Three bedside techniques to quantify dynamic pulmonary hyperinflation in mechanically ventilated patients with chronic obstructive pulmonary disease

L. H. Roesthuis1, J. G. van der Hoeven1, C. Guérin2, J. Doorduin3 and L. M. A. Heunks4

Abstract

Background: Dynamic pulmonary hyperinflation may develop in patients with chronic obstructive pulmonary disease (COPD) due to dynamic airway collapse and/or increased airway resistance, increasing the risk of volutrauma and hemodynamic compromise. The reference standard to quantify dynamic pulmonary hyperinflation is the measurement of the volume at end-inspiration (Vei). As this is cumbersome, the aim of this study was to evaluate if methods that are easier to perform at the bedside can accurately reflect Vei.

Methods: Vei was assessed in COPD patients under controlled protective mechanical ventilation (7 ± mL/kg) on zero end-expiratory pressure, using three techniques in a fixed order: (1) reference standard (Veireference): passive exhalation to atmosphere from end-inspiration in a calibrated glass burette; (2) ventilator maneuver (Veimaneuver): measuring the expired volume during a passive exhalation of 45s using the ventilator flow sensor; (3) formula (Veiformula): (Vt × Pplateau)/(Pplateau − PEEPi), with Vt tidal volume, Pplateau is plateau pressure after an end-inspiratory occlusion, and PEEPi is intrinsic positive end-expiratory pressure after an end-expiratory occlusion. A convenience sample of 17 patients was recruited.

Results: Veireference was 1030 ± 380 mL and had no significant correlation with Pplateau (r² = 0.06; P = 0.3710) or PEEPi (r² = 0.11; P = 0.2156), and was inversely related with Pdrive (calculated as Pplateau − PEEPi) (r² = 0.49; P = 0.0024). A low bias but rather wide limits of agreement and fairly good correlations were found when comparing Veimaneuver and Veiformula to Veireference. Vei remained stable during the study period (low bias 15 mL with high agreement (95% limits of agreement from −100 to 130 mL) and high correlation (r² = 0.98; P < 0.0001) between both measurements of Veireference).

Conclusions: In patients with COPD, airway pressures are not a valid representation of Vei. The three techniques to quantify Vei show low bias, but wide limits of agreement.

Keywords: Chronic obstructive pulmonary disease, Dynamic pulmonary hyperinflation, Mechanical ventilation, Volume at end-inspiration, Bedside techniques

Introduction

Dynamic pulmonary hyperinflation is defined as increased relaxation volume of the respiratory system at the end of a tidal expiration above the expected normal value [1]. Dynamic pulmonary hyperinflation is a cardinal feature in patients with chronic obstructive pulmonary disease. It is caused by dynamic airway collapse and/or increased airway resistance, which leads to volutrauma and hemodynamic compromise. The reference standard to quantify dynamic pulmonary hyperinflation is the measurement of the volume at end-inspiration (Vei). However, this method is cumbersome and not practical for bedside use. Therefore, the aim of this study was to evaluate if methods that are easier to perform at the bedside can accurately reflect Vei.
disease (COPD) and results from dynamic airway collapse and/or increased airway resistance. Furthermore, as highlighted by the word *dynamic*, dynamic pulmonary hyperinflation is a consequence of a discrepancy between the expiratory time constant and the expiratory time either adopted by the patient or set at the ventilator [1]. It increases the risk of volutrauma and hemodynamic compromise, especially during invasive mechanical ventilation and therefore should be monitored in both the intensive care unit (ICU) and operation theater [2]. The presence of dynamic pulmonary hyperinflation should be considered if expiratory flow does not cease at the end of expiration [1], although expiratory flow may be close to zero in severe expiratory flow limitation [2]. The reference technique to quantify dynamic pulmonary hyperinflation is measurement of the volume at end-inspiration (Vei) [3]. As shown in Fig. 1, Vei is the volume of air exhaled passively from end-inspiration to end-expiration at functional residual capacity (FRC). Williams and Tuxen showed almost 30 years ago that Vei best predicted the risk of volutrauma (pneumothorax and/or subcutaneous emphysema) and hypotension, and suggested to maintain Vei below 1400 mL (or 20 mL/kg predicted body weight) [4, 5]. Measurement of Vei requires specific equipment and is cumbersome, therefore intrinsic positive end-expiratory pressure (PEEPi) or end-inspiratory plateau pressure (P plateau) is commonly used as surrogates to quantify hyperinflation [6, 7]. Often, PEEPi is in the range of 10–15 cmH2O in patients with severe airway obstruction [8]. Maintaining P plateau below 25–30 cmH2O is mostly suggested to prevent risks of volutrauma and hypotension [6]. Safe upper limits for P plateau and PEEP, to limit risk of complications, however, are not well defined [6]. As airway pressures (PEEP, P plateau) at a certain lung volume (e.g., Vei) depend on respiratory elastance, safe airway pressures do not necessarily reflect safe Vei.

The aims of the current study were to evaluate in patients with severe COPD under controlled mechanical ventilation: (1) if airway pressures (i.e., P plateau and PEEP) are valid representations of Vei, and (2) if two methods to quantify Vei, which are easier to perform at the bedside, namely a simple physiology-based equation and the use of ventilator built-in equipment to measure Vei, could provide a valid alternative to its direct measurement.

**Methods**

**Study design and population**

This is an observational study in patients admitted to the Intensive Care Unit of the Radboud University Medical Center (Nijmegen, the Netherlands). Inclusion criteria were acute exacerbation of COPD, volume controlled mechanical ventilation, deep sedation and neuromuscular blockade. Patients with FiO2 > 0.70 or volutrauma (pneumothorax or pneumomediastinum/subcutaneous emphysema) were excluded. The protocol was approved by the local ethical committee. Written informed consent was obtained from the legal representative before inclusion.

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![Fig. 1](image-url)

**A** Schematic representation of the volume at end-inspiration (Vei), which is the volume at end-expiration (Vee) above the functional residual capacity plus tidal volume, measured after prolonged apnea. **B** Schematic representation explaining the rationale of the formula to estimate Vei, with pressure on the x-axis and volume on the y-axis. In a patient with dynamic pulmonary hyperinflation inspiration starts from the total amount of positive end-expiratory pressure (PEEP total) and hypotension, and suggested to maintain Vei below 1400 mL (or 20 mL/kg predicted body weight) [4, 5]. Measurement of Vei requires specific equipment and is cumbersome, therefore intrinsic positive end-expiratory pressure (PEEPi) or end-inspiratory plateau pressure (P plateau) is commonly used as surrogates to quantify hyperinflation [6, 7]. Often, PEEPi is in the range of 10–15 cmH2O in patients with severe airway obstruction [8]. Maintaining P plateau below 25–30 cmH2O is mostly suggested to prevent risks of volutrauma and hypotension [6]. Safe upper limits for P plateau and PEEP, to limit risk of complications, however, are not well defined [6]. As airway pressures (PEEP, P plateau) at a certain lung volume (e.g., Vei) depend on respiratory elastance, safe airway pressures do not necessarily reflect safe Vei.

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**Trial design and data acquisition**

Patients were studied in supine position with the head of the bed elevated 30° from horizontal position. They were ventilated with the Servo-i ventilator (Maquet, Sweden) using Fisher and Paykel (Auckland, New Zealand) breathing circuit (RT380) and heated humidifier (MR850). The compensation algorithm for circuit compliance was checked before use and running in all patients. After enrollment, arterial blood from an indwelling catheter was withdrawn and ventilator settings remained as set by treating clinicians. Vei was measured using three different techniques, which were applied in the following non-randomized order:

1) Reference standard (Veireference): during an end-inspiratory occlusion the endotracheal tube was briefly occluded with dedicated Kocher scissors (Additional file 1: Figure S1). The patient was disconnected from the ventilator and the endotracheal tube was immediately connected to a calibrated glass burette with a soap film bubble [9]. After release of the Kocher scissors, passive expiration was allowed and the exhaled volume was measured (Additional file 1: Figure S2). The setup was calibrated using a 500-mL calibration syringe. The exhaled volume was corrected for body temperature (BTPS correction factor 1.091 at ambient temperature 22 °C).

2) Ventilator maneuver (Veimanuever): while in volume controlled mode, an end-inspiratory occlusion was performed. While holding the ventilator knob for the occlusion maneuver, the ventilator was switched to pressure support mode with back-up time of 45 seconds, after which the end-inspiratory occlusion knob was released. Expiratory flow was measured with the built-in ventilator flow sensor (measurement range 0–3.2 L/s and inaccuracy of expiratory volume between the variables was tested using the Bland–Altman test and presented as mean±standard deviation (SD) and range. Linear regression analysis was used to model the relationships between airway pressures and Veireference and to compare Veimanuever and Veiformula with Veireference. The relationship of difference to average was tested using the Bland–Altman representation that provided bias and 95% limits of agreement. Furthermore, linear regression analysis was performed of the difference on the average. A two-tailed P<0.05 was considered statistically significant. Being a physiological study, a convenience sample of 17 patients was recruited and considered appropriate.

3) Formula (Veiformula): the formula is deciphered as follows (Fig. 1):

\[
C_{rs} = \frac{V_t}{P_{plateau} - P_{PEEP_i}},
\]

with Vt the tidal volume and Crs the static compliance of the respiratory system. Pplateau and PEEPi were measured 3–5 seconds after an end-inspiratory and end-expiratory occlusion, respectively, ensuring stable plateau pressures (i.e., no external PEEP was applied, therefore total amount of PEEP was equal to PEEPi).

\[
C_{rs} = \frac{\text{Veiformula}}{P_{plateau}} \quad (2)
\]

\[
\text{Veiformula} = C_{rs} \times P_{plateau} \quad (3)
\]

\[
\text{Veiformula} = \frac{V_t}{(P_{plateau} - P_{PEEP_i})} \times P_{plateau} \quad (4)
\]

\[
\text{Veiformula} = \frac{(V_t \times P_{plateau})}{(P_{plateau} - P_{PEEP_i})} \quad (5)
\]

It is assumed that Crs remains constant during expiration.

Vei was measured using these three techniques in each patient with at least 5-min interval between measurements. Before prolonged passive expiration (Veireference and Veimanuever) patients were preoxygenated with FiO2 1.0 for 1 min. Peripheral oxygen saturation, heart rate and arterial blood pressure were continuously monitored. To confirm that no changes in Vei developed during the study protocol and to test repeatability, Veireference was repeated after the three techniques and compared to the initial Veireference.

**Statistical analysis**

A data analysis and a statistical plan were written after the data were accessed. Statistical analysis was performed with Prism 5 (GraphPad Software, San Diego, CA, USA). Continuous data were tested for normality using the Shapiro–Wilk test and presented as mean±standard deviation (SD) and range. Linear regression analysis was used to test repeatability, Veireference was repeated after the three techniques and compared to the initial Veireference.

**Results**

Data at study enrollment are shown in Table 1. Patients had severe airway obstruction, indicated by normal to high Crs (58±19 (range 27–96) mL/cmH2O), high resistance of the respiratory system (27±9 (range 16–50) cmH2O/L/s), resulting in a long time constant (1.5±0.6 (range 0.6–2.7) s). Endotracheal tube diameter of the patients was 7.5±0.5 mm. In one patient it was not
feasible to measure $V_{eir}$ due to technical failure of the reference technique, therefore 16 patients were analyzed. No adverse events were reported during the study.

### Correlation between Ve and airway pressures

Figure 2 shows no significant correlation between $P_{\text{plateau}}$ and $V_{eir}$ ($r^2=0.06; P=0.3710$), between PEEP$_{V}$ and $V_{eir}$ ($r^2=0.11; P=0.2156$) and between $P_{\text{peak}}$ and $V_{eir}$ ($r^2=0.08; P=0.3021$). The driving pressure ($P_{\text{drive}}$ calculated as $P_{\text{plateau}}-\text{PEEP}_{V}$) was inversely related with $V_{eir}$ ($r^2=0.49; P=0.0024$), consequently a moderate positive correlation with almost the same correlation coefficient was found between $C_{rs}$ and $V_{eir}$ ($r^2=0.50; P=0.0023$) (Additional file 1: Table S1). The correlations between airway pressures and $V_{eir}$ corrected for predicted body weight are reported in Additional file 1: Table S1.

$V_{eir}$ did not change during the study and measurement according to the reference standard had a high repeatability: a low bias of 15 mL with high agreement (from $-100$ to $130$ mL) and high correlation ($r^2=0.98; P<0.0001$) were found between the first and last measurement of $V_{eir}$ (Fig. 3).

### Comparison of three bedside techniques to quantify hyperinflation

$V_{eir}$ was $1030 \pm 380$ mL, $V_{\text{mne}}$ was $998 \pm 377$ mL and $V_{\text{formula}}$ was $972 \pm 243$ mL (Fig. 4). Fairly good correlations were found when comparing $V_{\text{mne}}$ and $V_{\text{formula}}$ to $V_{eir}$ (Fig. 5A, B). A low bias but relatively wide limits of agreement were found when comparing $V_{\text{mne}}$ (bias $32$ mL, from $-406$ to $470$ mL) and $V_{\text{formula}}$ (bias $58$ mL, from $-387$ to $502$ mL) to $V_{eir}$, suggesting that bias is related to the magnitude of measurements. The comparisons and correlations for $V_{\text{mne}}$ and $V_{\text{formula}}$ with $V_{eir}$ corrected for predicted body weight are shown in Additional file 1: Figure S3. $C_{rs}$ was moderately correlated with $V_{\text{mne}}$ ($r^2=0.60; P=0.0004$) and $V_{\text{formula}}$ ($r^2=0.53; P=0.0013$) (Additional file 1: Table S1).

### Discussion

The main findings of our study can be summarized as follows: in invasively ventilated patients with acute exacerbation of COPD (1) $V_{eir}$ is not significantly correlated with PEEP$_{V}$, $P_{\text{plateau}}$ or $P_{\text{peak}}$. $V_{eir}$ is inversely correlated with $P_{\text{drive}}$; (2) $V_{eir}$ is significantly correlated with $V_{eir}$ measured with the ventilator maneuver or when calculated using a physiology-based formula and has a low bias, but rather wide limits of agreement. When accepted that $V_{eir}$ is the reference standard to quantify pulmonary hyperinflation, the current study suggests that both airway pressures ($P_{\text{plateau}}$ and PEEP$_{V}$) and the two alternative methods to measure $V_{eir}$ perform only moderately in clinical practice.

### Airway pressures to estimate $V_{eir}$

In clinical practice, PEEP$_{V}$ or $P_{\text{plateau}}$ are measured to estimate alveolar pressures in patients with COPD. The recommended safe upper limit for $P_{\text{plateau}}$ is below 25–30 cmH$_2$O [6, 7]. However, in our study no significant correlation was found between $P_{\text{plateau}}$ and $V_{eir}$ or PEEP$_{V}$ and $V_{eir}$. In fact, $P_{\text{plateau}}$ was lower than 20 cmH$_2$O in four patients, despite a $V_{eir}>1400$ mL. Williams [5] reported that complications due to pulmonary hyperinflation developed only when $V_{eir}$ was $>1400$ mL, although it should be mentioned that the study sample was too small to provide strong clinical recommendations. It should be recognized that previous studies [4, 5] also recruited patients with asthma, while we included

TABLE 1 Baseline parameters

| Parameter                        | Value                           |
|----------------------------------|---------------------------------|
| Gender (M/F)                     | 7/9                             |
| Age (yr)                         | 63 ± 10                         |
| Height (m)                       | 1.70 ± 0.10                     |
| Actual body weight (kg)          | 75 ± 15                         |
| Body mass index (kg/m$^2$)       | 25.9 ± 4.5                      |
| Days of mechanical ventilation   | 2.2 ± 1.6                       |
| Blood pressure (S/D, mmHg)       | 122 ± 17 / 59 ± 6               |

Data are presented as mean ± SD and range (if mentioned)

S/D, systolic/diastolic; RR, respiratory rate; Vt, tidal volume; VT/PBW, tidal volume normalized for predicted body weight; Ti, inspiratory time; Te, expiratory time; $P_{\text{peak}}$, peak pressure; $P_{\text{plateau}}$, plateau pressure; PEEP$_{V}$, intrinsic positive end-expiratory pressure; $R_{p}$, resistance of respiratory system; $C_{rs}$, compliance of respiratory system; HCO$_3^-$, plasma bicarbonate value.
only COPD patients. Previously, a poor correlation was reported between $P_{\text{plateau}}$ and $Vei_{\text{reference}}$, but in that study [5] no end-inspiratory occlusion (i.e., only a pause time of 0.5 s was applied) was performed and PEEP$_1$ was calculated instead of being measured. When accepting that complications (pneumothorax, subcutaneous

Fig. 2 Airway pressures are commonly used to quantify hyperinflation, especially $P_{\text{plateau}}$ and PEEP. No correlation was found between $P_{\text{plateau}}$ and $Vei_{\text{reference}}$ (A) nor between PEEP and $Vei_{\text{reference}}$ (B) or between $P_{\text{peak}}$ and $Vei_{\text{reference}}$ (C) (solid line with dashed 95% confidence interval (CI) lines). The driving pressure ($P_{\text{drive}}$) was significantly correlated with $Vei_{\text{reference}}$ (D).

Fig. 3 Dynamic pulmonary hyperinflation did not change during the study protocol: there was a low bias with high agreement (A) and high correlation between the two measurements of $Vei_{\text{reference}}$ (B) (solid line with dashed 95% CI lines).
Fig. 4 Individual (A) and mean ± SD (B) data of the different bedside techniques to quantify dynamic pulmonary hyperinflation

Fig. 5 Bedside techniques to quantify dynamic pulmonary hyperinflation compared with the gold standard ($V_{ei,\text{reference}}$). Fairly good correlations were found between $V_{ei,\text{reference}}$ and $V_{ei,\text{maneuver}}$ (A) and between $V_{ei,\text{reference}}$ and $V_{ei,\text{formula}}$ (B). Bland–Altman analysis showed low bias and wide limits of agreement between $V_{ei,\text{reference}}$ and $V_{ei,\text{maneuver}}$ (C) and between $V_{ei,\text{reference}}$ and $V_{ei,\text{formula}}$ (D). Furthermore, there is a relationship in the bias between $V_{ei,\text{reference}}$ and $V_{ei,\text{formula}}$ (solid line with dashed 95% CI lines).
emphysema) related to mechanical ventilation in patients with obstructive airway disease result from increased end-expiratory lung volume, assessment of volume (e.g., Vei) seems preferable. In this case, airway pressure, and therefore $P_{\text{plateau}}$ and PEEP, should be used cautiously to monitor dynamic pulmonary hyperinflation. The lack of correlation between $P_{\text{plateau}}$ and Vei$_{\text{reference}}$ or PEEP$_i$ and Vei$_{\text{reference}}$ (even when corrected for predicted body weight), is somewhat surprising. On the other hand, hemodynamic compromise in these patients is associated with increased intrathoracic pressure and may be better monitored with airway pressure ($P_{\text{plateau}}$ and PEEP$_i$). Obviously, volume and pressure in the respiratory system are coupled by respiratory elastance (inverse of compliance). The absence of a significant correlation between pressures and volumes (both Vei and Vt) indicate non-linearity of the respiratory system over the range of volumes used in measurements. We found an inverse relationship between $P_{\text{drive}}$ and Vei$_{\text{reference}}$ (absolute value or corrected for predicted bodyweight): patients with low $P_{\text{drive}}$ (calculated as $P_{\text{plateau}}$ − PEEP$_i$) have higher Vei, and vice versa. Possibly, patients with higher inspiratory driving pressure, may also have higher expiratory driving pressure (pressure difference between alveoli and airway opening during expiration) and as such limit pulmonary hyperinflation. Alternatively, an inspiratory lower driving pressure indicates higher compliance of the respiratory system (at constant Vt), causing a reduction in expiratory flow due to lower elastic recoil pressure, thereby promoting hyperinflation. This should be verified in future studies using esophageal and gastric balloons.

Different methods to quantify Vei

We compared two techniques to quantify Vei against the reference method. Although Vei measured with the ventilator maneuver is easy to perform at the bedside, without the need to disconnect the patients from the ventilator circuit, a limitation is that this maneuver cannot be performed with every type of ventilator (it requires change of mode, with persistent end-inspiratory occlusion). The variables required to calculate Vei with the formula can be obtained with every modern ICU ventilator and does not require disconnection of the patient from the ventilator.

Despite significant correlations and low bias between Vei$_{\text{reference}}$ and the other two techniques, we found rather wide limits of agreement between Vei$_{\text{reference}}$ and the two other bedside techniques to quantify Vei. Vei$_{\text{reference}}$ was similar at the start and end of the study protocol, virtually excluding biological variation as an explanation for these wide limits of agreement. A possible explanation for the suboptimal performance of Vei$_{\text{maneuver}}$ compared to Vei$_{\text{reference}}$ is that expired volume measured by the ventilator may deviate from the actual tidal volume due to application of ventilator algorithms that compensate for gas compression and changes in humidification/temperature. For the Servo-i ventilator used in this study, this means that delivered tidal volume can be 15–25% higher compared to set tidal volume [10]. The moderate performance of Vei$_{\text{formula}}$ may be related to the assumption that compliance remains the same over a wide volume range (Fig. 1). Small airway closure makes the relationship between volume and pressure nonlinear below end-expiratory lung volume [11]. Another important factor possibly explaining the wide limits of agreement between Vei$_{\text{reference}}$ and the other two bedside methods to quantify Vei, is expiratory valve resistance. When measuring Vei$_{\text{reference}}$, patients exhaled to atmosphere, bypassing the expiratory valve of the ventilator, but this is not true for the other two methods. Recently, Pinède et al. [12] performed a bench study and found that expiratory valve resistance highly differed among the ventilators that were tested. For the Servo-u (the Servo-i was not tested) expiratory valve resistance increased when higher PEEP levels were applied, increasing from 13.8 cmH$_2$O/L/s at PEEP 5 cmH$_2$O to 39.5 cmH$_2$O/L/s at PEEP 15 cmH$_2$O. The same might be true for PEEP$_i$ leading to a PEEP$_i$-depending difference between Vei$_{\text{reference}}$ and the other two methods.

The present study shows that when Vei$_{\text{reference}}$ is accepted as the reference technique, both static airway pressures ($P_{\text{plateau}}$ and PEEP$_i$) and Vei obtained from alternative techniques should be interpreted cautiously. In addition, the safe limits for Vei$_{\text{reference}}$ are derived from small studies [4, 5]. Despite the fact that Vei$_{\text{reference}}$ is not widely adopted in clinical care, the incidence of clinical complications due to pulmonary hyperinflation has decreased since the initial studies describing development of pulmonary hyperinflation (for review [1]). Apparently, more widespread use of lung protective ventilation (limiting minute ventilation and Vt) and permissive hypercapnia were already successful in decreasing the incidence of complications due to pulmonary hyperinflation. Our formula for Vei is easy to use at the bedside and may be a reasonable alternative to quantify hyperinflation when the chest wall has a disproportional impact on $P_{\text{plateau}}$. However, use of Vei$_{\text{formula}}$ carries the risk of underestimating dynamic pulmonary hyperinflation at relatively high levels of Vei.

Strengths and limitations

The strengths of this study include novelty of the data. It is surprising that 30 years after the classical studies by Tuxen and colleagues [3–5, 13], Vei has not been compared to $P_{\text{plateau}}$ and PEEP$_i$. Parameters commonly used in clinical practice to quantify dynamic hyperinflation. Also, although bedside tests to estimate Vei are much
needed, this study shows that available techniques do not perform adequately. The data from this study are of clinical importance and also of value for future trials that aim to test the effects of interventions on dynamic hyperinflation in patients with COPD. Also, we used a reference standard to assess Vei [9]. In the original studies by Tuxen [3–5, 13], Vei was measured using 2 calibrated 2.2-L volumetric spirometers (Puritan Bennett), although it is unclear if these were directly connected to the endotracheal tube, or in the ventilator circuit. Care should be taken when measuring Vei from the ventilator circuit, given the presence of bias flow delivered by the ventilator. Another strength of the study is the high repeatability of Vei reference, therefore poor agreement with the other methods cannot be explained by poor repeatability of the reference standard [14].

Several limitations should be addressed. First, this is a single-center physiological study without sample size analysis and patients were recruited only when the study team was available. Second, we did not randomize the order of the techniques to measure Vei. However, the high repeatability and low bias in the Bland–Altman plots of Vei reference (measured at beginning and end of the study), makes it extremely unlikely that Vei changed during the course of the study. Third, patients had a severe airway obstruction, as indicated by a long time constant, but Pplateau was below 25 cmH2O in all patients and Vei measured with the reference standard above 1400 mL in only four patients. This may due to the fact that data were obtained in an ICU with expertise in mechanical ventilation and quantification of Vei using Vei formula is part of the clinical protocol. Indeed, none of the patients developed complications associated with dynamic pulmonary hyperinflation. Also, it should be noted that there is increased attention for lung protective ventilation in the last decade as compared to 30 years ago, thereby limiting minute ventilation and especially tidal volumes (i.e., both were almost halved in our study as compared to Williams et al. [5]). However, it should be acknowledged that severe complications resulting from dynamic pulmonary hyperinflation are still reported, highlighting the need for bedside monitoring tools to quantify dynamic pulmonary hyperinflation [1, 6, 7]. Fourth, we did not change ventilator settings. Fifth, we did not measure airway opening pressure, which may exist above PEEP, and, if present, affects calculations of respiratory mechanics [15]. However, it is not expected that this would lead to differences between the methods. Sixth, expiratory flow limitation is an important contributing factor of dynamic pulmonary hyperinflation [16–18], which has not been assessed in this study. If expiratory flow limitation is present in a patient, one would expect that it would disappear with a long expiratory time, which is the case using Vei reference and Vei maneuver. Alveoli with the longest time constants (i.e., with the highest PEEPi) may remain closed during an occlusion maneuver [1] and therefore lead to underestimation of Vei using the formula. Seventh, measurements are only feasible under fully controlled mechanical ventilation. Finally, there is no firm threshold for a safe Vei.

Conclusions
Hemodynamic consequences and increased risk of volutrauma resulting from severe dynamic pulmonary hyperinflation in patients with COPD and asthma has been reported 3 decades ago. However, quantification of dynamic pulmonary hyperinflation is seldom performed at the bedside as state of the art techniques are cumbersome. In the current study, bedside techniques to quantify dynamic pulmonary hyperinflation were evaluated in patients with severe COPD. We conclude that end-inspiratory and end-expiratory occlusion pressures are not valid representations of Vei reference. A physiology-based formula to estimate Vei reference shows excellent correlation and low bias, but the wide limits of agreement should be recognized.

Abbreviations
BTPS: Body temperature pressure saturated; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; Crs: Compliance of the respiratory system; ICU: Intensive Care Unit; PBW: Predicted body weight; Pplateau: Driving pressure of the respiratory system; PEEP: Intrinsic positive end-expiratory pressure; PEEP total: Total amount of positive end-expiratory pressure; Peak: Peak airway pressure of the respiratory system; Pplateau: Plateau pressure of the respiratory system; RR: Respiratory rate; Rs: Resistance of the respiratory system; S/D: Systolic/diastolic; SD: Standard deviation; TC: Time constant; Ti: Inspiratory time; Te: Expiratory time; Vei: End-inspiratory lung volume; Vee: End-expiratory lung volume; Vt: Tidal volume.

Supplementary Information
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Authors’ contributions
Study conceptions and design: LHR, LMAH; data acquisition: LHR; data analysis: LHR, JD, LMAH; data interpretation: LHR, JD, LMAH; manuscript drafting and revising: all authors. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the local ethical committee (CMO Regio Arnhem-Nijmegen). Written informed consent was obtained from the legal representative before inclusion.

Consent for publication
Not applicable.

Competing interests
LHR, JGH, CG and JD declare no competing interests. LMAH has received speakers fee from Maquet (Sweden) and Fisher & Paykel (Netherlands). His department has received research grants from Liberate medical (USA) and InflaRx (USA).

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References
1. Marini JJ. Dynamic hyperinflation and auto-positive end-expiratory pressure: lessons learned over 30 years. Am J Respir Crit Care Med. 2011;184(7):756–62.
2. Laghi F, Goyal A. Auto-PEEP in respiratory failure. Minerva Anestesiol. 2012;78(2):201–21.
3. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. Am Rev Respir Dis. 1987;136(4):872–9.
4. Tuxen DV, Williams TJ, Scheinkestel CD, Czarny D, Bowes G. Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma. Am Rev Respir Dis. 1992;146(5 Pt 1):1136–42.
5. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. Am Rev Respir Dis. 1992;146(3):607–15.
6. Leatherman J. Mechanical ventilation for severe asthma. Chest. 2015;147(6):1671–80.
7. Demoule A, Brochard L, Dres M, Heunks L, Jubran A, Laghi F, et al. How to ventilate obstructive and asthmatic patients. Intensive Care Med. 2020;46(12):2436–49.
8. Leatherman JW, McArthur C, Shapiro RS. Effect of prolongation of expiratory time on dynamic hyperinflation in mechanically ventilated patients with severe asthma. Crit Care Med. 2004;32(7):1542–5.
9. Smith TC. Calibration of gas flowmeters with the bubble burette. Anesthesiology. 1970;33(5):553–5.
10. Lyazidi A, Thille AW, Carteaux G, Gala F, Brochard L, Richard JC. Bench test evaluation of volume delivered by modern ICU ventilators during volume-controlled ventilation. Intensive Care Med. 2010;36(12):2074–80.
11. Guerin C, LeMasson S, de Varax R, Milic-Emili J, Fournier G. Small airway closure and positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155(6):1949–56.
12. Pinede A, Cour M, Diegyvri F, Louis B, Argaud L, Guerin C. Bench assessment of expiratory valve resistance of current ICU ventilators in dynamic conditions. Respir Care. 2020;66(4):610–8.
13. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. Am Rev Respir Dis. 1989;140(1):5–9.
14. Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res. 1999;8(2):135–60.
15. Chen L, Del Sorbo L, Greco DL, Junhasavasdikul D, Rittayama N, Soliman I, et al. Potential for lung recruitment estimated by the recruitment-to-inflation ratio in acute respiratory distress syndrome: a clinical trial. Am J Respir Crit Care Med. 2020;201(2):178–87.
16. Alvisi V, Romanelli A, Badet M, Gaillard S, Philit F, Guerin C. Time course of expiratory flow limitation in COPD patients during acute respiratory failure requiring mechanical ventilation. Chest. 2003;123(5):1625–32.
17. Junhasavasdikul D, Telias I, Greco DL, Chen L, Gutierrez CM, Piraino T, et al. Expiratory flow limitation during mechanical ventilation. Chest. 2018;154(4):948–62.
18. Volta CA, Dalla Corte F, Ragazzi R, Marangoni E, Fogagnolo A, Scaramuzzo G, et al. Expiratory flow limitation in intensive care: prevalence and risk factors. Crit Care. 2019;23(1):395.

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