Ultrasound evaluation of diaphragm function in mechanically-ventilated patients: comparison to phrenic stimulation and prognostic implications

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Online supplement

Patients and methods

The study was conducted from November 2014 to June 2015 in a 10-bed ICU within an 1800-bed university hospital. The protocol was approved by the Comité de Protection des Personnes Ile de France VI. Informed consent was obtained from the patients or their relatives. Thirty-five patients from the present study were also enrolled in a previously published study by our group.[1]

Patients

Patients were eligible for inclusion as soon as intubation was completed and if they had an expected duration of MV of >24h. Exclusion criteria were: contraindications to magnetic stimulation of the phrenic nerves (cardiac pacemaker or defibrillator, cervical implants), suspicion of underlying hemidiaphragm paralysis (defined as an elevation of >2·5 cm of one hemidiaphragm compared to the other on chest radiograph), pre-existing neuromuscular disorders, cervical spine injury, pregnancy, age <18 years and a decision to withhold life-sustaining treatment.

Protocol

Diaphragm function was assessed with two techniques: 1) measurement of pressure generating capacity in response to bilateral magnetic stimulation of the phrenic nerves and 2) ultrasound measurement of diaphragm thickness, excursion and thickening fraction. Whenever possible, diaphragm assessment was performed for each patient at two time points: 1) within 24 hours of intubation, while patients were receiving assist-control ventilation ("initiation of MV") and 2) as soon as patients could sustain pressure support ventilation (PSV, termed "switch to PSV") for least 1 hour with a PS ≤24 cmH_2O, a positive end-expiratory pressure (PEEP) ≤12 cmH_2O, a total level of inspiratory pressure <30 cmH_2O, a respiratory rate ≤24/min, and tidal volume ≥5 ml/kg ideal body weight, without signs of labored breathing, as defined by retractions or recessions - sucking in of the skin around the ribs and the top of the sternum, or prominent use of accessory respiratory muscles. These criteria are those that are routinely used by attending physicians in our ICU to evaluate, on a daily basis, the possibility of

switching patients to PSV. When initiated, pressure support is titrated to target a tidal volume of 6–8 ml/kg ideal body weight.

Diaphragm assessment

Diaphragm assessment was performed at the aforementioned time points unless a transient condition compromising the reliability of the measurements was present. These conditions were 1) the use of neuromuscular blocking agents within the preceding 24 hours (with the exception of succinylcholine used during rapid-sequence intubation), and 2) factors interfering with phrenic nerve stimulation (multiple functioning chest drains, high intrinsic positive end expiratory pressure, *see* below).

Phrenic nerves stimulation

The pressure generating capacity of the diaphragm was assessed in terms of the change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation (Ptr,stim), as already described.[2-4] Two figure-of-eight coils connected to a pair of Magstim 200 stimulators (The Magstim Company, Dyfed, UK) were positioned immediately posterior to the sternomastoid muscles at the level of the cricoid cartilage. Stimulations were delivered at the maximum intensity allowed by the stimulator, which has been showed to result in supramaximal stimulation in the majority of cases.[2 4-7] Patients were studied in a standardized semi-recumbent position, as follows: end-expiratory pressure was set to zero and the patient was allowed to exhale during an end-expiratory pause until expiratory airflow reached zero (relaxed equilibrium volume of the respiratory system). The absence of active respiratory efforts in response to stimulation

was determined by checking the stability of the airway pressure signal. The endotracheal tube was then briefly disconnected and manually occluded. When the absence of intrinsic PEEP was confirmed by ensuring that endotracheal pressure tracing at that moment was zero, bilateral anterolateral magnetic stimulation was delivered. Measurements were repeated at least three times and the mean of all valid measurements was reported. Ptr,stim was defined as the amplitude of the negative pressure wave following stimulation, taken from baseline to peak. It was measured at the proximal tip of the endotracheal tube, using a linear differential pressure transducer (MP45 ±100 cmH2O, Validyne, Northridge, Calif., USA). The pressure signal was sampled and digitized (MP30, Biopac Systems, Santa Barbara, Calif., USA or Powerlab, AD Instruments, Bella Vista, Australia) for subsequent data analysis.

Ultrasound assessment of diaphragmatic thickness, excursion and thickening

Ultrasound measurements were performed by one of the two first authors. Measurements were initially attempted on both hemidiaphragms, but evaluation of the left side was abandoned after the first 25 patients because of lower inter-observer agreement (*see* online supplemental material, e-table 1). The measurement of diaphragmatic excursion was added to the protocol three months after the beginning of the study, by which time 51 patients had already been recruited. The inter-observer reliability of the ultrasound measurements of the right hemidiaphragm between the two authors has already been reported, with intra-class correlation coefficients for the measurement of end-expiratory and end-inspiratory diaphragm thickness and diaphragm thickening fraction all >0.87.[1]

Ultrasound assessment of diaphragm thickness, excursion and thickening was performed using a 4-12 MHz linear array transducer (Sparq ultrasound system, Phillips, Philips Healthcare, Andover, MA, USA) while patients remained connected to the ventilator. As previously reported,[8] the probe was placed perpendicular to the right chest wall, at the midaxillary line between the 9th and 10th right intercostal spaces (at the level of the zone of apposition) and the diaphragm was identified as a three-layered structure comprising two hyperechoic lines representing the pleural and peritoneal membranes and a middle hypoechoic layer representing the diaphragmatic muscle. Using M-mode at a sweep speed of 10 mm/s, at least three breathing cycles were recorded. Diaphragm thickness was measured at end-expiration and end-inspiration using electronic calipers. The thickening fraction of the diaphragm (TFdi) was calculated as [(end-inspiratory thickness – end-expiratory thickness)/end-expiratory thickness]. Three valid breathing cycles were recorded, and the average of the individual values was reported. Diaphragm excursion (EXdi) was measured using M-mode, by placing the probe in the right sub-costal region and targeting the beam at the highest point of the diaphragmatic dome.[8]

Clinical data collection

Demographic and physiological variables and medication were recovered from the medical charts of patients. Sepsis was identified according to current guidelines.[9] The duration of mechanical ventilation, time to successful extubation, ICU and hospital stay and ICU and hospital mortality were recorded. We defined successful extubation as extubation not followed by reintubation within 48 hours.

Outcomes

Total duration of mechanical ventilation and ICU stay, remaining duration of mechanical ventilation after measurement at switch to PSV and ICU and hospital death were used as clinical outcomes. Predictor variables are listed in the Statistical Analysis section.

Statistical Analysis

Normality of the data was evaluated with the Kolmogorov-Smirnov test. Continuous variables are presented as median and interquartile range and categorical variables are expressed as absolute and relative frequency. Mixed linear regression analyses were used to compare variables measured at initiation of mechanical ventilation to those measured at switch to PSV. T-tests, Mann-Whitney U-tests or Chi-square tests, where appropriate, were used to compare outcomes between subgroups of patients. Relationships between diaphragm thickness, EXdi, TFdi and Ptr,stim were assessed using linear regression analysis and Spearman correlation. Receiver operating characteristic (ROC) curves were performed to identify optimal cut-off values of diaphragm thickness, EXdi and TFdi in predicting diaphragm dysfunction, and these estimates were cross-validated using bootstrapping with 1000 replications. Diaphragm dysfunction was defined as Ptr,stim<11 cmH_2O.[2 5 10-12]

To assess the prognostic value of diaphragm measurements, univariate analyses were performed to evaluate the relationship between clinically relevant variables and selected outcomes. Predictor variables included age, gender, chronic obstructive pulmonary disease (COPD), diabetes, cirrhosis, tobacco smoking, Sequential Organ Failure assessment (SOFA) score on admission, positive end-expiratory pressure (PEEP) level, tidal volume, respiratory rate, mean arterial pressure, heart rate, PaO_2/FiO_2 ratio, $PaCO_2$,

Ptr,stim, diaphragm thickness and TFdi. Then, for each outcome, two separated multiple linear regression or binary logistic regression models were performed. Ptr,stim and TFdi were each entered into separate multivariate analyses, along with other variables with a *p* value of <0.05 in univariate analysis, to identify independent predictors of clinical outcomes.

Statistical significance was defined as $p \leq 0.05$. Analyses were performed using SPSS v21 (SPSS Inc., Chicago, IL).

E-tables

e-table 1. Inter-observer reliability for the measurements of left diaphragm thickness and thickening fraction

Variable	Intra-class correlation coefficient	95% confidence interval	p-value
At initiation of MV			
End-expiratory diaphragm thickness	0.72	0.27 – 0.91	0.003
Inspiratory diaphragm thickness	0.68	0.18 – 0.90	0.007
Diaphragm thickening fraction	0.24	-0.37 – 0.70	0.22
At switch to PSV			
End-expiratory diaphragm thickness	0.67	0.25 – 0.89	0.003
Inspiratory diaphragm thickness	0.58	0.06 – 0.85	0.02
Diaphragm thickening fraction	0.68	0.24 – 0.89	0.004
All measurements			
End-expiratory diaphragm thickness	0.76	0.53 – 0.89	<0.001
Inspiratory diaphragm thickness	0.72	0.45 – 0.87	<0.001
Diaphragm thickening fraction	0.44	0.06 – 0.71	0.02

MV, mechanical ventilation; PSV, pressure-support ventilation

e-table 2. Characteristics of the patients according to number and time of measurements

	Patients with a single measurement			Patients with two measurements		
	Initiation of MV	Switch to PSV	p-value	Initiation of MV	Switch to PSV	p-value
n	13	36	-	63	63	-
Ventilatory mode						
Assist-control ventilation, *n (%)*	13 (100)	0 (0)	-	63 (100)	0 (0)	-
Pressure-support ventilation, *n (%)*	0 (0)	36 (100)	-	0 (0)	63 (100)	-
Time since intubation, *days*	1 (1–1)	2 (1–4)	0.02	1 (1 – 1)	4 (3 – 7)	<0.01
Active medication						
Benzodiazepines, *n (%)*	5 (39)	19 (53)	0.52	28 (44)	15 (24)	0.02
Norepinephrine, *n (%)*	7 (54)	15 (42)	0.53	39 (61)	21 (33)	<0.01
Propofol, *n (%)*	6 (46)	24 (67)	0.32	32 (51)	23 (37)	0.15
Opiates, *n (%)*	10 (77)	24 (67)	0.73	43 (68)	23 (37)	0.001
Corticosteroids, *n (%)*	2 (15)	7 (19)	0.99	11 (18)	6 (10)	0.30
Mean arterial pressure, *mmHg*	80 (71 – 94)	83 (70 – 99)	0.34	78 (70 – 89)	80 (71 – 91)	0.67
Heart rate, *bpm*	79 (66 – 110)	85 (75 – 101)	0.98	89 (72 – 102)	91 (80 – 105)	0.08
Ventilatory variables						
Spontaneous triggering of ventilator, *yes*	1 (7)	36 (100)	<0.01	10 (16)	63 (100)	<0.01
Pressure support level, *cm H_2O*	-	8 (7 – 10)	-	-	10 (8 – 12)	-
PEEP level, *cmH_2O*	6 (5 – 8)	5 (5 – 6)	0.21	5 (5 – 8)	5 (5 – 8)	0.59
Tidal volume, *ml/kg ideal body weight*	6.6 (6.2 – 7.4)	7.0 (6.0 – 8.4)	0.30	6.3 (6.1 – 6.8)	7.3 (5.9 – 8.7)	<0.01
Respiratory rate, *br/min*	20 (18 – 23)	20 (19 – 22)	0.67	21 (19 – 22)	21 (18 – 24)	0.80
Arterial blood gases						
pH	7·32 (7.27 – 7.43)	7·44 (7·40 – 7.47)	<0.001	7.37 (7.29 – 7.44)	7.43 (7.36 – 7.45)	0.001
PaO_2/FiO_2 ratio	205 (136 – 229)	300 (215 – 407)	0.02	238 (164 – 294)	247 (202 – 309)	0.21
$PaCO_2$, *mmHg*	43 (36 – 51)	37 (34 – 41)	0.22	39 (33 – 46)	38 (34 – 49)	0.65
Blood lactates, *mmol/L*	1.9 (1.2 – 4.7)	1.4 (1.2 – 2.1)	0.003	1.7 (1.1 – 2.5)	1.5 (1.1 – 1.9)	0.05
Bicarbonates, *mmol/L*	23 (18 – 26)	25 (23 – 27)	0.06	22 (19 – 26)	24 (21 – 29)	<0.01

Continuous variables are presented as median (interquartile range) and categorical variables are expressed as absolute and relative frequency. PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; NA, not applicable.

[a] In assist-control ventilation, spontaneous triggering of the ventilator was considered present when the observed respiratory rate was higher than the respiratory rate set on the ventilator

e-table 3. Univariate and multiple linear regression analyses for the prediction of remaining time of mechanical ventilation after switch to PSV.

Univariate regression analysis

	B	95% CI	p-value
Age	0.05	-0.03 – 0.12	0.22
Gender	0.31	-2.19 – 2.79	0.81
COPD	0.67	-2.13 – 3.47	0.64
Diabetes	1.89	-0.88 – 4.67	0.18
Tobacco smoking	1.51	-0.81 – 3.83	0.20
Cirrhosis	-1.14	-4.29 – 2.01	0.47
SOFA on admission	-0.04	-0.37 – 0.28	0.78
Variables measured at time of switch to PSV:			
PEEP	0.36	-0.38 – 1.11	0.34
Tidal volume	-0.48	-1.10 – 0.15	0.13
Respiratory rate	0.02	-0.34 – 0.37	0.93
PaO_2/FiO_2 ratio	-0.01	-0.02 - -0.01	**0.05**
$PaCO_2$	0.001	-0.13 – 0.13	0.99
Ptr,stim	-0.28	-0.46 - -0.09	**0.005**
Diaphragm thickness	-0.003	-0.02 – 0.02	0.77
TFdi	-0.11	-0.19 - -0.02	**0.02**
EXdi	0.12	-2.09 – 2.32	0.92

Multiple linear regression model (model with Ptr,stim)

	B	95% CI	p-value
PaO_2/FiO_2 ratio	-0.01	-0.02 – 0.004	0.20
Ptr,stim	-0.20	-0.40 - -0.01	**0.04**

Multiple linear regression model (model with TFdi)

	B	95% CI	p-value
PaO_2/FiO_2 ratio	-0.01	-0.02 – 0.003	0.14
TFdi	-0.10	**-0.18 - -0.01**	**0.03**

B, unstandardized regression coefficient; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

e-table 4. Univariate and multiple logistic regression analyses for the prediction of intensive care unit mortality.

Univariate regression analysis

	OR	95% CI	p-value
Age	1.03	0.99 – 1.07	0.20
Gender	0.63	0.21 – 1.83	0.39
COPD	1.59	0.49 – 5.14	0.44
Diabetes	1.09	0.32 – 3.77	0.89
Tobacco smoking	1.14	0.40 – 3.24	0.81
Cirrhosis	1.14	0.29 – 4.52	0.86
SOFA on admission	1.22	1.06 – 1.41	**0.006**
Variables measured at time of switch to PSV:			
PEEP	1.27	0.93 – 1.72	0.13
Tidal volume	0.91	0.66 – 1.25	0.45
Respiratory rate	1.02	0.87 – 1.21	0.80
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.001**
$PaCO_2$	1.04	0.98 – 1.10	0.19
Ptr,stim	0.79	0.66 – 0.94	**0.008**
Diaphragm thickness	0.99	0.98 – 1.00	0.26
TFdi	0.94	0.89 – 0.98	**0.01**
EXdi	1.18	0.27 – 5.08	0.82

Multiple logistic regression model (model with Ptr,stim)

	OR	95% CI	p-value
SOFA on admission	1.14	0.98 – 1.34	0.10
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.007**
Ptr,stim	0.82	0.69 – 9.98	**0.03**

Multiple logistic regression model (model with TFdi)

	OR	95% CI	p-value
SOFA on admission	1.13	0.96 – 1.32	0.14
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.006**
TFdi	0.95	0.90 – 0.99	**0.04**

OR, odds ratio; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

e-table 5. Univariate and multiple logistic regression analyses for the prediction of hospital mortality.

Univariate regression analysis

	OR	95% CI	p-value
Age	1.03	0.99 – 1.01	0.10
Gender	0.56	0.21 – 1.50	0.25
COPD	1.55	0.52 – 4.63	0.43
Diabetes	1.12	0.36 – 3.50	0.84
Tobacco smoking	1.18	0.45 – 3.10	0.74
Cirrhosis	1.29	0.37 – 4.52	0.69
SOFA on admission	**1.22**	1.07 – 1.40	**0.004**
Variables measured at time of switch to PSV:			
PEEP	1.13	0.84 – 1.51	0.43
Tidal volume	0.83	0.61 – 1.13	0.25
Respiratory rate	1.06	0.90 – 1.24	0.48
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.001**
$PaCO_2$	1.04	0.98 – 1.09	0.18
Ptr,stim	0.76	0.64 – 0.90	**0.002**
Diaphragm thickness	1.01	0.99 – 1.01	0.72
TFdi	0.93	0.88 – 0.97	**0.003**
EXdi	0.80	0.19 – 3.34	0.76

Multiple logistic regression model (model with Ptr,stim)

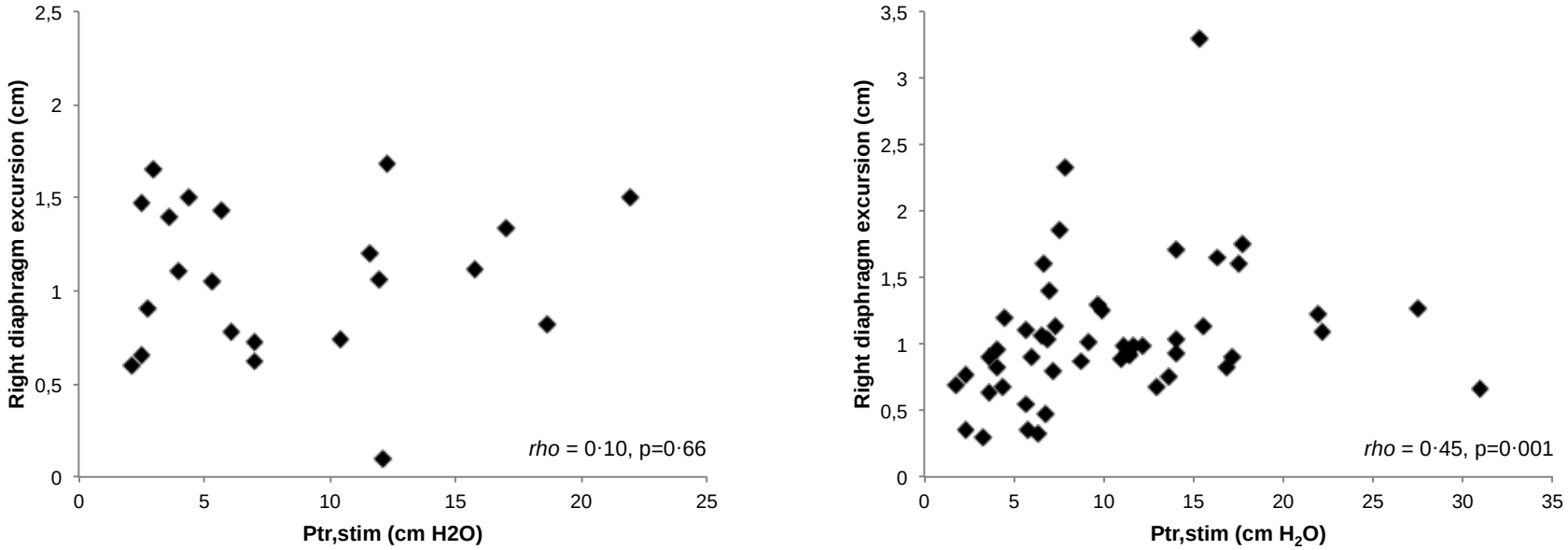
	OR	95% CI	p-value
SOFA on admission	1.15	0.99 – 1.35	0.07
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.01**
Ptr,stim	0.79	0.66 – 0.94	**0.01**

Multiple logistic regression model (model with TFdi)

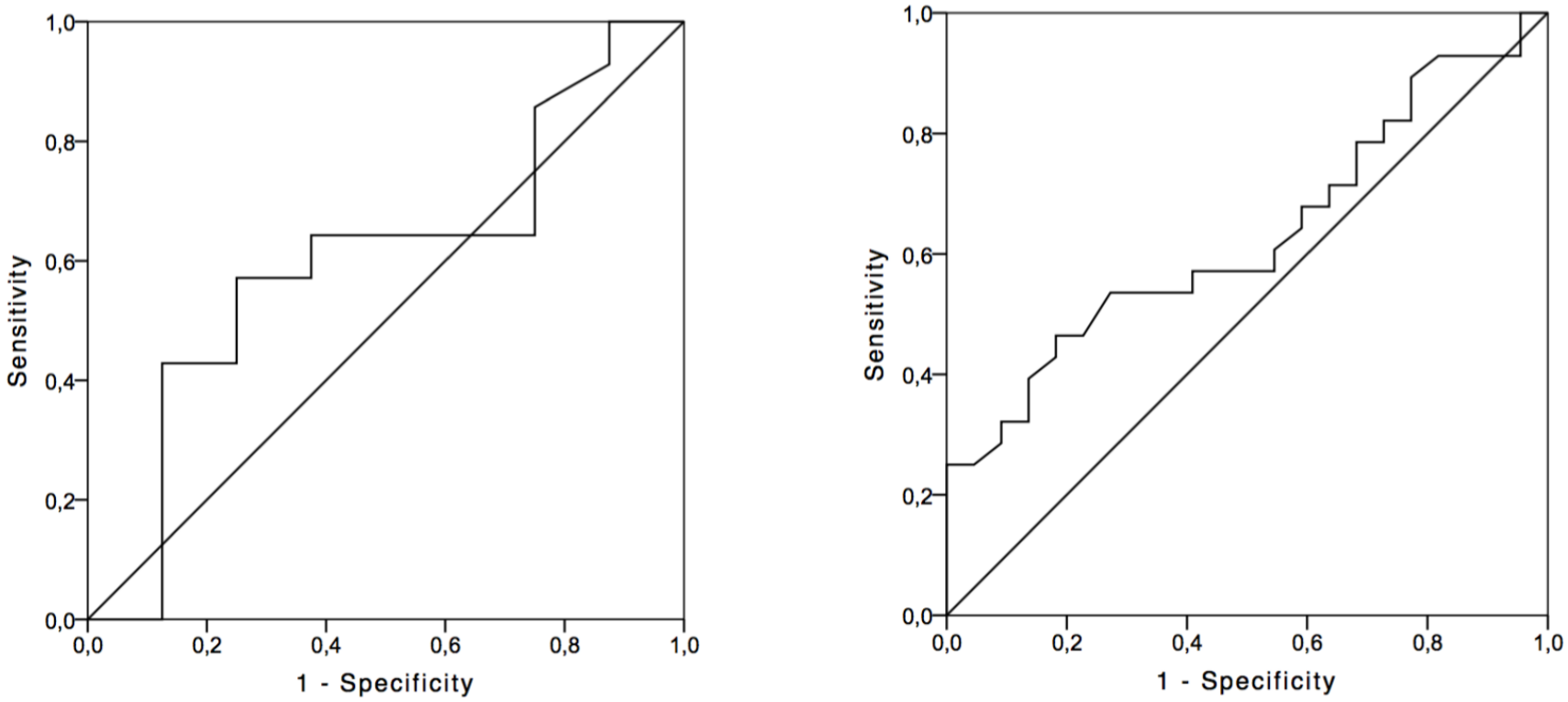
	OR	95% CI	p-value
SOFA on admission	1.14	0.97 – 1.33	0.10
PaO_2/FiO_2 ratio	0.99	0.98 – 0.99	**0.01**
TFdi	0.94	0.89 – 9.98	**0.01**

OR, odds ratio; COPD, chronic pulmonary obstructive disease; SOFA, sequential organ failure assessment score measured on admission; PEEP, positive end-expiratory pressure; PaO_2, arterial partial pressure of oxygen; FiO2, fraction of inspired oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; Ptr,stim; twitch pressure in response to bilateral phrenic nerve stimulation; TFdi, thickening fraction of the diaphragm; EXdi, diaphragmatic excursion; CI, confidence interval.

E-figures



e-figure 1. Correlation analysis between changes in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation during manual airway occlusion (Ptr,stim) and diaphragm excursion on initiation of mechanical ventilation (right panel) and at the moment of switch to pressure-support ventilation (left panel).



e-figure 2. Receiver operating characteristic (ROC) curve for the diagnosis of diaphragm dysfunction (defined as a change in endotracheal tube pressure induced by bilateral anterior magnetic phrenic nerve stimulation < 11 cmH_2O) for diaphragm excursion on initiation of mechanical ventilation (left panel) and switch to pressure support ventilation (right panel).

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