FAILURE OF NONINVASIVE VENTILATION FOR *DE NOVO* ACUTE HYPOXEMIC RESPIRATORY FAILURE: ROLE OF TIDAL VOLUME

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ADDITIONAL METHODS

During the study, noninvasive ventilation (NIV) was performed via a non-vented oro-nasal mask (FreeMotionTM RT041, Fisher & Paykel, Auckland, New Zealand), using an ICU ventilator equipped with a heated humidifier (MR850, Fisher & Paykel, Auckland, New Zealand), with its NIV algorithm engaged (Evita XL, Dräger, Lübeck, Germany, or Engström Carestation, GE Healthcare, Fairfield, CT, USA).

Noninvasive ventilation protocol

Every ventilator adjustment in this study was made according to a simple algorithm, developed within a multidisciplinary working group involving ICU physicians, nurses and respiratory therapists, and implemented in our unit since 2008 (1, 2). This algorithm aimed at empowering nurses to adjust the ventilator settings following a rational decision algorithm. Its goals are the followings: to improve patient's tolerance at the onset of the NIV session, to adjust the pressure support level in order to target a desired expired tidal volume range, to use the lowest efficient inspiratory and expiratory pressures and minimize the deleterious effects of leaks (3), and to allow re-adjustments of the settings during the NIV session. Its main principles are the followings (1, 2):

- The physician provides on a daily prescription form:
    - The minimal number of NIV sessions per day.
    - The minimal total duration of NIV per day.
    - The expired tidal volume (Vte) target range.
    - The minimal pressure support level (PSL) allowed.
    - The pulse oximetry (SpO2) target range.
    - The positive end expiratory pressure (PEEP) level.

For patients with acute hypoxemic respiratory failure (AHRF), the prescribed minimal total duration of NIV per day was ≥ 8 hours; the Vte target ranged between 6 to 8 mL/kg of predicted body weight (PBW) (4), and the minimal PSL allowed was usually set at 7 cm H_2O. The Vte target range of 6 to 8 mL/kg PBW weight was calculated by the clinician and reported in mL on the prescription in order to facilitate its application by the nurse.

- At each NIV session, the nurse connected the patient to the ventilator with the following standardized settings: PSL = 8 cm H_2O, PEEP = 0 cm H_2O, inspiratory trigger = 3 L/min, maximal insufflation time = one second. Within the first minutes after the connection, the nurse adjusted the ventilator settings in a standardized order:
    - The FiO_2 was adjusted by 5% steps until the SpO_2 objective was reached.
    - The pressure support level was adjusted by 2 cm H_2O steps every 1-2 minutes until the Vte target range was reached: if the Vte observed was below the target range, the pressure support level was increased, if the Vte was above the target range, the pressure support level was decreased. The pressure support level was never allowed to decrease below the prescribed minimal value.
    - The PEEP was increased every 1-2 minutes until the prescribed PEEP level was reached.
    - Several times during each NIV session, the nurse monitored clinical and ventilatory parameters (see below). If the monitored Vte was not within the target range, the nurse readjusted the PSL.
- Arterial blood gases were systematically drawn after one hour of NIV during the first NIV session.
- The nurse monitored every NIV session on a daily form and recorded at least twice during each NIV session:
    - Ventilator settings (FiO_2, PSL, PEEP), respiratory parameters (Vte, respiratory rate, minute ventilation, SpO_2), hemodynamic parameters (heart rate, blood pressure), and the Richmond Agitation Sedation Scale (RASS) (5).

Criteria for endotracheal intubation

The following criteria were used for endotracheal intubation: intolerance, loss of consciousness or psychomotor agitation hindering the safe continuation of NIV and requiring sedation; shock, defined by systolic arterial blood pressure below 90 mm Hg or a mean arterial blood pressure below 65 mm Hg despite fluid resuscitation, or need for vasopressors;

refractory hypoxemia, defined as SpO_2 remaining below 90% despite FiO_2 at 100%; frank worsening of respiratory distress under NIV or occurrence of signs of respiratory exhaustion with: pH < 7.35 and hypercapnia.

Data collection and definitions

We built a prospective registry in which the following data were recorded twice at each NIV session: duration of the NIV session, FiO_2, PSL, PEEP, respiratory rate, minute ventilation, SpO_2, heart rate, blood pressure, RASS. The Vte was recorded twice at each NIV session into the prospective registry. The mean value of every parameter was computed from these recordings at each NIV session. Vte are reported in mL/kg of PBW, which was computed using the following formula: 50 + 0.91 × (centimeters of height – 152.4) for male patients and 45.5 + 0.91 × (centimeters of height − 152.4) for female patients (4).

Arterial blood gases were recorded before the first NIV session, and after one hour of NIV during the first NIV session in every patient.

Patients were followed until ICU discharge.

NIV failure was defined as the need for intubation.

ADDITIONAL TABLES

eTable 1 Demographic and clinical characteristics of 62 patients with *de novo* acute hypoxemic respiratory failure at NIV initiation depending on the ARDS status

	ARDS (n = 47)	Non ARDS (n = 15)	*P* value
Age, yrs	61 (48-76)	66 (51-77)	.69
Male gender, n (%)	29 (62)	11 (73)	.41
SAPS II on admission	36 (28-45)	38 (30-49)	.57
SOFA at NIV start	6 (4-8)	5 (4-8)	.51
Respiratory SOFA	3 (2-4)	2 (2-3)	.06
Coagulation SOFA	0 (0-2)	0 (0-2)	.89
Liver SOFA	0 (0-1)	1 (0-2)	.06
Cardiovascular SOFA	0 (0-1)	0 (0-1)	.83
CNS SOFA	0 (0-0)	0 (0-1)	.35
Renal SOFA	0 (0-2)	1 (0-1)	.64
Immunosuppression	26 (55)	6 (40)	.30
Arterial blood gases before NIV			
pH	7.42 (7.39-7.47)	7.39 (7.34-7.46)	.39
PaO_2, mm Hg	69 (57-81)	69 (52-103)	.77

FiO_2	0.51 (0.36-0.66)	0.66 (0.31-0.66)	.76
PaO_2/FiO_2, mm Hg	147 (114-194)	170 (101-233)	.66
$PaCO_2$, mm Hg	33 (30-41)	34 (30-43)	.66
CO_2t, mmol/L	24 (20-26)	23 (21-26)	.79
Lactates, mmol/L	1.5 (1.0-2.6)	2.0 (1.7-2.7)	.049
PaO_2/FiO_2 categorization*			.003
mild hypoxemia, n (%)	17 (36)	12 (80)	
moderate-to-severe hypoxemia, n (%)	30 (64)	3 (20)	

Definitions of abbreviations: ARDS: Acute Respiratory Distress Syndrome; SAPS II: Simplified Acute Physiology Score (6); SOFA: Sequential Organ Failure Assessment score (7); CNS: central nervous system; mild hypoxemia: acute hypoxemic respiratory failure with 200 mm Hg< $PaO_2/FiO_2 \leq$ 300 mm Hg after one hour of NIV; moderate-to-severe hypoxemia: acute hypoxemic respiratory failure with $PaO_2/FiO_2 \leq$ 200 mm Hg after one hour of NIV.

* Evaluated at the first hour of NIV.

eTable 2 Ventilatory and hemodynamic variables during NIV and after intubation depending on the ARDS status

	ARDS (n = 47)	Non ARDS (n = 15)	*P* value
Days with NIV treatment†	2 (1-4)	2 (2-4)	.32
Number of NIV sessions, n	6 (2-10)	5 (4-11)	.57
Total time spent under NIV, hours	15.2 (6.2-25.2)	16.3 (8.0-27.0)	.49
PEEP, cm H_2O			
During NIV	5 (5-5)	5 (5-5)	.52
After intubation	12 (8-15)	5 (5-7)	.02
Pressure support level, cm H_2O			
During NIV	8 (7-9)	8 (7-9)	.93
NIV H1	8 (7-10)	8 (7-10)	.57
Ventilator driving pressure‡, cm H_2O			
After intubation	14 (11-19)	19 (12-26)	.43
PaO_2, mm Hg			
Before NIV	69 (57-81)	69 (52-103)	.77
NIV H1	121 (82-157)	224 (123-264)	.001
After intubation	135 (78-170)	77 (57-110)	.06

FiO_2			
Before NIV	0.51 (0.36-0.66)	0.66 (0.31-0.66)	.76
NIV H1	0.8 (0.6-1.0)	1.0 (0.5-1.0)	.35
After intubation	0.9 (0.6-1.0)	0.7 (0.5-0.8)	.11
PaO_2/FiO_2, mm Hg			
Before NIV	147 (114-194)	170 (101-233)	.66
NIV H1	168 (124-225)	254 (212-284)	<.001
After intubation	159 (102-242)	137 (81-250)	.71
$PaCO_2$, mm Hg			
Before NIV	33 (30-41)	34 (30-43)	.66
NIV H1	36 (32-40)	36 (33-39)	.78
After intubation	39 (35-55)	40 (35-56)	.78
V_E, L/min			
During NIV	19.0 (15.1-21.0)	19.7 (15.6-22.9)	.43
After intubation	12.6 (9.7-13.3)	13.5 (12.0-15.0)	.23
Vte, mL/kg PBW			
During NIV	10.3 (8.3-11.3)	8.6 (8.0-9.9)	.14
After intubation	6.0 (5.5-6.5)	6.7 (6.0-7.3)	.16
RR, cycles/min			

Before NIV	35 (30-40)	36 (30-40)	.76
During NIV	30 (27-35)	37 (30-38)	.02
After intubation	30 (27-33)	31 (29-35)	.52
BPs, mm Hg			
Before NIV	127 (116-141)	137 (123-158)	.17
During NIV	125 (112-138)	128 (105-133)	.69
HR, cycles/min			
Before NIV	108 (90-120)	125 (98-133)	.08
During NIV	100 (89-107)	108 (100-140)	.06
Respiratory mechanics after intubation			
Static compliance of the respiratory system, ml. cmH_2O^{-1}	31 (21-36)	22 (18-44)	.62
Resistance of the respiratory system, $cmH_2O.L^{-1}.s^{-1}$	11 (10-20)	11 (4-18)	.49

Definitions of abbreviations: ARDS: Acute Respiratory Distress Syndrome; NIV: noninvasive ventilation; During NIV denotes mean value over all noninvasive ventilation sessions; NIV H1 denotes value under NIV after one hour of treatment; Before intubation denotes value under NIV during the last NIV session before intubation; After intubation denotes value after twelve hours of invasive mechanical ventilation (failure group); PEEP: positive end expiratory pressure, V_E: minute ventilation; Vte: expired tidal volume; PBW:

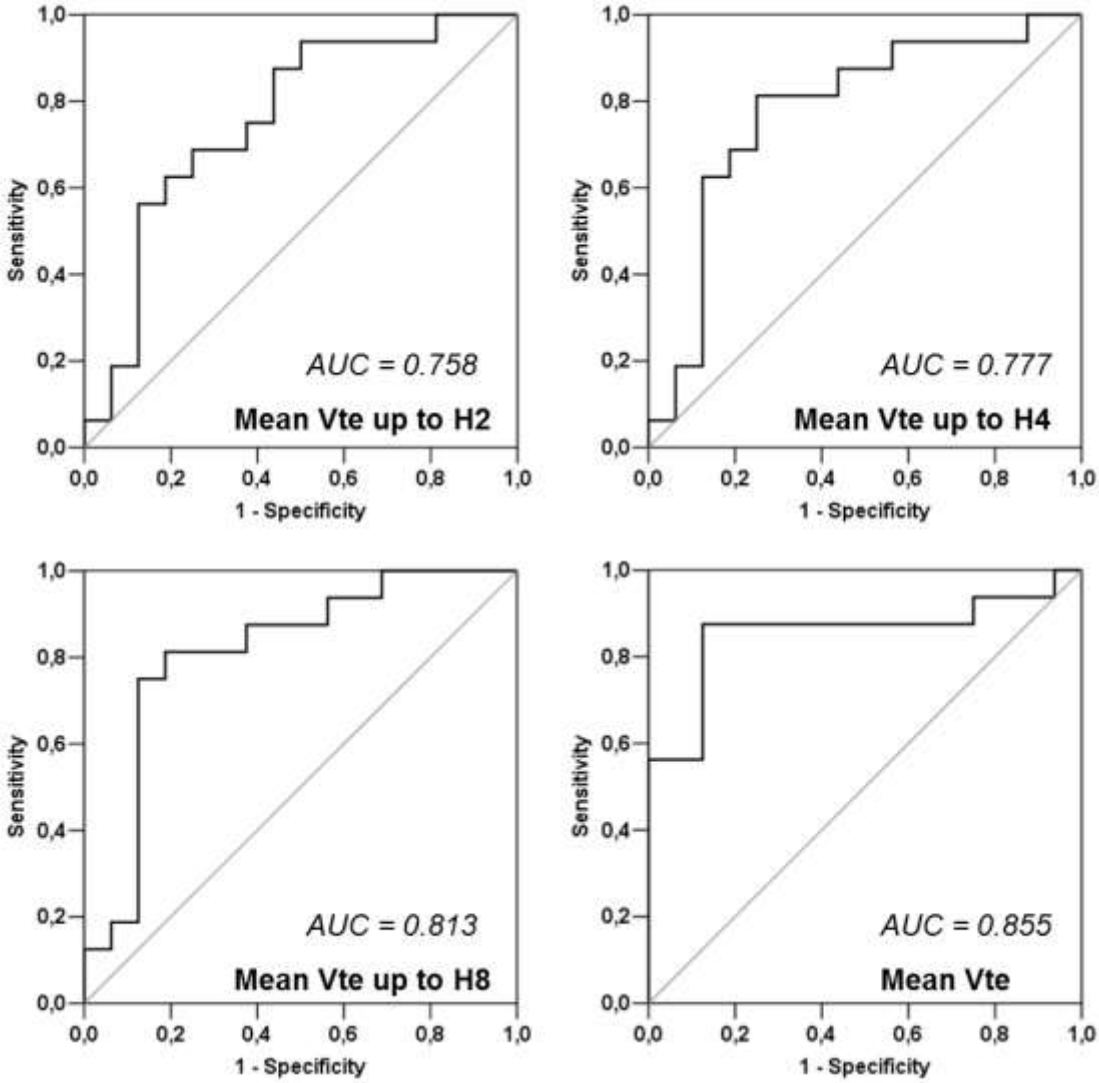
predicted body weight; RR: respiratory rate; BPs: systolic blood pressure; HR: heart rate; * $p < .05$ as compared to the value during NIV (failure group); †defined as time from the onset of NIV until either NIV failure or NIV weaning; ‡defined as the difference between the plateau pressure and the PEEP during assist control ventilation after intubation.

ADDITIONAL FIGURE LEGEND

eFigure 1

Receiver operating characteristic (ROC) curves of mean expired tidal volume (Vte) during noninvasive ventilation (NIV) to predict NIV failure in patients with moderate-to-severe hypoxemia (PaO_2/FiO_2 ratio ≤ 200 mm Hg, n = 33). Mean Vte up to H2, H4, and H8 denote the average of Vte measurements over the first two, four, and eight cumulative hours of NIV, respectively. Mean Vte denotes the average of Vte over all NIV sessions.

eFigure 1



	% Area under the curve	Standard error	95% confidence interval	*P* value
Mean Vte up to H2	0.758	0.088	0.585-0.930	.013
Mean Vte up to H4	0.777	0.087	0.606-0.949	.007
Mean Vte up to H8	0.813	0.081	0.654-0.971	.003
Mean Vte	0.855	0.075	0.709-1.002	.001

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