Expiratory Flow-Volume Loop Profile and Patient Outcome in Chronic Obstructive Pulmonary Disease in Acute Respiratory Failure: A Prospective Observational Study in a Single Intensive Care Unit

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For editorial comment see p. 14

Key Words

Chronic obstructive pulmonary disease • Respiratory mechanics • Expiratory flow-volume loop • Mechanical ventilation • Patient outcome

Abstract

Background: Expiratory flow-volume (EFV) loops are continuously displayed on the screen of intensive care unit (ICU) ventilators. **Objectives:** It was the aim of this study to investigate the relationships of EFV to chronic obstructive pulmonary disease (COPD) patient outcome. **Methods:** This is a prospective study on COPD patients who received invasive mechanical ventilation for acute respiratory failure in the ICU. Within the 24-hour post-intubation period, the angle of the EFV slope during the last 50% of expiration was computed and patients were stratified into 4 quartiles. Resistance, compliance of the respiratory system and change in end-expiratory lung volume above relaxation volume were assessed. Patients were followed up to hospital discharge. The main outcome was hospital mortality. Secondary outcomes were ICU mortality, length of ICU stay, duration of invasive ventilation, number of intubations, oxygen and non-invasive venti-

lation. **Results:** Thirty-eight patients were analysed. The first quartile comprised 9 patients (median angle 11°, interquartile range 8–12), the second 10 patients (median angle 26°, range 19–30), the third 10 patients (median angle 42°, range 39–46), and the fourth 9 patients (median angle 53°, range 49–64). Hospital and ICU mortality were not different between groups. Lengths of ICU and hospital stay and length of invasive ventilation were significantly different between groups, with the highest values observed in the first quartile. The rate of oxygen use and non-invasive ventilation in the ICU and at hospital discharge was significantly different between groups, with the highest rate observed in the first quartile. There was a significant negative correlation between angle and resistance, compliance of the respiratory system and change in end-expiratory lung volume above the relaxation volume. **Conclusion:** The slope of the angle during the last 50% of expired volume in the COPD patients was associated with worsened respiratory mechanics and higher morbidity.

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Introduction

In patients with chronic obstructive pulmonary disease (COPD) receiving invasive mechanical ventilation for acute respiratory failure (ARF) in the intensive care unit (ICU), intrinsic positive end-expiratory pressure (PEEPi) [1, 2] and expiratory flow limitation are very common on admission [3]. The quantification of PEEPi requires a specific manoeuvre [4]. The visual inspection of the dynamic expiratory flow-volume (EFV) loops in COPD patients could be a simple approach, as already pointed out by Dhand [1] and Lourens et al. [5]. EFV loops are continuously displayed on the screen of all ICU ventilators. However, there is no quantitative information on the visual inspection of the tracings. The measurement of the expiratory time constant provides quantification [6, 7]. A single exponential model fitted to passive expiration assumes constant resistance (Rrs) and elastance of the respiratory system which is not the case in COPD due to lung heterogeneity, i.e. regional time constant inequalities, in association with impaired viscoelastic properties of the respiratory system [8], expiratory flow limitation and increased airway resistance [9]. A bi-exponential model has been fitted to passive expiration [10], but this requires more complex computation and may be less accurate.

In the present study, we used the slope of the EFV curve during the last 50% of the expiration as previously described by others [11, 12]. We wondered whether the slope of the EFV curve might be associated with a change in outcomes in patients with COPD receiving mechanical ventilation in the ICU. Therefore, we carried out the present study with the following aims: (1) to assess the slope of the EFV curve very soon after onset of invasive mechanical ventilation for ARF in COPD patients, and (2) to correlate it to patient outcome. Our working hypothesis was that the lower the slope, the worse the patient outcome.

Patients and Methods

Patients

Patients of both gender were included if they met all of the following criteria: (1) ≥ 18 years of age, (2) intubation or tracheotomy, mechanical ventilation, and sedation and/or neuromuscular blockade for ARF in our 14-bed medical ICU, (3) proven COPD of GOLD grade ≥ 1 or suspected COPD from at least one amongst the following: daily cough and sputum for at least 3 months for 2 consecutive years, current or past lung imaging showing diffuse and/or focal lung hyperaeration and/or diaphragm flattening and/or emphysema, $\text{PaCO}_2 > 45$ mm Hg and plasma bicarbonate

> 26 mmol/l, PEEPi on ICU admission. The non-inclusion criteria were: (1) absence of proven or suspected COPD; (2) absence of intubation or tracheotomy; (3) pregnancy, and (4) patient placed in the care of a guardian. The protocol was approved and classified as current standard-of-care investigation by the ethical committee of our institution that waived informed consent.

Study Design

This was a prospective observational cohort investigation. All patients staying in our ICU were screened for eligibility. All intubated patients admitted to our ICU and all patients who were intubated during their ICU stay were screened for COPD detection. From analysis of the medical record and the interview of the next of kin of the patient, it turned out that COPD was either known or unknown. Known COPD was defined as grade ≥ 1 from the GOLD classification [13]. If COPD was not known, its systematic detection was carried out by family interview, as wells by analysis of radiological findings, arterial blood gases and pulmonary function tests performed during the ICU stay. From this, suspected COPD was defined from the inclusion criteria mentioned above. The patient was included within the first 24 h of ICU admission if already intubated or tracheotomized, or within the first 24 h after intubation if the patient was intubated after ICU admission. The patient was followed-up to hospital discharge. Pulmonary function tests were performed after ICU discharge of alive patients with suspected COPD to confirm obstructive lung disease or not.

The following data were recorded on a specific case record form: age, gender, dates of ICU and hospital admission and discharge, date of intubation, long-term use of non-invasive mechanical ventilation or oxygen before ICU admission, GOLD scale, brand of the ventilator, Simplified Acute Physiology Score (SAPS) [14], height, weight, smoking habit, cause of ARF, patient status at ICU and hospital discharge, date of successful extubation, number of intubations in the ICU, oxygen or non-invasive ventilation in the ICU and at hospital discharge.

Procedure

Our usual practice of sedation in the 24 h following intubation for ARF is to use continuous intravenous sedation (midazolam) and analgesia (morphin chlorydrate) adjusted to obtain a Ramsay scale of 6 [15]. The ventilatory settings in intubated COPD patients are standardized in the daily practice as follows: volume-controlled mode, constant flow inflation, tidal volume 6–8 ml/kg predicted body weight, respiratory rate 10–14 breaths per minute, inspiratory time/total duration of the breathing cycle 25%, inspired oxygen in air set to maintain transcutaneous oxygen saturation between 88 and 95%, PEEP 5 cm H_2O . The predicted body weight (kg) was computed according to the following formula [16]: $50 + 2.3 [\text{height (in)} - 60]$ for males and $45.5 + 2.3 [\text{height (in)} - 60]$ for females.

The measurements were performed as follows. The target level of the Ramsay scale of 6 and the absence of inspiratory efforts were checked and sedation/analgesia adjusted if needed. The patient was positioned in the supine position 30–40° from the horizontal line. The standard ventilatory settings were checked and applied if needed for 5 min.

The measurements were then performed in the following order:

- (1) blood was withdrawn from the arterial line and immediately sent to the laboratory for arterial blood gas analysis.
- (2)

Signals of airway pressure and airflow (Flow sensor PN 155362, Hamilton Medical, Rhäzüns, Switzerland) were recorded proximal to the endotracheal tube by using hardware (Biopac MP150, Biopac Systems, Inc.) for 3 min; then a 3-second end-expiratory occlusion followed by a 3-second end-inspiratory occlusion was performed by pressing the specific knobs at the ventilator. (3) The patient was disconnected from the ventilator to exhale to the atmosphere up to the flow reaching 0 (relaxation volume of the respiratory system) and reconnected. (4) Then, the measurement set-up was removed.

Care was taken to make the measurements just before the next bronchodilator and steroid administration.

During the measurements, transcutaneous oxygen saturation, heart rate, arterial blood pressure and ventilatory signals were continuously monitored.

Data Analysis

The signals of airway pressure and airflow were analysed using AcqKnowledge® software version 3.8.2 (Biopac Systems, Inc.). For the two consecutive breaths just before the end-expiratory occlusion, we measured the following: inspired tidal volume, inspiratory and expiratory times, PEEP applied and peak expiratory flow. Furthermore, for these breaths, the angle of the slope of the EFV curve between 50 and 100% of exhaled volume was computed according to the following equation [12]:

$$\text{Angle (degrees)} = \arctangent (V'50\% - V'100\%) / VT50\% \quad (1)$$

where $V'50\%$ is the expired flow at 50% of the expired volume (VT), and $V'100\%$ is the expired flow at the end of expiration.

The values obtained for these two breaths were averaged.

The values of airway pressure at the end of the expiratory occlusion, first at zero flow and at 3 s after end-inspiratory occlusion, and of inspiratory flow just before end-inspiratory occlusion were measured [8]. The change in end-expiratory lung volume between mechanical breath and relaxation volume of the respiratory system (ΔFRC) was measured, as previously described [8]. Total Rrs, including that of the endotracheal tube, and compliance of the respiratory system (Crs) were obtained from classical equations [8].

The patients were followed up to their hospital discharge by 2 of the authors (V.P. and S.E.) to assess their status (dead or alive) and to obtain the pulmonary function test results.

The primary outcome was hospital mortality. The secondary outcomes were ICU mortality, number of intubations in the ICU, length of invasive mechanical ventilation, oxygen and non-invasive requirement in the ICU or at hospital discharge.

The patients were stratified into quartiles for the values of the angle of the slope of the EFV curve between 50 and 100% of the expired volume.

The normal distribution of the quantitative variables was verified by the Anderson-Darling test. The values were expressed as the median (with interquartile ranges) and counts (percent in groups) as required. The comparisons between the four groups were performed by using non-parametric tests. Spearman's ρ correlation coefficient was used to assess the strength of the statistical association between quantitative variables. A receiving operating characteristics (ROC) analysis was performed to test the accuracy of the slope of the EFV curve between 50 and 100% of the expired volume to assess patient outcome. Furthermore, we compared the capability of the ROC curves pertaining to angle of the

slope, PEEPi, Rrs and forced expiratory volume in 1 s (FEV_1) to assess patient outcome. The accuracy was measured by the area under the ROC curve (AUC) expressed together with its 95% confidence intervals. The accuracy was classified into the following 5 AUC categories as excellent for AUC between 0.90 and 1, good for AUC 0.80–0.90, fair for AUC 0.70–0.80, poor for AUC 0.60–0.70, and failed for AUC 0.50–0.60. The diagnostic performance was compared to guessing by using the asymptotic test. Finally, we estimated the sensitivity and specificity of the physiological variables with good to excellent AUCs at a specific threshold that was picked up in the table of sensitivity against 1 – specificity. For the outcome expressed as a continuous variable, a dichotomous variable was created, splitting the sample into two groups relative to the median value of that outcome.

The statistical analysis was performed by using R software version 2.9.0 [17]. A p value <0.05 was set as the statistically significant threshold.

Results

Cohort Characteristics

From March 1, 2009 to May 31, 2010, 275 patients received invasive mechanical ventilation in our ICU. Among them, 118 were not eligible for the present study and 29 were not evaluable for eligibility because of early death ($n = 9$) or early weaning ($n = 20$). Among the 128 eligible patients, 68 were not included for the following reasons: early death ($n = 6$), severe hypoxaemia that precludes measurement at PEEP 0 ($n = 24$), early weaning ($n = 22$), and researchers not available ($n = 22$). Among the 60 remaining patients, 42 had a known and 18 a suspected COPD. Among the 42 patients with a known COPD, the pulmonary function test before the ICU stay showed that 2 had no COPD, 1 record was lost, and 5 had no pulmonary function test after ICU discharge. Among the 18 patients with a suspected COPD, 11 died in the ICU and did not complete the pulmonary function tests and 3 had no pulmonary function test after ICU discharge.

As a result, 38 patients (32 men) with a proven COPD were analysed. Their age was 69 years (range 62–77), actual weight 68 kg (range 57–79), predicted body weight 65 kg (range 55–69), height 170 cm (range 162–173), and body mass index 23 (range 20–28). Two patients were classified as GOLD 1, 8 as GOLD 2, 11 as GOLD 3 and 17 as GOLD 4. Long-term home oxygen therapy was administered in 12 and non-invasive ventilation in 4 patients. The baseline FEV_1 was 1 litre (range 0.7–1.4; 42% predicted, range 26–53). ARF was due to infection in 32 patients, cardiac arrest in 2, acute cardiogenic pulmonary oedema in 1, suicide in 1, cancer in 1 and due to an unknown reason in 1 patient. The SAPS II on ICU admis-

Fig. 1. Representative EFV loop. ΔV = Change in volume during the last 50% of expiration; $\Delta V'$ = corresponding change in flow.

Table 1. Baseline characteristics

	Quartile 1 (n = 9)	Quartile 2 (n = 10)	Quartile 3 (n = 10)	Quartile 4 (n = 9)	p value between groups ¹
GOLD grade					
1	0	0	1	1	0.003 (Fisher's exact test)
2	0	1	4	3	
3	0	5	2	4	
4	9	4	3	1	
Long-term use of oxygen	6	3	2	1	0.09 (Fisher's exact test)
Long-term use of NIV	2	1	0	1	0.47 (Fisher's exact test)
FEV ₁ , litres	0.7 [0.6–0.8]	0.9 [0.7–1.2]	1.4 [1.0–1.7]	1.3 [1.0–1.7]	0.001 (Kruskal-Wallis test)
FEV ₁ , % predicted	24 [20–34]	35 [18–43]	54 [42–72]	49 [43–61]	0.001 (Kruskal-Wallis test)

Values are medians, with interquartile ranges in brackets, or counts. NIV = Non-invasive ventilation.

¹ Statistical tests used are given in parentheses.

sion was 56 (range 42–64). Thirty-one patients were ventilated with a Drager ventilator, 5 with a Nellcor-Puritan Bennett 840 ventilator and 2 with a Horus ventilator (Air Liquide Medical Systems) at the time of measurements.

Expiratory Profiles

The coefficient of variation between the two analysed breaths was 1.92%. Stratification for the angle of the slope of the EFV curve resulted in the following four groups: the first quartile consisted of 9 patients (median angle 11°, range 8–12) (fig. 1), the second quartile of 10 patients (median angle 26°, range 19–30), the third quartile of 10 patients (median angle 42°, range 39–46), and the fourth quartile of 9 patients (median angle 53°, range 49–64). Across the quartiles, the patients were not different for gender, age, actual and predicted body weight, height and body mass index. Before ARF, FEV₁ and the GOLD scale

were significantly different between groups (table 1). There was a significant positive correlation between the angle and FEV₁, and a significant negative correlation between the angle and the GOLD scale (fig. 2).

Groups were not different for SAPS II and cause of ARF. Between groups, inspiratory flow, tidal volume, inspiratory time, PEEP and inspired oxygen in the air were similar (table 2). However, the respiratory rate, inspiratory to total duration of breathing cycle ratio, and hence, the expiratory time were different between groups (table 2). Patients in the first quartile received a lower respiratory rate and lower inspiratory to total duration of the breathing cycle ratio, and hence, a higher expiratory time than the other groups (table 2). There was a significant negative correlation between the angle and Rrs, Crs and Δ FRC (fig. 3). Between groups, PaO₂, PaCO₂ and pH were not significantly different (data not shown).

Fig. 2. Relationships between the angle of the slope between the last 50% of the expiration and FEV₁ and the GOLD scale. Spearman's ρ correlation coefficient is indicated. The line in each plot is the regression line across data points.

Table 2. Ventilatory settings and respiratory mechanics

	Quartile 1 (n = 9)	Quartile 2 (n = 10)	Quartile 3 (n = 10)	Quartile 4 (n = 9)	p value (Kruskal-Wallis test)
Inspiratory flow, l/s	1.0 [0.8–1.1]	1.0 [0.7–1.1]	1.0 [0.7–1.1]	1.0 [0.7–1.0]	0.78
Tidal volume, ml/kg predicted body weight	6 [5–7]	5 [5–6]	5 [5–6]	6 [5–6]	0.57
Respiratory rate, breaths/min	14 [13–21]	18 [15–27]	26 [22–28]	22 [14–31]	0.01
Inspiratory time, s	0.6 [0.6–0.8]	0.7 [0.5–0.9]	0.6 [0.5–0.7]	0.6 [0.5–0.8]	0.60
Expiratory time, s	3.4 [2.3–3.8]	2.6 [1.7–3.2]	1.8 [1.7–2.0]	2.0 [1.5–3.4]	0.004
Inspiratory time/total duration, %	18 [14–19]	21 [19–27]	24 [22–28]	23 [19–27]	0.007
Peak expiratory flow, l/s	0.6 [0.5–0.7]	0.6 [0.4–0.7]	0.6 [0.4–0.8]	0.7 [0.6–0.8]	0.42
Total PEEP, cm H ₂ O	7 [5–9]	6 [2–9]	5 [3–11]	3 [1–8]	0.34
PEEPi, cm H ₂ O	7 [4–8]	5 [2–8]	4 [2–7]	2 [0–7]	0.33
Rrs, cm H ₂ O/l/s	25 [23–32]	20 [18–22]	21 [18–29]	15 [12–24]	0.05
Crs, ml/cm H ₂ O	63 [33–89]	50 [41–67]	44 [32–54]	36 [31–49]	0.17
Δ FRC, litres	0.5 [0.3–0.7]	0.3 [0.1–0.5]	0.3 [0.1–0.3]	0.0 [0.0–0.2]	0.004

Values are medians, with interquartile ranges in brackets.

Fig. 3. Relationships between the angle of the slope between the last 50% of the expiration and total Rrs, Crs and Δ FRC. Spearman's ρ correlation coefficient is indicated. The line in each plot is the regression line across data points.

Patient Outcomes

The hospital and ICU fatality rates were not significantly different between groups (table 3). Duration of invasive mechanical ventilation, ICU and hospital lengths of stay were significantly different between groups, whereas the first quartile exhibiting greater duration than the other groups (table 3). The proportion of patients who underwent more than one intubation in the ICU was significantly different between groups, with the highest rate for the patients in the first quartile (table 3). The rate of oxygen and non-invasive ventilation in the ICU and at hospital discharge was significantly different between groups, with the highest rate for the patient in the first quartile (table 3). The incidence of tracheotomy in the ICU was the same between groups (table 3). There were significant negative correlations between angle and duration of intubation ($\rho = -0.40$, $p = 0.014$), ICU ($\rho = -0.46$,

$p = 0.004$) and hospital lengths of stay ($\rho = -0.55$, $p = 0.0001$). The ROC curve analysis of the accuracy of the angle of the slope for patient outcome is depicted in table 4. The ROC curve was good to assess <30-day hospital length of stay, non-invasive ventilation need at ICU discharge and oxygen supplementation at hospital discharge; it was excellent to evaluate the non-invasive ventilation need at hospital discharge. Angle thresholds of $\leq 34^\circ$ had 79% sensitivity and 79% specificity to predict <30-day hospital length of stay, thresholds of $\leq 14^\circ$ had 88% sensitivity and 83% specificity to predict the need of non-invasive ventilation at ICU discharge, thresholds of $\leq 26^\circ$ had 81% sensitivity and 75% specificity to predict the need of oxygen supplementation at hospital discharge, and thresholds of $\leq 14^\circ$ had 88% sensitivity and 100% specificity to predict the need of non-invasive ventilation at hospital discharge. The AUCs for PEEP_i and Rrs per-

Table 3. Patient outcomes

	Quartile				p value ¹
	1 (n = 9)	2 (n = 10)	3 (n = 10)	4 (n = 9)	
Hospital mortality	1	3	7	4	0.06 (Fisher's exact test)
ICU mortality	1	2	4	4	0.39 (Fisher's exact test)
Length of ICU stay, days	37 [24–72]	12 [6–19]	6 [4–10]	15 [7–25]	0.001 (Kruskal-Wallis test)
Length of hospital stay, days	52 [43–72]	42 [19–53]	15 [7–30]	24 [13–31]	0.007 (Kruskal-Wallis test)
Oxygen at ICU discharge	8	3	1	3	0.004 (Fisher's exact test)
Oxygen at hospital discharge	8	2	0	2	0.0001 (Fisher's exact test)
Non-invasive ventilation at ICU discharge	5	1	0	0	0.0003 (Fisher's exact test)
Non-invasive ventilation at hospital discharge	5	0	0	0	0.0005 (Fisher's exact test)
Tracheotomy at ICU discharge	2	0	0	1	0.13 (Fisher's exact test)
Number of patients with re-intubation	5	4	0	2	0.04 (Fisher's exact test)
Length of intubation, days	31 [11–43]	9 [3–16]	5 [2–9]	10 [4–14]	0.009 (Kruskal-Wallis test)

Values are medians, with interquartile ranges in brackets, or counts. ¹ Statistical tests used are given in parentheses.

Table 4. Diagnostic accuracy of the angle of the slope for patient outcomes

Outcomes	AUC	Classification of the AUC	p value
Hospital mortality	0.67 (0.50–0.85)	poor	0.076
ICU mortality	0.67 (0.40–0.78)	poor	0.104
Length of intubation <10 days ¹	0.59 (0.40–0.78)	failed	0.335
ICU length of stay <15 days ¹	0.70 (0.53–0.88)	poor	0.033
Hospital length of stay <30 days ¹	0.86 (0.73–0.98)	good	0.0001
Re-intubation needed	0.74 (0.55–0.94)	fair	0.02
Absence of oxygen at ICU discharge	0.71 (0.53–0.89)	fair	0.03
Absence of non-invasive ventilation at ICU discharge	0.88 (0.77–0.99)	good	0.003
Absence of oxygen at hospital discharge	0.81 (0.63–0.98)	good	0.003
Absence of non-invasive ventilation at hospital discharge	0.91 (0.81–1.00)	excellent	0.004
Tracheotomy at ICU discharge	0.68 (0–1)	poor	0.317

Figures in parentheses are 95% confidence intervals. ¹ Less than the median of the sample.

formed much less than the angle of the slope and were classified as failed or poor for every outcome variable. The AUCs for FEV₁ were greater than the angle of the slope for ICU mortality (0.74, range 0.54–0.94), the need of oxygen supplementation at ICU discharge (0.81, range 0.66–0.95), the need of non-invasive ventilation at ICU discharge (0.90, range 0.78–1.00) and the need of oxygen supplementation at hospital discharge (0.80, range 0.60–0.96). The AUCs of FEV₁ performed less than the angle of the slope for hospital length of stay and the need of non-invasive ventilation at hospital discharge. Both AUCs were similar for re-intubation need.

Discussion

The main finding of the present study was that the angle of the slope of the EFV curve in the last 50% of the expired volume was associated with no change in mortality but with a significantly greater occurrence of morbidity-related outcomes in COPD patients intubated for ARF in the ICU.

Study Limitations and Strengths

First of all, limitations of the present study should be acknowledged. The main limitation is the relatively small

number of patients analysed. This was due to an unexpectedly high rate of exclusion of eligible patients. The small number of patients has lowered the power of the present study. The second limitation is that the angle of the slope of the EFV curve during the last 50% of expiration is based on the mono-exponential model of passive expiration which is not fulfilled in COPD patients.

Our study has strengths. It was prospective, and great care was taken to detect true COPD patients, by making efforts to track suspected COPD and to confirm COPD. Since non-invasive mechanical ventilation is the standard of care in COPD patients with ARF, there are a few recent studies that investigated intubated COPD patients.

Significance of the Angle

We selected the angle of the slope of the EFV curve during the last 50% of the expired volume because it is easy to record, can be visually handled and has been shown to be a robust method to investigate respiratory mechanics in ventilated patients [12]. Of note, it is not affected by the exhalation valve [12] that can differ from one ICU ventilator to the other, as in the present study. It is also very reproducible from breath to breath in passively mechanically ventilated patients and is independent of the tidal volume [11], a finding which was confirmed in the present study.

The angle of the slope of the EFV curve is closely related to the single exponential time constant but is less sensitive to change in flow than the time constant [12]. The values of the angle measured in the first quartile of present patients were very close to those obtained in 9 COPD patients by Lourens et al. [12] and in 27 mechanically ventilated patients by Aerts et al. [11]. The values of the angle in the present study correlated with physiological variables before ARF. An even stronger correlation ($R = 0.90$) between angle and FEV_1 than in the present study was found in 27 mechanically ventilated COPD patients in the study by Aerts et al. [11]. The correlation of the angle with the pre-ARF FEV_1 suggests that the angle should be able to reflect the underlying functional alteration of the respiratory mechanics in COPD patients. Interestingly, we also found that the angle correlated with the respiratory mechanics measured during inspiration at the time of mechanical ventilation. The angle decreased when R_{rs} and C_{rs} increased. Increase in both R_{rs} and C_{rs} results in a rise in the time constant of the respiratory system. The inverse relationship between the angle and the time constant of the respiratory system explains the observed negative correlation between the angle and R_{rs} and C_{rs} . Furthermore, the angle negatively correlated

with the amount of dynamic hyperinflation across the patients. Such a negative correlation between angle and hyperinflation has already been reported in 5 patients [11]. However, in the study by Aerts et al. [11], the angle did not vary when hyperinflation was increased or decreased as a result of concomitant change in tidal volume in every given patient, indicating that other covariates are involved in this relationship. Further study of the time course of the angle during recovery of hyperinflation in this setting could assess this relationship. It should be noted that in the present study, total positive end-expiratory pressure and $PEEP_i$ were not different between groups, contrary to ΔFRC . This is likely due to the non-linear relationship between $PEEP_i$ and ΔFRC in COPD patients with ARF, which reflects the closure of small airways [18].

Prognostic Value of the Angle

Overall, hospital mortality in the present cohort was as high as 41%. The angle was not associated with a significant change in mortality in univariate analysis, a result that can be explained by insufficient power of the study (table 3). Contrary to our expectations, the first quartile group was associated with a trend toward lower ICU and hospital mortality rate. The prediction of mortality in COPD patients receiving mechanical ventilation in the ICU for ARF is not clear [19]. It is not clear that the prediction of in-hospital mortality can be done from covariates recorded at the time of intubation, including physiologic variables [20]. However, in the present study, the increase in the burden of morbidity was significantly associated with the angle (table 3). This result is important because the simple inspection of the EFV curve together with the simple computation to obtain the angle would indicate to the caring people that the mechanical ventilation might be particularly difficult and prolonged.

The results obtained with the ROC curve analysis are in line with the findings obtained with univariate comparisons between quartiles and even extended them in some ways. This analysis confirmed that the angle of the slope was associated with significantly more requirement of oxygen supplementation and non-invasive ventilation at hospital discharge and with longer hospital length of stay. We found that for these outcomes, the angle of the slope performed as FEV_1 did no better. This can be seen as a disappointing result. However, this finding indicates that the angle of the slope can be used as a surrogate of FEV_1 . This can be of value in COPD patients who did not pass pulmonary function tests just before, or nearly so, the ARF occurrence and the ICU stay. Furthermore,

monitoring of the angle of the slope could be a simple way to follow airflow obstruction over time during the ARF course in the ICU without any requirement of patient cooperation and effort. Finally, we found that the risk of non-invasive requirement at hospital discharge could be predicted at a threshold of 14°. The fact that the performance of the ROC curve analysis was not significant for PEEPi contrasts with the better correlation found be-

tween clinical symptoms or exercise capacity and hyperinflation compared with FEV₁ [21].

In conclusion, the slope of the angle of the EFV during the last 50% of the expired volume in COPD patients receiving invasive mechanical ventilation in the ICU was associated with worsened respiratory mechanics and higher morbidity.

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