between rIL-1ra and placebo in non-HBD/DIC patients, it was significantly lower in HBD/DIC patients who received rIL-1ra (34.6%) than in those who received placebo (64.7%) ($p = 0.0006$). After adjusting for some of the baseline imbalances, the Cox multivariable regression analysis showed a significant mortality reduction with rIL-1ra when compared with that with placebo (hazard ratio, 0.28 [0.11–0.71]) in this sub-population. Important strengths from the statistical perspective include the absence of multicollinearity and the significantly positive interaction test for rIL-1ra treatment by HBD/DIC status done by the logistic regression model, that is, the drug effect on survival was dependent on the HBD/DIC status. These statistical analyses further supported the authors' hypothesis.

There are several limitations that must be noted in this study: 1) this subgroup analysis was not prospectively defined before study initiation; 2) the pooling of patients with a disorder definition (MAS) distinct from the original study inclusion criteria annuls the original randomization process, which may have introduced postrandomization selection bias; 3) the several significant baseline imbalances are suggestive of the introduction of selection bias; 4) regression analyses were necessary to account for these imbalances, but the very small sample size of the HBD/DIC patient group may have severely limited the reliability of the regression models; 5) several variables that are known to be relevant to survival outcomes in sepsis were not available for this study's retrospective analysis: site of infection, microorganisms, rate of bacteremia, and use of appropriate antibiotics; 6) the original study was performed almost 20 years ago, hence its generalizability becomes very limited for patients in 2015.

In conclusion, although blockade of IL-1 is not ready for prime time, this post hoc subgroup analysis brings motivation and generates a new hypothesis for its potential efficacy in patients with sepsis-induced MAS. A randomized clinical trial for patients with sepsis and MAS in the current era is needed to test this new hypothesis.

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Noninvasive Ventilation in Acute Hypoxemic Respiratory Failure: Songs of Love and Hate*

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Since its inception in modern critical care practice, noninvasive ventilation (NIV) has revolutionized the treatment of respiratory failure. Years of physiologic research into the mechanisms underlying acute decompensations, coupled with well-designed and well-conducted clinical trials and substantial technological advances, has paid off. Intubation and mortality have decreased markedly compared with usual treatment (intubation of the trachea and mechanical ventilation when current medical therapy fails). As a result, NIV along with medical treatment is now standard care for acute exacerbations of a chronic obstructive pulmonary disease and cardiogenic pulmonary edema (1, 2).

But what about NIV in acute hypoxemic respiratory failure, particularly acute respiratory distress syndrome (ARDS)? The seminal study by Antonelli et al (3) in ARDS patients showed that implementing NIV as pressure support ventilation (PS) plus positive end-expiratory pressure (PEEP) improved arterial oxygenation to the same extent as conventional mechanical ventilation, and differences in ICU mortality rates were also similar. In addition, only 31% of patients (10/32) treated with NIV required tracheal intubation. In a subsequent study in acutely hypoxemic patients with bilateral infiltrates, Delclaux

*See also p. 282.

Key Words: acute hypoxemic respiratory failure; acute respiratory distress syndrome; noninvasive ventilation

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et al (4) compared oxygen delivered via continuous positive airway pressure administered with a face mask with oxygen delivered via conventional face masks. Their findings were similar. Intubation was needed in 34% of patients (21/62) in the continuous positive airway pressure group and in 39% patients (24/61) in the conventional treatment group. ICU and hospital mortality rates were also similar in the two groups. However, both these studies also had some disappointing results. Antonelli et al (3) found that nine of 10 patients who were intubated after failing the NIV attempt died in the ICU (90%), whereas only 15 of 32 (47%) who had been intubated without a previous NIV trial died. Delclaux et al (4) observed a significantly higher number of adverse events in the continuous positive airway pressure group than in the conventional group despite a significant improvement in arterial oxygenation in the former. Numerous studies have since confirmed that although NIV may avoid the need for invasive mechanical ventilation in ARDS patients, a trial of failed NIV (i.e., eventually leading to intubation and invasive mechanical ventilation) portends a worse prognosis than the use of invasive mechanical ventilation without a previous NIV trial (5, 6). Recently, Frat et al (7) aimed to determine whether high-flow heated and humidified oxygen administered through a large-bore close-fitting nasal cannula or NIV could reduce the intubation rate and improve outcomes in acutely hypoxemic patients compared with standard oxygen administration. The intubation rate did not differ significantly among the three groups, but the hazard ratio for death at 90 days after randomization was 2.01 in the standard oxygen group versus the high-flow oxygen group ($p = 0.046$) and 2.5 in the NIV group versus the high-flow oxygen group ($p = 0.006$).

In this issue of *Critical Care Medicine*, Carteaux et al (8) provide highly relevant clinical data from a large prospective observational single-center study in 62 patients with acute hypoxemic respiratory failure (47 with ARDS). They investigated whether a high tidal volume (VT) during NIV could be deleterious and associated with NIV failure (defined as the need for intubation). The PS level was targeted to reach an expired VT (eVT) of 6–8 mL/kg of predicted body weight (PBW), and PEEP was kept below 10 cm H_2O. The mean eVT was 9.8 mL/kg of PBW, and most patients (77%) had a mean VT above 8 mL/kg of PBW. Of note, none had a mean eVT of less than 6 mL/kg PBW, and about 50% had a mean eVT of at least 10 mL/kg of PBW. NIV failed in 52% of patients, and mortality in this group once again was very high (64%). A multivariate analysis identified Simplified Acute Physiology Score II at admission and mean eVT as independent risk factors for NIV failure. For each 1-mL/kg PBW increase above mean eVT, the risk of failure increased 29%. The time to failure was 12 to 16 hours and was similar between survivors and nonsurvivors.

The study by Carteaux et al (8) also shows indirectly, because drive and respiratory muscle effort were unfortunately not measured, that ARDS patients under NIV make a colossal effort to breathe. One could argue that support levels were too low (average PS and PEEP were 8 and 5 cm H_2O, respectively), but previous research in similar patients has shown that increasing the levels of PS does not further reduce effort, although it further increases VT (9). Why is the effort so high? The authors provide crucial data on passive mechanics immediately after intubation and measured at VT of 6 mL/kg of PBW and PEEP of 10 cm H_2O. Under these settings, respiratory system compliance was 27 mL/cm H_2O and resistance was 11 cm H_2O/L/s, three times lower and two times higher, respectively, than normal values. The authors pointed out that eVT during NIV was about 590 mL, meaning about 30 cm H_2O of transpulmonary pressure was required at every noninvasively supported breath. Developing such transpulmonary pressure swings takes a huge respiratory muscle effort and drive. The $Paco_2$ levels were close to normal, and minute ventilation was very high (respiratory rate was between 30 and 36 breaths/min). Consequently, I do not think that the authors' proposal to administer sedatives to decrease drive and effort is a good option because it would likely lead to a rapid hypercapnic acidosis. The high mortality rate of patients who failed an NIV trial could be attributed to the high transpulmonary pressure swings and high VTs that generate lung injury (10). Another mechanism that may play a role in this scenario is possible intrinsic respiratory muscle injury: a high effort per breath, at a high rate, and for more than 10 hours had been developed before the patients were intubated. It has been shown in animal models that high inspiratory loading causes diaphragmatic injury, inflammation, upregulation of cytokines that can lead to systemic effects, and lung injury (11–13). In the experimental setting, these effects occur within short periods of time (less than 3 hr). Last but not least, high transmural intravascular pulmonary pressures may also play a role.

This study is the first to obtain data that provide a plausible mechanism to explain NIV failure in patients with acute hypoxemic respiratory failure, mainly ARDS, and the authors are to be commended. But where do we go from here in clinical practice? One option might be to give NIV a chance: many patients would perhaps avoid the need for invasive mechanical ventilation and its related complications. Second, using NIV with a tightly fitting mask would allow us to measure eVT, an extremely difficult task in nonintubated patients. The authors' new data strongly suggest that intubation should be considered if the monitored eVT is above 10 mL/kg of PBW during the first 2 hours of NIV. Finally, time is ripe to conduct a randomized trial comparing an early intubation strategy versus the conventional approach in ARDS patients making strenuous efforts to breath.

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Improved Outcomes in Critically Ill Patients With AIDS: How Does This Trend Continue?*

"Success needs no explanation. Failure does not have one that matters." –Jesse Jackson

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In this issue of *Critical Care Medicine*, Huson et al (1) thoughtfully describe the clinical characteristics and outcomes of patients with AIDS admitted to Dutch ICUs during the era of combination antiretroviral therapy (cART) from 1997 to 2014. Their findings show that major progress has been made during this time period such that patients with AIDS being treated in ICUs now have mortality rates approaching that of patients without AIDS. Although it could be argued that this success story needs no explanation, the true impact of this study may lie with the questions it raises. This study challenges care providers to search for the treatment modifications that may explain this trend so as to promote further improvement in the care of critically ill patients with AIDS.

Huson et al (1) performed a retrospective analysis of 1,127 AIDS patients and 4,479 controls (non-AIDS patients matched for age, sex, and admission type [medical or surgical and planned or unplanned]) treated in Dutch ICUs from 1997 to 2014. In general, AIDS patients had significantly more comorbidities, were more acutely ill based on Acute Physiology and Chronic Health Evaluation (APACHE) II scores, and were more likely to be admitted with another infection—typically a respiratory infection or sepsis. Not surprisingly, AIDS patients experienced a higher overall mortality rate than controls (28.2% vs 17.8%; $p < 0.0001$).

More interesting and encouraging than these data are the favorable trends that were identified in critically ill AIDS patients from 1999 to 2014. Although the mortality rate for both AIDS and non-AIDS patients declined over the study period (39–16% and 22–14%, respectively), the average annual percentage change was greater for patients with AIDS than controls (–6.0 [–8.0 to –3.9] vs –2.1 [–4.1 to –0.1]; $p = 0.02$). This greater decline in mortality among AIDS patients coincided with a downward trend in the proportion of AIDS patients being admitted with a respiratory infection. Further analyses suggest that decline in mortality was largely a function of the improved outcome in the subset of AIDS patients admitted with an infectious diagnosis. Using standardized mortality rates to control

*See also p. 291.

Key Words: acquired immunodeficiency syndrome; antiretroviral therapy; intensive care; mortality; noninvasive ventilation

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Failure of Noninvasive Ventilation for De Novo Acute Hypoxemic Respiratory Failure: Role of Tidal Volume*

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Objectives: A low or moderate expired tidal volume can be difficult to achieve during noninvasive ventilation for de novo acute hypoxemic respiratory failure (i.e., not due to exacerbation of chronic lung disease or cardiac failure). We assessed expired tidal volume and its association with noninvasive ventilation outcome.

Design: Prospective observational study.

Setting: Twenty-four bed university medical ICU.

Patients: Consecutive patients receiving noninvasive ventilation for acute hypoxemic respiratory failure between August 2010 and February 2013.

Interventions: Noninvasive ventilation was uniformly delivered using a simple algorithm targeting the expired tidal volume between 6 and 8 mL/kg of predicted body weight.

Measurements: Expired tidal volume was averaged and respiratory and hemodynamic variables were systematically recorded at each noninvasive ventilation session.

Main Results: Sixty-two patients were enrolled, including 47 meeting criteria for acute respiratory distress syndrome, and 32 failed noninvasive ventilation (51%). Pneumonia ($n = 51$, 82%) was the main etiology of acute hypoxemic respiratory failure. The median (interquartile range) expired tidal volume averaged over all noninvasive ventilation sessions (mean expired tidal volume) was 9.8 mL/kg predicted body weight (8.1–11.1 mL/kg predicted body weight). The mean expired tidal volume was significantly higher in patients who failed noninvasive ventilation as compared with those who succeeded (10.6 mL/kg predicted body weight [9.6–12.0] vs 8.5 mL/kg predicted body weight [7.6–10.2]; $p = 0.001$), and expired tidal volume was independently associated with noninvasive ventilation failure in multivariate analysis. This effect was mainly driven by patients with Pao_2/Fio_2 up to 200 mm Hg. In these patients, the expired tidal volume above 9.5 mL/kg predicted body weight predicted noninvasive ventilation failure with a sensitivity of 82% and a specificity of 87%.

Conclusions: A low expired tidal volume is almost impossible to achieve in the majority of patients receiving noninvasive ventilation for de novo acute hypoxemic respiratory failure, and a high expired tidal volume is independently associated with noninvasive ventilation failure. In patients with moderate-to-severe hypoxemia, the expired tidal volume above 9.5 mL/kg predicted body weight accurately predicts noninvasive ventilation failure. (*Crit Care Med* 2016; 44:282–290)

Key Words: acute lung injury; acute respiratory distress syndrome; noninvasive ventilation; pneumonia; respiratory insufficiency; tidal volume

***See also p. 444.**

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There is strong evidence that high tidal volumes increase mortality in patients with acute respiratory distress syndrome (ARDS) receiving invasive mechanical

ventilation (1, 2). The benefits of tidal volume reduction are also strongly suggested in critically ill patients without ARDS (3, 4) and were recently demonstrated in anesthetized patients undergoing major surgery (5).

Noninvasive ventilation (NIV) has been increasingly used as the first-line ventilatory support in de novo (i.e., not due to exacerbation of chronic lung disease or cardiac failure) (6) acute hypoxemic respiratory failure (AHRF) over the past decades (6–8). During NIV, the tidal volume results from both the airway pressure delivered by the ventilator and the respiratory muscle pressure generated by the patient's respiratory drive. Information about the tidal volume reached during NIV for de novo AHRF is scarce in the literature, but levels of drive and respiratory efforts have been reported to be high (9–11). We, therefore, hypothesized that a protective low tidal volume may be difficult to achieve in most patients receiving NIV for de novo AHRF. Furthermore, as lung injury resulting from high tidal volume ventilation experimentally occurs irrespective of whether the tidal volume is generated by a positive airway pressure (e.g., ventilator insufflation) and/or a negative pleural pressure (e.g., negative extrathoracic pressure or spontaneous breathing effort), we wondered whether high tidal volume during NIV could be deleterious and associated with NIV failure.

We, therefore, performed this study to: 1) assess the expired tidal volume (Vte) values reached by patients receiving NIV for de novo AHRF and 2) examine the relationships between tidal volume value and NIV failure.

METHODS

This was a single-center observational study conducted in the 24-bed medical ICU of Henri Mondor University Hospital, Créteil, France. The study was approved by the Institutional Review Board of the French Respiratory Medicine Society—Société de Pneumologie de Langue Française (no. 2014–051). Because of the observational nature of the study, patient's consent was waived. Follow-up for the study was performed until ICU discharge.

Patients

All consecutive patients receiving NIV as the first-line ventilatory support for de novo AHRF between August 2010 and February 2013 were included. AHRF was defined as acute dyspnea (with a respiratory rate > 25 breaths/min and/or active contraction of accessory respiratory muscles) with new pulmonary infiltrates on chest radiograph and a $Paco_2$ below or equal to 45 mm Hg (12). Patients whose respiratory failure was due to an exacerbation of chronic lung disease or cardiac failure were not included.

NIV Protocol

Pressure support adjustments were made in an attempt to target a predefined Vte range (12, 13) of 6–8 mL/kg of predicted body weight (PBW) (14). Vte was targeted and not inspired tidal volume because the latter includes inspiratory leaks and the Vte better reflects what the patient is really receiving. Briefly, a daily NIV prescription by the physician indicated the Vte target range in mL, and the lowest pressure support level allowed. The latter was set at 7 cm H_2O, to ensure a significant level of assistance in these patients usually exhibiting high levels of respiratory efforts, while minimizing leaks. NIV was started with a pressure support level of 8 cm H_2O and then adjusted by the nurses using a simple algorithm (12, 13) to reach the targeted Vte range. Positive end-expiratory pressure (PEEP) level was kept below 10 cm H_2O to minimize leaks (15). No sedative drug was administered during NIV treatment. It was recommended to deliver NIV at least 8 hr/d at the onset of NIV treatment. Additional details on patients and methods are provided in the **supplemental data** (Supplemental Digital Content 1, http://links.lww.com/CCM/B480).

Data Collection and Definitions

Clinical and ventilatory data (including Fio_2, pressure support level, PEEP, respiratory rate, minute ventilation, Spo_2, heart rate, blood pressure, and Richmond Agitation Sedation Scale) (16) were recorded twice during each NIV session on a specific monitoring form (collected in a prospective registry). Simplified Acute Physiology Score (SAPS) II score (17) at ICU admission, Sequential Organ Failure Assessment (SOFA) score (18) at NIV initiation, and arterial blood gases after 1 hour of NIV were also collected. Patients were categorized in two groups depending on their Pao_2/Fio_2 ratio after 1 hour of NIV treatment as follows: mild hypoxemia (200 mm Hg < Pao_2/Fio_2 ≤ 300 mm Hg), and moderate-to-severe hypoxemia (Pao_2/Fio_2 ratio ≤ 200 mm Hg), as per thresholds defined in the Berlin criteria for the ARDS (19, 20). The Vte was averaged at each NIV session from two measurements: the first and the last one. The mean Vte was computed for every patient from the averaged values of all NIV sessions over the whole duration of NIV. Criteria for intubation were predefined (supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/B480). NIV failure was defined as the need for intubation; patients fulfilling predefined intubation criteria but who died from cardiac arrest before intubation were considered as failures.

Statistical Analysis

Data were analyzed using the SPSS Base 13.0 statistical software package (SPSS, Chicago, IL). Continuous data were expressed as median (25th–75th percentiles) and compared using the Friedman and/or Wilcoxon paired test for related variables and the Kruskal-Wallis test and/or Mann-Whitney test for independent variables, as appropriate. Correction for multiple testing was performed with the Benjamini-Hochberg method. Categorical variables, expressed as percentages, were evaluated using the chi-square test or Fisher exact test as appropriate. Survival without intubation was evaluated using standard Kaplan-Meier actuarial techniques for estimation of survival probabilities. To evaluate independent factors associated with NIV failure, significant and marginally significant ($p < 0.15$) univariate risk factors were examined using backward stepwise Cox proportional hazards regression model. Among related factors (SAPS II at admission, SOFA at NIV start, and age for severity; Pao_2/Fio_2 ratio and pH

before the onset of NIV treatment, Vte and minute ventilation during NIV for respiratory variables), only the most clinically relevant (SAPS II for severity; Vte and Pao_2/Fio_2 ratio before the onset of NIV treatment for respiratory variables) were entered into the multivariable model to minimize the effect of collinearity. Thus, the four variables entered into the NIV failure multivariable analysis were immunosuppression, SAPS II at admission, Pao_2/Fio_2 ratio before the onset of NIV treatment, and mean Vte during NIV. The accuracy of mean Vte during NIV to predict NIV failure in patients with moderate-to-severe de novo respiratory failure was assessed by the mean of receiver operating characteristic (ROC) curves. The threshold value of mean Vte to predict NIV failure was then determined from analysis of the ROC curves as the value that led to the best compromise between sensitivity and specificity.

Two-sided *p* values less than 0.05 were considered significant.

RESULTS

Patients

Sixty-three patients received NIV for de novo AHRF during the study period. One patient was excluded because he was rapidly diagnosed with a complete left lung atelectasis and pleural effusion due to a lung cancer without possible curative treatment and NIV was promptly stopped; 62 patients remained for analysis. **Table 1** shows their main demographic and clinical

TABLE 1. Demographic and Clinical Characteristics of 62 Patients With De Novo Acute Hypoxemic Respiratory Failure at Noninvasive Ventilation Initiation

Demographic and Clinical Data	NIV Success (*n* = 30)	NIV Failure (*n* = 32)	*p*
Age, yr	58 (39–67)	65 (58–77)	0.06
Male gender, *n* (%)	18 (60.0)	22 (68.7)	0.60
Simplified Acute Physiology Score II at admission (30)	30 (22–38)	41 (35–51)	< 0.001
SOFA at NIV start	4 (3–7)	6 (5–8)	0.01
Respiratory SOFA	3 (2–3)	3 (2–4)	0.05
Coagulation SOFA	0 (0–1)	0 (0–2)	0.26
Liver SOFA	0 (0–1)	0 (0–1)	0.81
Cardiovascular SOFA	0 (0–0)	0 (0–2)	0.09
CNS SOFA	0 (0–0)	0 (0–1)	0.02
Renal SOFA	0 (0–1)	1 (0–2)	0.21
Immunosuppression	2 (6.7)	12 (37.5)	0.005
Arterial blood gases before NIV			
pH	7.41 (7.38–7.45)	7.45 (7.38–7.48)	0.09
Pao_2, mm Hg	70 (58–92)	69 (53–81)	0.14
Fio_2	0.5 (0.3–0.7)	0.6 (0.4–0.7)	0.45
Pao_2/Fio_2, mm Hg	177 (133–219)	122 (98–191)	0.02
$Paco_2$, mm Hg	36 (32–42)	32 (29–40)	0.15
Co_2t, mmol/L	25 (20–26)	23 (20–26)	0.50
Lactates, mmol/L	1.4 (0.9–2.9)	1.7 (1.3–2.6)	0.30
Increase in Pao_2/Fio_2 ratio after 1 hr of NIV	44 (–67 to 91)	41 (6–104)	0.43
Pao_2/Fio_2 categorization, *n* (%)[a]			1.00
Mild hypoxemia	14 (47)	15 (47)	
Moderate-to-severe hypoxemia	16 (53)	17 (53)	
Bilateral infiltrates on chest radiograph, *n* (%)	22 (73)	25 (78)	0.77

NIV = noninvasive ventilation, SOFA = Sequential Organ Failure Assessment score (31),mild hypoxemia = acute hypoxemic respiratory failure with 200 mm Hg< Pao_2/Fio_2 ≤ 300 mm Hg after 1 hr of NIV, moderate-to-severe hypoxemia = acute hypoxemic respiratory failure with Pao_2/Fio_2 ≤ 200 mm Hg after 1 hr of NIV.

[a]Evaluated at the first hour of NIV.

Continuous data are expressed as median (25th-75th percentile).

characteristics. Twenty-nine patients had mild hypoxemia, and 33 patients had moderate-to-severe hypoxemia. Etiologies of the AHRF were the followings: pneumonia (n = 51), intra-alveolar hemorrhage (n = 5), ARDS from extrapulmonary cause (n = 4), drug-induced pneumonia (n = 1), or interstitial pneumonia (n = 1). Fifteen patients had unilateral infiltrates on the chest radiograph and 47 fulfilled ARDS criteria.

Tidal Volume

We analyzed 968 Vte values over a total of 484 NIV sessions (two Vte per NIV session with no missing data). Despite pressure support adjustments aiming at targeting a Vte between 6 and 8 mL/kg PBW, the median value of Vte averaged over all NIV sessions (mean Vte) was 9.8 mL/kg PBW (8.1–11.1 mL/kg PBW), with a median value of pressure support level of 7 cm H_2O (7–9 cm H_2O). Only 14 patients (23%) had a mean Vte between 6 and 8 mL/kg PBW during all NIV sessions, and all other patients (77%) having a mean Vte above 8 mL/kg PBW (**Fig. 1**). The mean Vte during NIV was similar between patients with mild or moderate-to-severe hypoxemia (9.9 mL/kg PBW [8.2–10.9] vs 9.2 mL/kg PBW [7.9–11.5], respectively; p = 0.90).

When invasive mechanical ventilation was required after NIV failure, the Vte set by the clinician after intubation was decreased by a median of 39% (28–47%) as compared with Vte under NIV (**Table 2**).

NIV Outcome

NIV failed in 32 patients (52%; 95% CI, 35–64), including two patients with hypoxemic cardiac arrest before intubation. Reasons for NIV failure included refractory hypoxemia (recorded as the main cause for intubation in all patients, n = 32; 100%), persistent signs of respiratory distress and hypercarbia (n = 4; 12%), shock (n = 2; 6%), and poor tolerance and psychomotor agitation (n = 3; 9%). Twenty-one patients (34%) died in the ICU. The SAPS II–based standardized mortality ratio was 1.62 (95% CI, 2.49–0.99).

Characteristics associated with NIV failure by univariate analysis included immunosuppression, lower value of Pao_2/Fio_2 ratio before the initiation of NIV treatment, SAPS II score at ICU admission and SOFA score at NIV initiation, minute ventilation, and Vte under NIV (Table 2). Although the Pao_2/Fio_2 ratio differed between the success and failure groups before initiation of NIV, this difference did not persist after 1 hour of NIV (Tables 1 and 2). The multivariate analysis identified the mean Vte as an independent risk factor for NIV failure, along with the SAPS II at admission (**Table 3**).

Among patients who failed NIV, the duration of NIV treatment did not differ significantly between survivors and non-survivors [12.0 hr (6.2–25.2) vs 15.9 hr (6.7–20.3), respectively; p = 0.87].

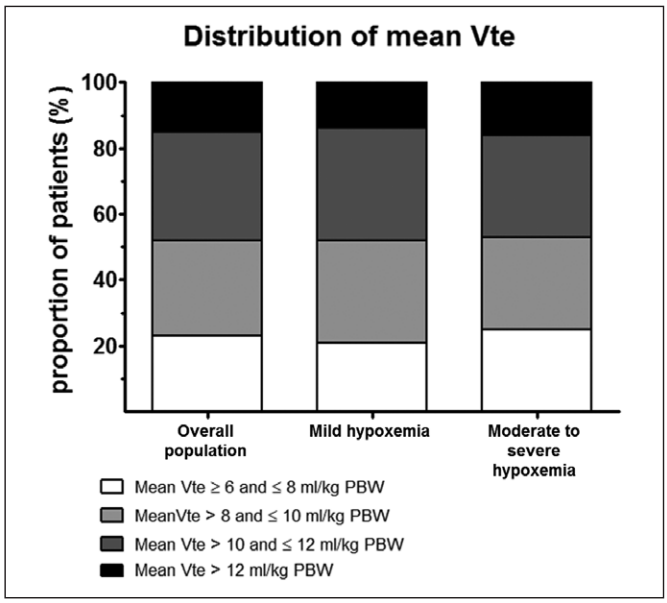

Figure 1. Relative distribution of mean expired tidal volume (Vte) over the total duration of noninvasive ventilation according to predefined ranges in the overall population (n = 62) and in patients with mild hypoxemia (200 < Pao_2/Fio_2 ratio ≤ 300 mm Hg; n = 29) or moderate-to-severe hypoxemia (Pao_2/Fio_2 ratio ≤ 200 mm Hg; n = 33). No patient had a mean Vte below 6 mL/kg predicted body weight (PBW).

Subgroup Analyses

The difference in mean Vte observed between NIV success and failure was mainly driven by patients with moderate-to-severe hypoxemia (**Fig. 2**). In this subgroup, the area under the ROC curve assessing the accuracy of mean Vte in predicting NIV failure reached 0.85 (95% CI, 0.71–1.00; p = 0.001) (**Fig. 3**). The mean Vte threshold value of 9.5 mL/kg PBW was identified from the ROC curve as the most accurate to predict NIV failure, with a sensitivity of 82% and specificity of 87%, a positive predictive value of 87%, and a negative predictive value of 82%. ROC curves assessing the mean Vte in predicting NIV failure at various duration of NIV treatment are available in **eFigure 1** (Supplemental Digital Content 1, http://links.lww.com/CCM/B480). Patients with a Pao_2/Fio_2 ratio up to 200 mm Hg having a mean Vte above 9.5 mL/kg PBW over the first 4 hours of NIV had a significantly higher cumulative probability of NIV failure as compared with others (p = 0.003, Log-rank test) (**Fig. 4**).

DISCUSSION

The main finding of our study was that targeting a 6–8 mL/kg PBW range of Vte during NIV for de novo AHRF could not be obtained in the majority of patients. A higher mean Vte (averaged over all NIV sessions) was independently associated with NIV failure. In patients with moderate-to-severe hypoxemia, a mean Vte more than 9.5 mL/kg PBW recorded over the first four cumulative hours of NIV accurately predicted NIV failure.

Tidal Volume Ranges

To our knowledge, our study is the first to explore values of Vte over the whole duration of NIV in patients with AHRF. In most clinical studies assessing NIV in AHRF, Vte values were not reported (21–29). In a physiologic assessment of NIV effects in 10 patients with ARDS, L'Her et al (11) recorded a Vte of 483 ± 247 mL and 591 ± 229 mL with a pressure support level of 10 and 15 cm H_2O, respectively. Thille et al (12) observed a mean

TABLE 2. Ventilatory and Hemodynamic Variables During Noninvasive Ventilation and After Intubation in Case of Noninvasive Ventilation Failure in Patients With De Novo Acute Hypoxemic Respiratory Failure

Ventilatory and Hemodynamic Data	NIV Success (*n* = 30)	NIV Failure (*n* = 32)	*p*
Days with NIV treatment[a]	3.0 (2.0–4)	2.0 (1.0–3)	0.05
Number of NIV sessions, *n*	7 (4–14)	5 (2–9)	0.07
Total time spent under NIV, hr	16.3 (7.0–27.7)	15 (6.5–22.6)	0.50
Positive end-expiratory pressure, cm H_2O			
During NIV	5 (5–5)	5 (5–5)	0.50
After intubation	NA	10 (5–14)[b]	
Pressure support level, cm H_2O			
During NIV	7.8 (7.2–9.3)	7.5 (7.0–8.3)	0.28
NIV H1	8.0 (7.0–10.5)	8.0 (7.0–10.0)	0.07
Before intubation	NA	8.0 (7.0–8.0)	
Ventilator driving pressure,[c] cm H_2O			
After intubation	NA	15 (11–20)[b]	
Pao_2, mm Hg			
Before NIV	70 (58–92)	69 (53–81)	0.14
NIV H1	124 (91–219)	129 (83–175)	0.67
After intubation	NA	118 (75–160)	
Fio_2			
Before NIV	0.5 (0.3–0.7)	0.6 (0.4–0.7)	0.45
NIV H1	1.0 (0.6–1.0)	0.7 (0.5–1.0)	0.11
After intubation	NA	0.8 (0.6–1.0)	
Pao_2/Fio_2, mm Hg			
Before NIV	177 (133–219)	122 (98–191)	0.02
NIV H1	189 (148–264)	198 (130–256)	0.88
After intubation	NA	146 (108–250)	
$Paco_2$, mm Hg			
Before NIV	36 (32–42)	32 (29–40)	0.15
NIV H1	37 (32–41)	35 (31–38)	0.14
After intubation	NA	39 (35–55)	
Minute ventilation, L/min			
During NIV	17.0 (13.4–20.0)	21.0 (19.0–23.5)	< 0.001
After intubation	NA	12.5 (9.9–14.6)[b]	
Vte, mL/kg PBW			
During NIV	8.5 (7.6–10.2)	10.6 (9.6–12.0)	0.001
After intubation	NA	6.0 (5.4–6.7)[b]	
Vte > 9.5 mL/kg PBW, *n* (%)			
During NIV	9 (30)	24 (75)	0.001

(*Continued*)

TABLE 2. (*Continued*). Ventilatory and Hemodynamic Variables During Noninvasive Ventilation and After Intubation in Case of Noninvasive Ventilation Failure in Patients With De Novo Acute Hypoxemic Respiratory Failure

Ventilatory and Hemodynamic Data	NIV Success ($n = 30$)	NIV Failure ($n = 32$)	p
Respiratory rate, cycles/min			
Before NIV	33 (30–39)	36 (30–40)	0.61
During NIV	30 (27–34)	30 (26–37)	0.69
After intubation	NA	30 (27–35)	
Systolic blood pressure, mm Hg			
Before NIV	132 (119–154)	128 (116–140)	0.15
During NIV	127 (115–134)	127 (112–137)	0.85
Heart rate, cycles/min			
Before NIV	111 (90–125)	110 (89–132)	0.89
During NIV	100 (92–111)	103 (87–108)	0.89
Respiratory mechanics after intubation			
Static compliance of the respiratory system, mL/cm H_2O	NA	27 (18–36)	
Resistance of the respiratory system, cm H_2O/L/s	NA	11 (10–20)	

NIV = noninvasive ventilation, during NIV = mean value over all NIV sessions, after intubation = value after 12 hr of invasive mechanical ventilation (failure group), NA = not applicable, NIV H1 = value under NIV after 1 hr of treatment, before intubation = value under NIV during the last NIV session before intubation, Vte = expired tidal volume, PBW = predicted body weight.

[a]Defined as time from the onset of NIV until either NIV failure or NIV weaning.

[b]$p < 0.05$ as compared with the value during NIV (failure group).

[c]Defined as the difference between the plateau pressure and the positive end-expiratory pressure during assist-control ventilation after intubation.

Continuous data are expressed as median (25th-75th percentile).

Vte of 613 mL after 1 hour of NIV in patients with moderate-to-severe ARDS. In a more recent clinical study, Frat et al (30) reported a mean Vte of 9.2 ± 3.0 mL/kg PBW at the initiation of NIV in 110 patients with de novo AHRF. Our results are consistent with these previous reports, as the absolute and relative values of mean Vte in our study were 592 mL (507–704) and 9.8 mL/kg PBW (8.1–11.1), respectively. These results demonstrate that targeting a Vte between 6 and 8 mL/kg PBW during NIV for AHRF (as proposed for mild ARDS) (19) is not achievable in most patients in clinical practice. It is unclear whether the use of pressure levels below 7 cm H_2O may mitigate the increase in Vte during NIV for de novo AHRF. Anjos et al (31) reported a Vte above 550 mL with a pressure support level of 5 cm H_2O and a PEEP level at least 5 cm H_2O in 30 patients with AHRF complicating acquired immune deficiency syndrome.

NIV Outcome

In patients with AHRF, NIV fails far more frequently in case of de novo respiratory failure than in patients with cardiogenic pulmonary edema (21–29, 32–34). Previous studies assessing NIV in AHRF, however, frequently mixed these two groups of patients (22, 23, 26, 29), clouding interpretation of the outcome of NIV regarding the de novo subgroup. In our cohort, about 50% of patients with ARDS (25/47) succeeded NIV,

TABLE 3. Multivariate Analysis of Risk Factors for Noninvasive Ventilation Failure in Patients With De Novo Acute Hypoxemic Respiratory Failure

Risk Factors	Unadjusted Hazard Ratio (95% CI)	p	Adjusted Hazard Ratio (95% CI)[a]	p
Simplified Acute Physiology Score II (30)	1.026 (1.008–1.043)	0.011	1.024 (1.007–1.041)	0.013
Immunosuppression	2.207 (1.054–4.622)	0.045	1.351 (0.598–3.056)	0.476
Pao_2/Fio_2 before NIV	0.995 (0.990–1.001)	0.114	0.995 (0.989–1.001)	0.109
Mean expired tidal volume during NIV, per mL/kg predicted body weight	1.318 (1.109–1.567)	0.002	1.286 (1.069–1.547)	0.008

NIV = noninvasive ventilation.

[a]Adjusted hazard ratio obtained by Cox regression.

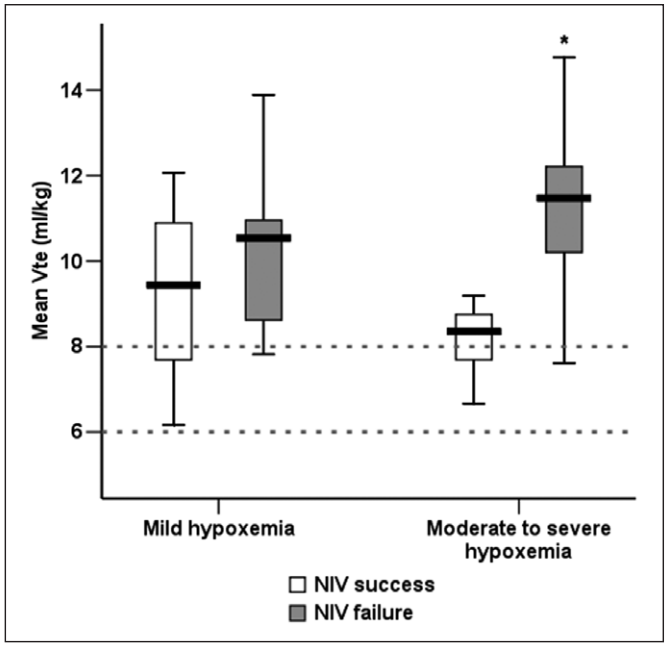

Figure 2. Expired tidal volume (Vte) averaged over the whole duration of noninvasive ventilation (NIV) in patients with mild hypoxemia (200 < Pao_2/FIO_2 ratio ≤ 300 mm Hg; $n = 29$) or moderate-to-severe hypoxemia (Pao_2/FIO_2 ratio ≤ 200 mm Hg; $n = 33$). The box plots represent median (*thick horizontal bar*), 25th and 75th percentiles (extremities of the boxes), fifth and 95th percentiles (*thin horizontal bars*). *$p < 0.05$ versus NIV success.

confirming previous studies reporting success rates ranging from 34% to 75% (21–31).

We found that a higher mean Vte was associated with NIV failure, with a 29% increased risk of failure for each 1 mL/kg PBW increase of mean Vte (Table 3). Different hypotheses that are not mutually exclusive may be proposed to explain this observation. First, a high Vte may represent a surrogate for the severity of the ongoing disease process. However, Vte remained

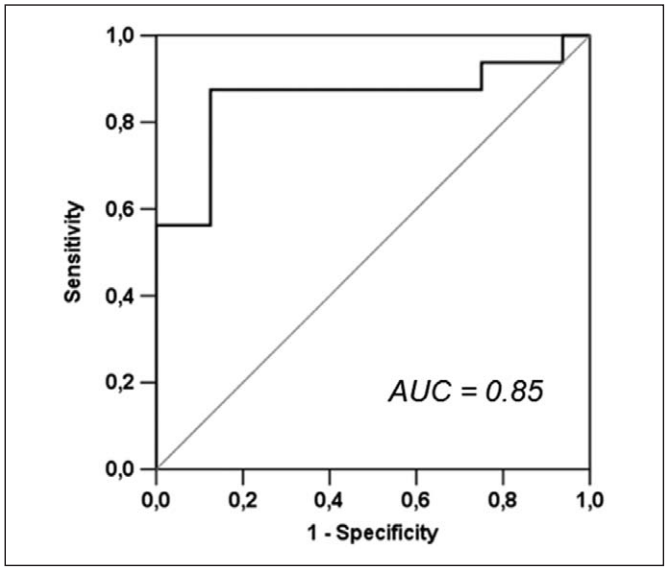

Figure 3. Receiver operating characteristic (ROC) curves of mean expired tidal volume (Vte) during noninvasive ventilation (NIV) to predict NIV failure in patients with moderate-to-severe hypoxemia (Pao_2/FIO_2 ratio ≤ 200 mm Hg; $n = 33$). AUC = area under the ROC curve.

an independent risk factor for NIV failure when controlling for patient severity and organ failures. Second, a high Vte may act as a worsening factor during NIV for de novo AHRF, by inducing superimposed ventilator-induced lung injury (VILI). In invasively ventilated patients, Needham et al (35) recently pointed out the importance of controlling Vte at the very onset of the ARDS. In fact, one of the main determinants of VILI in experimental reports is the tidal volume size, and injury has been demonstrated or suggested whether mechanical ventilation is delivered via a positive or a negative pressure (36–38). Lung injury was also reported during pharmacologically induced spontaneous hyperventilation in an experimental animal study (39). A preexisting insult (e.g., pneumonia) may potentiate the deleterious effect of nonprotective ventilation (according to the "double hit" theory) (40), and lung injury may also worsen during spontaneous breathing, especially if the preexisting insult is severe (41–43). In our study, the impact of Vte on NIV outcome was mainly driven by the most hypoxemic patients with the worst lung injury. Interestingly, in the recently published clinical trial comparing oxygen therapy, high-flow oxygen therapy, and NIV in de novo AHRF, Frat et al (30) reported that adding NIV to high-flow oxygen therapy increased the intubation rate as compared with high-flow oxygen therapy alone in patient with a Pao_2/FIO_2 ratio up to 200 mm Hg. Our data are, therefore, consistent with these results and may contribute to explain them.

Clinical Implications

Our study suggests that high Vte is a possible worsening factor during NIV for de novo AHRF, while it may be difficult to control its value in this setting. During NIV, Vte results both from the pressure support level delivered by the ventilator and the respiratory muscles pressure generated by the patient. When pressure support level is reduced during pressure support ventilation, Vte usually decreases (44); however, the pressure support level often reached the lowest value allowed (7 cm H_2O) in our study, suggesting that the persistently high Vte was mainly driven by continued strong patient's inspiratory efforts as discussed above. Administering sedative drugs to decrease spontaneous breathing efforts might be considered. In the few reports available where sedatives drugs were administered during NIV to improve NIV tolerance (45, 46), their effect on Vte was not reported. The use of sedatives with the goal of decreasing the respiratory drive during NIV for de novo AHRF should, therefore, be specifically assessed in dedicated studies before being considered in the clinical settings. Early intubation represents another possibility to limit high Vte under NIV. Assessing the mean Vte during the first hours of NIV could help selecting patients at risk of NIV failure. The potential benefit of a strategy of early intubation in patients receiving NIV for de novo AHRF and having a persistently high Vte should be tested in randomized clinical trials.

Strengths and Limitations

Strengths of our study include the comprehensive collection of respiratory parameters during all NIV sessions and the standardization of NIV settings adjustments. Several limitations should also be underlined. First, this was a single-center

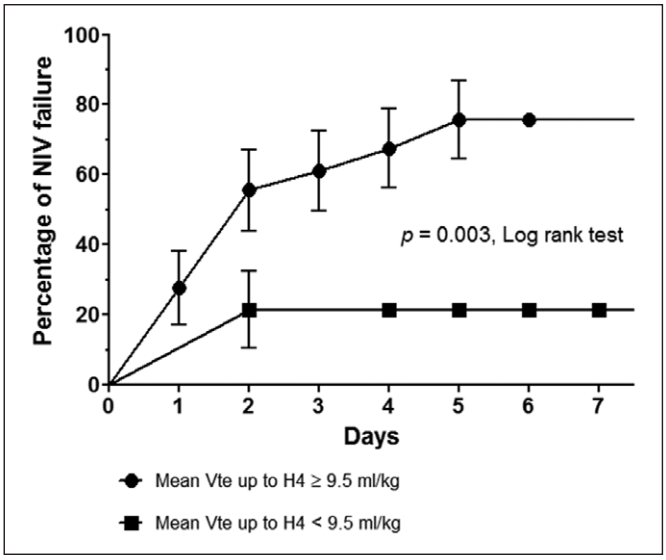

Figure 4. Kaplan-Meier estimate of the cumulative probability of noninvasive ventilation (NIV) failure according to the mean tidal volume (Vte) during the first four cumulative hours of NIV (higher or lower than 9.5 mL/kg) in patients with moderate-to-severe hypoxemia (Pao_2/Fio_2 ratio ≤ 200 mm Hg; $n = 33$).

study, conducted in a unit highly trained in the management of patients under NIV. NIV failure rate and causes of NIV failure might therefore be different in other settings. Furthermore, the ventilator settings adjustments may differ across centers. In fact, whereas some physicians may be prone to decrease the pressure support level below 7 cm H_2O in attempt to further decrease the Vte, others may conversely increase the pressure support and PEEP levels in attempt to alleviate the respiratory effort and derecruitment. It is important to note, however, that the level of pressure support was not different between success and failure (Table 2), whereas failure patients had higher tidal volumes. Although the PS level may have been too low, a higher level would have led to even higher levels of tidal volumes. Measuring the respiratory drive might be useful to better tailor the pressure support level, but this is not routinely feasible during NIV. Last, Vte was recorded two times per NIV session, but was not continuously monitored, and no marker of lung injury was assessed.

CONCLUSIONS

A Vte target range of 6–8 mL/kg was impossible to achieve in the majority of patients receiving NIV for de novo AHRF. A higher Vte was independently associated with NIV failure. In the subgroup of patients with a Pao_2/Fio_2 ratio up to 200 mm Hg, a mean Vte of more than 9.5 mL/kg PBW over the first four cumulative hours of NIV accurately predicted NIV failure.

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