of inspiration at the point of P_{ES} at which 25% of the time had elapsed from its maximum deflection to return to baseline (assuming that the final part of the esophageal curve is simply due to chest wall relaxation) (1). Transpulmonary pressure was defined as the airway pressure minus the P_{ES}. We measured the following P_{ES}-related parameters: the respiratory rate per minute; inspiratory effort (ΔP_{ES}, the negative inspiratory swing of P_{ES}); simplified P_{ES} pressure–time product ($sPTP_{ES}$) as a surrogate of the work of breathing (WOB) per breath (defined as the area under the curve of P_{ES} during the inspiration) and per minute (defined as the sum of the areas under the curve of P_{ES} during the inspiration over the recording time divided by the number of minutes of recording); dynamic end-expiratory transpulmonary pressure ($P_{L}ee$, defined as the difference between the airway pressure and P_{ES} at the end of expiration); dynamic end-inspiratory transpulmonary pressure ($P_{L}ei$, defined as the difference between the airway pressure and P_{ES} at the end of inspiration); and dynamic transpulmonary driving pressure (ΔP_{L}, defined as the maximal positive swing of the transpulmonary pressure during inspiration).

Expiratory CO_2 measurement and related parameters

The exhaled CO_2 waveform, as a function of time, was digitalized at 50 Hz and exported from the S1 ventilator to a laptop computer for an offline analysis. The end-tidal partial pressure of CO_2 ($EtCO_2$) was measured over the last five consecutive breathing cycles, and the results were averaged for each study step. We then computed the arterial to end-tidal CO_2 difference ($PaCO_2$ - $EtCO_2$) by using the $PaCO_2$ that was obtained from the blood gas that was sampled prior to the patient breathing through the mouthpiece. Thereafter, we used the following predictive equation to estimate the physiological dead space to tidal volume ratio as an index of ventilatory inefficiency: $V_D/V_T = 0.32 + 0.0106 (PaCO_2 - EtCO_2) + 0.003 (RR) + 0.0015 (age)$, where RR was respiratory rate (3).

Sample size calculation

According to the results of previous studies, we hypothesized that the PaO_2/F_IO_2 ratio would be 30 mmHg higher at the end of PP than at the end of SRP. Assuming an individual standard deviation of 40 mmHg, an α level of 5% and a β level of 20%, 16 patients were needed to reject the null hypothesis. Anticipating a dropout rate of approximately 10%, we extended the sample size to 18 patients.

Adverse events

Adverse events were defined as any device displacement or removal, desaturation was defined as $SpO_2<90\%$, and hemodynamic instability was defined as a heart rate > 120/min or a systolic blood pressure < 90 mmHg for >1 minute.

RESULTS

Gas flow and airway pressure estimation

Among the studied population, the gas flow was maintained at 30 L/min in 10 patients (59%) and was increased to 40 L/min in 1 patient (6%), to 50 L/min in 4 patients (24%) and to 60 L/min in 2 patients (12%). We assumed that the airway pressure remained constant throughout the breathing cycle and depended on the airflow according to the following estimation: 1.5 cmH_2O at 30 L/min, 2.2 cmH_2O at 40 L/min and 3.1 cmH_2O at 50 L/min or more (4). In this study, the median gas flow was 30 L/min (IQR, 30-50), providing a median airway pressure of 1.5 cmH2O (IQR, 1.5-3.1).

Effect of APP on oxygenation in responders

The mixed model analysis identified significant variations in PaO2/FIO2 with the position but not with the sequence or period. During PP, PaO2/FIO2 increased above 20% in 11 patients (65%), and these patients were classified as responders. Among them, PaO2/FIO2 was already significantly increased at 30 minutes compared to baseline ($p<0.05$, eFig. 2) and did not further improve until the second hour. The variation in PaO2/FIO2 among responders and nonresponders was 96 [15,195] and 14 [-17,26] Torr, respectively ($p=0.007$; Fig. 1c). The change in PaO2/FIO2 during PP did not correlate with the baseline level ($r=-0.31$, $p=0.23$).

Respiratory parameters associated with intubation

The main physiological parameters that were recorded at study entry are displayed in eTable 2. Compared to the patients not requiring intubation, the five patients who were intubated during their ICU stay had lower PaO2/FIO2 ($p=0.045$) and higher ΔPES ($p=0.012$), ΔPL ($p=0.011$) and

sPTPES per minute (p=0.048, eFig. 4). Among these parameters, the ΔPES and sPTPES per minute had the highest AUC (0.855 for both) at the respective cutoff values of >11.4 cmH2O (p=0.001) and >233.4 cmH2O.s.min-1 (p=0.006; eFig. 5).

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eTable 1. CT-based lung extension severity at study entry in the thirteen patients with available chest CT-scan.

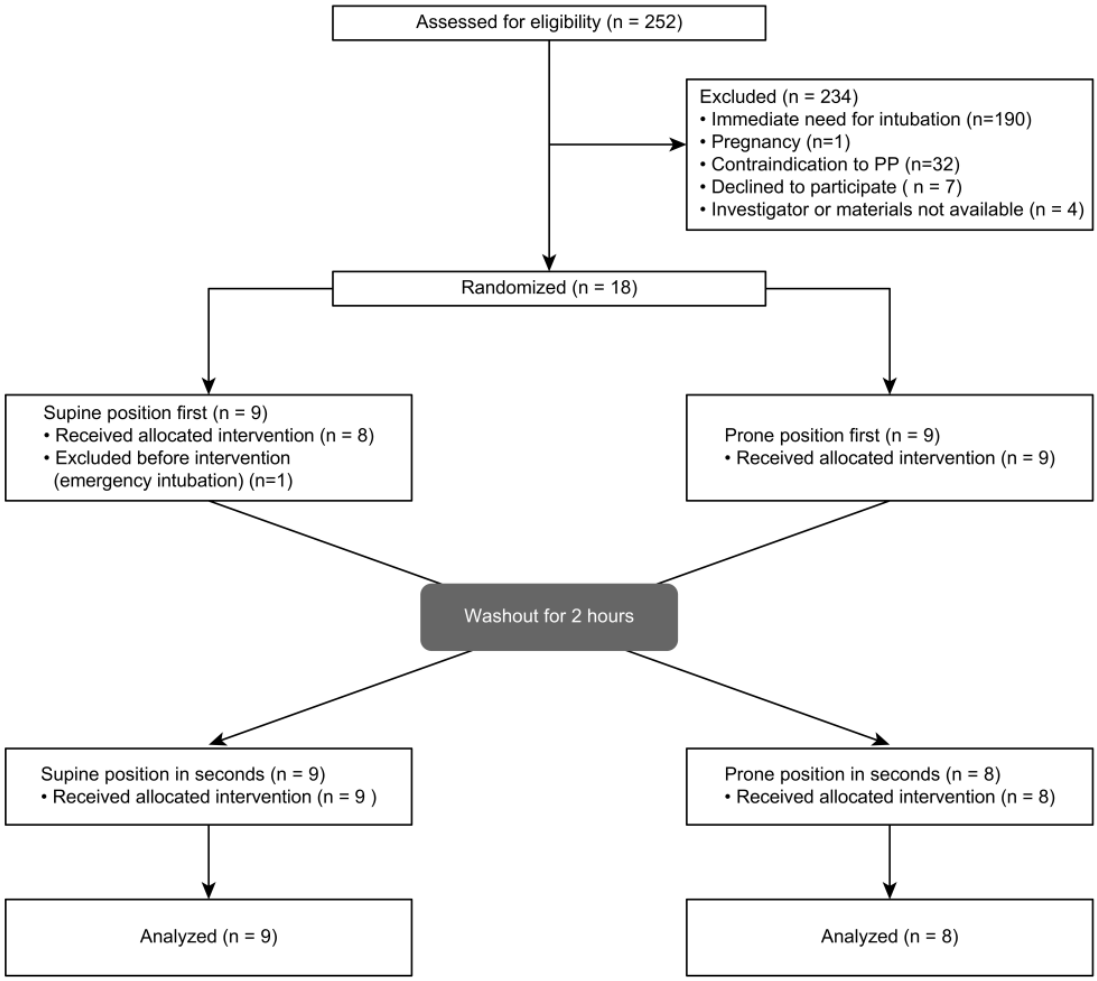
Variables, units	**Overall** n=13	**PP first** n=7	**SRP first** n=6
CT-based lung extension severity scale, n (%)			
< 10% of the total lung volume	1 (8)	0	1 (17)
10 to 25% of the total lung volume	0	0	0
25 to 50% of the total lung volume	4 (31)	3 (43)	1 (17)
50 to 75% of the total lung volume	7 (54)	4 (57)	3 (50)
75% of the total lung volume	1 (8)	0	1 (17)

eTable 2. Comparisons of physiological parameters measured at study entry in patients subsequently intubated and nonintubated.

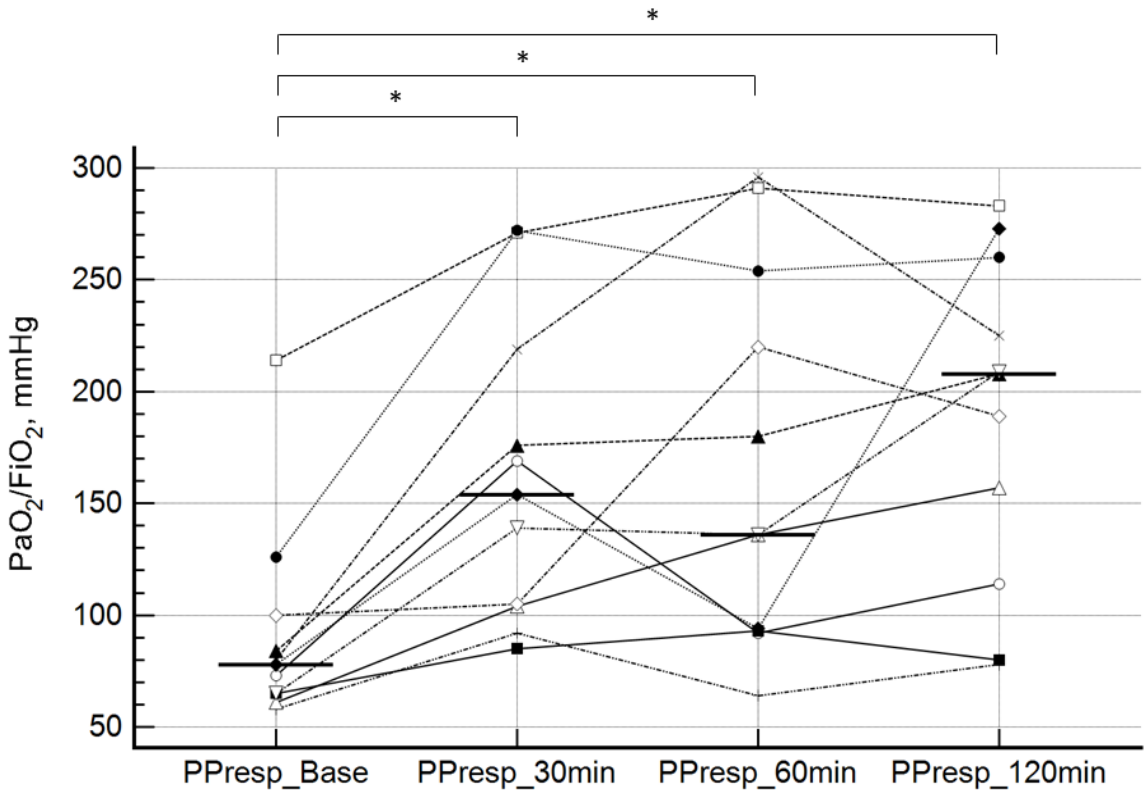
Variables, units	**Overall** (n=17)	**Intubated** (n=5)	**Nonintubated** (n=12)	P Values
Gas flow, L/min	30 (30,50)	50 (50,60)	30 (30,33)	0.015
pH_a	7.45 (7.44,7.50)	7.44 (7.44,7.44)	7.47 (7.44,7.50)	0.363
P_aO_2, mmHg	69.5 (64,85.1)	65.6 (57,63)	77.5 (65.9,109)	0.011
F_IO_2	0.8 (0.7,0.9)	0.94 (0.9,1)	0.7 (0.7,0.9)	0.118
P_aO_2/F_IO_2, mmHg	93 (73,126)	63 (58,79)	99 (79,205)	0.045
P_aCO_2, mmHg	32 (30,33)	32.4 (32,33)	32.0 (29.5,33.1)	0.699
E_TCO_2, mmHg	30.4 (26.8,31.4)	29.0 (26.4,31.2)	30.6 (27.6,32.7)	0.671
V_D/V_T	0.53 (0.47,0.58)	0.58(0.53,0.59)	0.49 (0.47,0.55)	0.154
Borg dyspnea scale, VAS	29 (15,50)	29 (28.0,53)	27.5 (11.8,46.3)	0.288
RR, breaths/min	25 (20,32)	32.0 (25.0,42.0)	23.0 (20,30.5)	0.104
ΔP_{ES}, cmH_2O*	10.9 (7.4,14.9)	16.6 (12.5,20.6)	7.98 (6.82,11.3)	0.012
ΔP_L, cmH_2O*	10.9 (6.8,14.9)	16.6 (12.5,20.6)	7.54 (6.41,11.3)	0.011
$sPTP_{ES}$/breath, $cmH_2O.s$*	6.1 (4.6,11.3)	11.7 (6.3,12.1)	5.6 (4.2,10.8)	0.1981
$sPTP_{ES}$/min, $cmH_2O.s/min$*	215 (145,273)	330 (264,338)	201 (142,227)	0.048

Definition of abbreviations: pHa = arterial pH; PaO_2 = arterial oxygen tension; F_IO_2 = fraction of inspired oxygen; PaO_2/F_IO_2 = ratio of arterial oxygen tension by inspired oxygen fraction; $PaCO_2$ = arterial carbon dioxide tension; E_TCO_2 = end-tidal carbon dioxide tension; V_D/V_T = dead space fraction of ventilation; VAS= visual analog scales with values ranging from 0 (minimal) to 100 (maximal); ΔP_{ES} = delta of esophageal pressure between end-expiratory and end-inspiratory values; ΔP_L = delta of transpulmonary pressure (airway minus esophageal) between end-inspiratory and end-expiratory values; $sPTP_{ES}$/breath = simplified esophageal pressure time product per breath; $sPTP_{ES}$/min = simplified esophageal pressure time product per minute.
Data are expressed as the median (interquartile range 25-75%).
The intubated and nonintubated patients were compared using Mann–Whitney U tests.
* The respiratory mechanic parameters of the nonintubated group were available in 11 patients.

eFigure 1. Flow chart and study design.



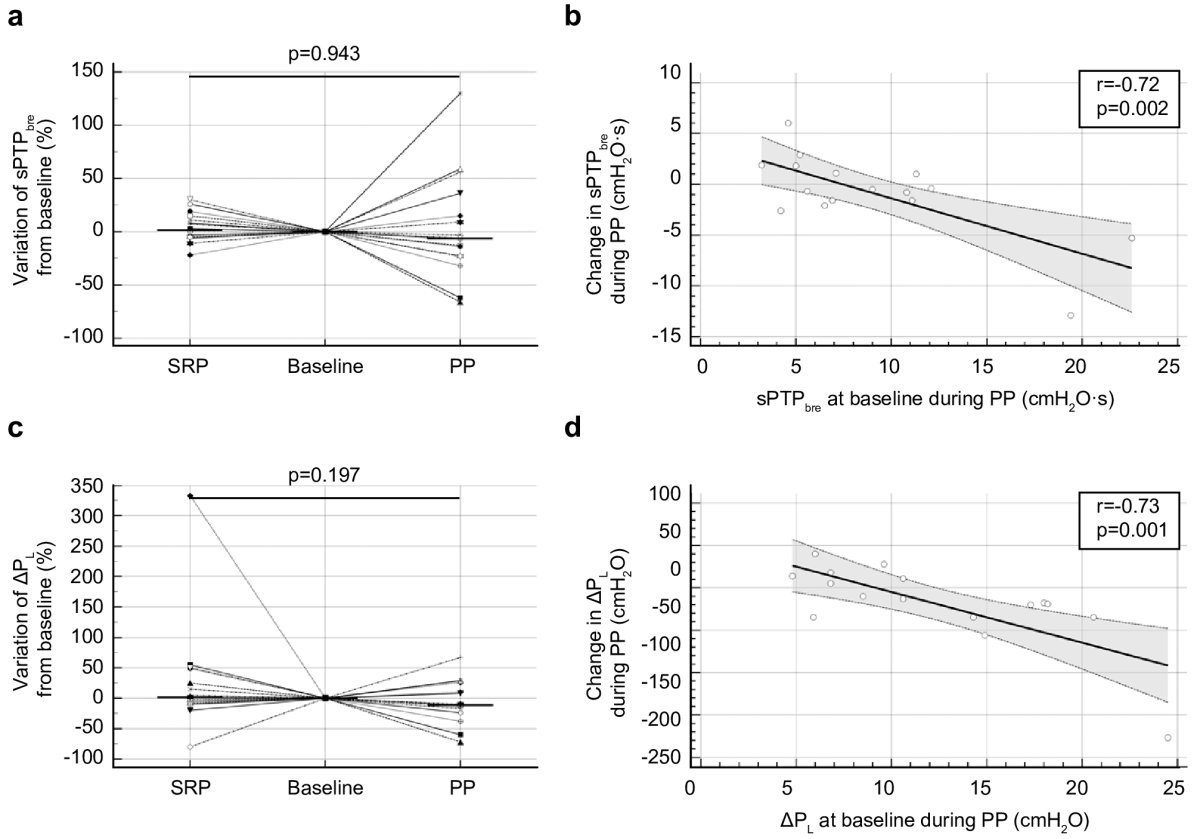
eFigure 2. Time course of the PaO_2/F_IO_2 ratio among responders in the prone position (PP).



The horizontal bars indicate the median values.

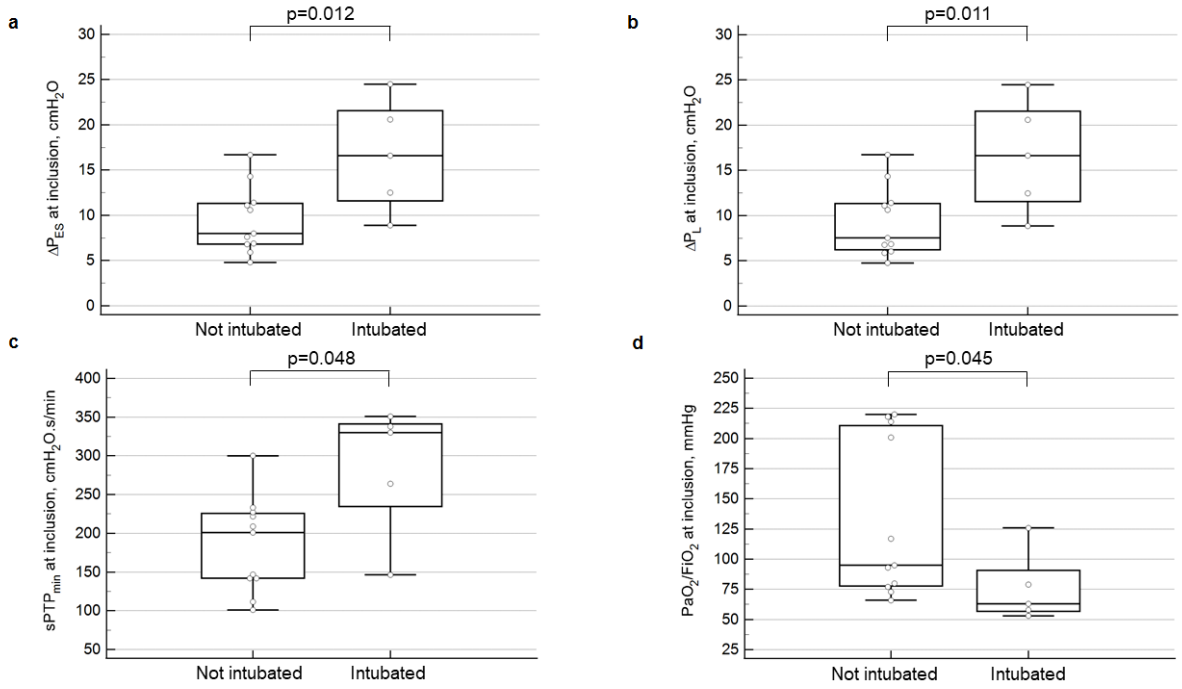
* P value < 0.05.

eFigure 3. Effect of the semirecumbent (SRP) and prone (PP) positions on inspiratory muscle effort and transpulmonary pressure.



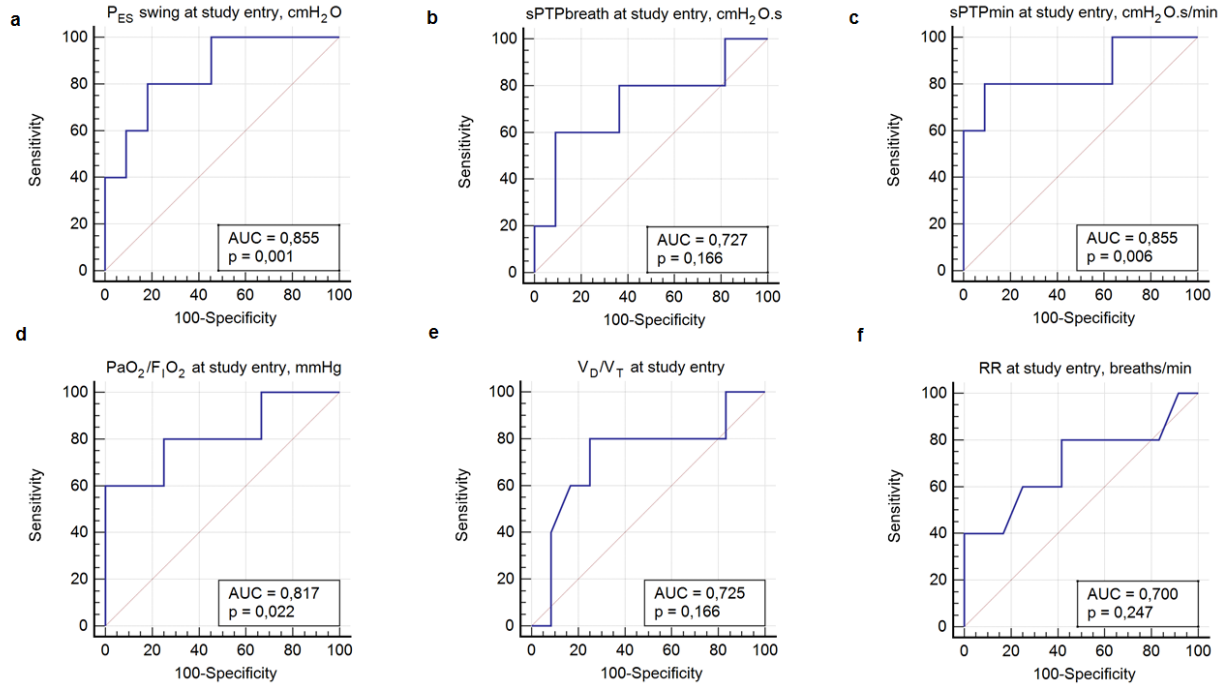
a: Dot plots and lines of the relative variation of the simplified esophageal pressure–time product per breath ($sPTP_{bre}$) during SRP and PP computed as 100*(End Value – Baseline Value)/Baseline Value). The baseline of each period was normalized to the reference level (zero). The horizontal bars indicate the median values. b: Scatter plot and regression between the baseline sPTPbre and the relative variation of sPTPbre during PP. The dashed lines indicate the 95% confidence interval of the regression line. c: Dot plots and lines of the relative variation of the transpulmonary pressure swing (ΔPL) during SRP and PP. The baseline of each period was normalized to the reference level (zero). The horizontal bars indicate the median values. d: Scatter plot and regression between the baseline ΔP_L and the relative variation of the ΔP_L during PP. The dashed lines indicate the 95% confidence interval of the regression line.

eFigure 4. Box plot representation of physiologic parameters at study entry in intubated and nonintubated patients.



a: Esophageal pressure swing (ΔP_{ES}). **b**: Transpulmonary pressure swing (ΔP_L). **c**: Esophageal pressure–time product per minute ($sPTP_{ES}$ min). **d**: PaO_2/F_IO_2 ratio.

eFigure 5. Receiver operating characteristic curves of physiological parameters measured at study entry to predict the intubation.



a: Esophageal pressure swing (ΔP_{ES}). **b**: Esophageal pressure–time product per breath ($sPTP_{ES}$ breath). **c**: Esophageal pressure–time product per minute ($sPTP_{ES}$ min). **d**: PaO_2/F_IO_2 ratio. e: Physiolog