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Intrinsic Dynamic Positive End-Expiratory Pressure in Stable Patients with Chronic Obstructive Pulmonary Disease

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Keywords
Hyperinflation · Home mechanical ventilation · Hypercapnia · Rehabilitation · Noninvasive ventilation

Abstract
Background: Assessment of intrinsic dynamic positive end-expiratory pressure (PEEPi,dyn) may be clinically important in stable patients with chronic obstructive pulmonary disease (COPD), but epidemiological data are scant. ***Objectives:*** The aim of our study was (i) to assess the PEEPi,dyn in a large population of stable patients with COPD and (ii) to evaluate the correlations with some noninvasive measurements routinely assessed. ***Method:*** Retrospective analysis of lung mechanics, dynamic volumes, arterial blood gases, dyspnoea by means of the Medical Research Council (MRC) scale, the COPD Assessment Test score, and maximal inspiratory/expiratory pressures in 87 hypercapnic and 62 normocapnic patients. ***Results:*** The mean PEEPi,dyn was significantly higher in hypercapnic than normocapnic patients (2.8 ± 2.2 vs. 1.9 ± 1.6 cm H_2O, respectively, $p = 0.0094$). PEEPi,dyn did not differ according to Global Initiative for Chronic Obstructive Lung Disease stage, MRC score, or use or not of long-term oxygen therapy. There were significant although weak correlations between PEEPi,dyn and airway obstruction, hyperinflation, respiratory muscle function, arterial CO_2 tension, and number of exacerbations/year. The transdiaphragmatic pressure was the strongest variable associated to PEEPi,dyn ($R = 0.5713$, $p = 0.001$). ***Conclusion:*** In stable patients with COPD, PEEPi,dyn is higher in hypercapnic patients and weakly correlated to noninvasive measures of lung and respiratory muscle function.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease, characterized by persistent and progressive airflow limitation [1]. Chronic respiratory failure develops very frequently in the late stage of the disease and, when it does, 1 or both of the respiratory system functions fail, that is, gas exchange (leading to hypoxemia) and/or pump function (leading to hypercapnia). Severe stable patients with COPD and chronic hypercapnia have a combination of high inspiratory re-

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sistance, dynamic hyperinflation, and muscle dysfunction [2, 3]. Hypercapnia in these patients can result also from a high dead space to tidal volume (VD/VT) ratio [4].

Dynamic hyperinflation may occur during acute respiratory failure [5] and also chronically [6, 7] when the rate of lung emptying is prolonged: the elastic equilibrium point of the respiratory system is not reached at the end of expiration, and therefore, the alveolar pressure remains positive generating the auto- or intrinsic dynamic positive end-expiratory pressure (PEEPi,dyn). Studies performed more than 30 years ago assessed PEEPi,dyn in relatively small samples of stable patients with COPD and chronic hypercapnia [6, 7] using the esophageal pressure (Poes) as a reference, while in the calculation of PEEPi,dyn the so-called "gastric" contribution should also be taken into account [8]. Since then, many clinical conditions have changed, including the definition, classification, and pharmacological and non-pharmacological treatment of the disease. In particular home nocturnal, noninvasive ventilation (NIV) is increasingly used in stable patients with chronic hypercapnia. This use requires the setting of an inspiratory positive airway pressure to reduce hypercapnia and of an expiratory positive airway pressure (EPAP) tailored to PEEPi,dyn to reduce the work of breathing and inspiratory triggering asynchronies [9]. A better understanding of PEEPi,dyn in stable COPD is thus of clinical importance, but epidemiological data are scant. Therefore, the aim of this retrospective study was (i) to assess the PEEPi,dyn in a large population of stable patients with COPD and (ii) to evaluate the correlations, if any, of PEEPi,dyn with some noninvasive measurements routinely assessed in these patients.

Methods

The protocol was approved by the Ethical Committee of the Istituti Clinici Scientifici (ICS) Maugeri, IRCCS, Pavia, Italy (2374CE, Pavia, December 3, 2019). All patients admitted to the scientific institutions that took part gave their informed consent to the scientific use of their clinical and physiological data in compliance with the Helsinki Declaration.

Patients

This retrospective study was conducted on the Hospital Database Registers of patients admitted from January 1, 1999, to December 31, 2015, to the Respiratory Units of ICS Maugeri, Lumezzane, and Pavia and of Alma Mater Bologna University, referral centers for the diagnosis, management, and rehabilitation of COPD [10]. Diagnosis and severity of COPD were confirmed by spirometry according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. At the time of evaluation, all patients were in stable conditions, that is, absence of worsening in symptoms (no change in dyspnoea, cough, and/or sputum beyond day-to-day variability) which would warrant a change in management and stability in arterial blood gases (e.g., no respiratory acidosis) [1]. All patients received their regular treatment as indicated for their disease stage according to current guidelines. Patients on home mechanical ventilation were excluded as well as those with oncological, neurological, severe cardiovascular and neuromuscular comorbidities.

Measurements

The following data were recorded:

- Demographics, anthropometrics, and use of long-term oxygen therapy (LTOT).
- Number of exacerbations/year defined as "an acute worsening of respiratory symptoms resulting in additional therapy" [1].
- Dynamic lung volumes, assessed according to standard methods [11], using the predicted values of Quanjer [12].
- Arterial blood gases. Patients on LTOT were assessed under their usual inspiratory oxygen fraction.
- Dyspnoea evaluated with the Medical Research Council (MRC) scale [13].
- The COPD Assessment Test (CAT) score [14].
- Maximal inspiratory (MIP) and expiratory pressures, according to the ATS/ERS guidelines [15], the predicted values were those by Bruschi et al. [16].
- Lung mechanics. For the experimental procedure of this study, flow was measured during unsupported breathing through a disposable mouthpiece, by means of a heated pneumotachograph connected to a differential pressure transducer in patients in semi-recumbent position, 15 min after the setup. Patients already on LTOT used oxygen [17].

Tidal volume (VT), respiratory frequency (*f*), and minute ventilation (VE) were computed from the volume signal and calculated from the flow signal as average values from 5 min of continuous recording of flow and volume. The *f*/VT ratio was also calculated. Changes in pleural and abdominal pressures were estimated from changes in Poes and gastric pressure (Pga), respectively, by means of the balloon catheter technique. The transdiaphragmatic (Pdi) pressure was obtained by subtraction of Poes from Pga [18]. PEEPi,dyn was obtained from the Pdi signal, as the value of Pdi at zero flow. A representative graph is shown in Figure 1.

Statistical Analysis

Descriptive statistics are reported as mean ± standard deviation for continuous variables and as numbers (*n*) and percentage frequency (%) for discrete variables. Due to the retrospective and descriptive nature of the study, power calculation was not possible. Low- and high-PEEPi,dyn values were defined according to the median value (1.8 cm H_2O).

The ANOVA test was used to compare continuous variables among groups and, if the test was significant, a post hoc analysis with unpaired *t* test using Bonferroni correction was performed. For comparisons between categorical and binary variables among groups, the χ^2 test was used. Comparisons between mean data of 1999–2007 versus 2008–2015 were analyzed with an unpaired *t* test. The correlations between PEEPi,dyn and demographic, anthropometric, clinical, physiological variables were analyzed with Spearman correlation. Statistical significance was set at $p < 0.05$. All analyses were carried out using STATA software package (release 11, StataCorp LP).

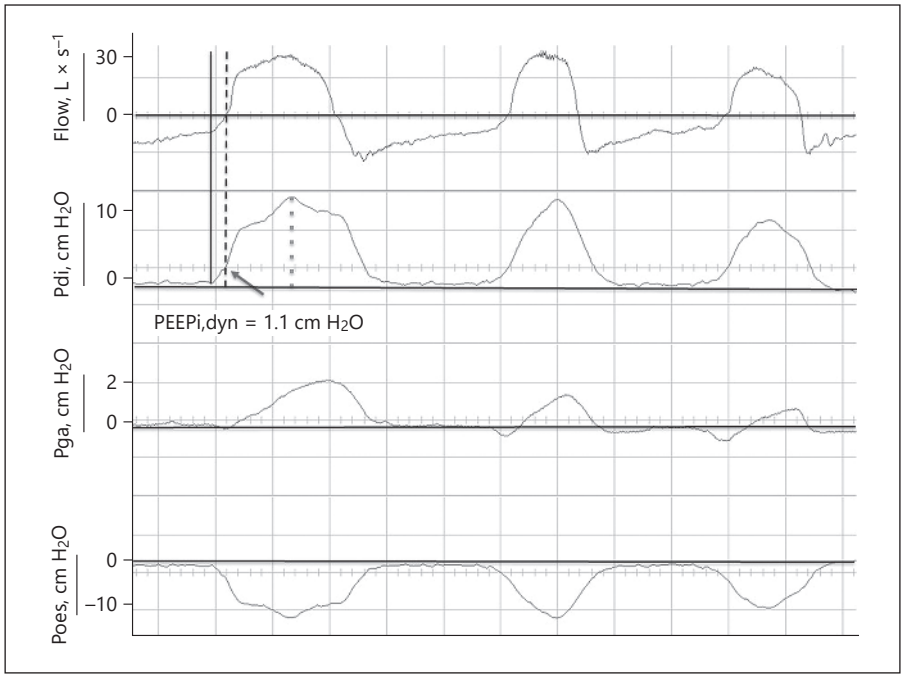

Fig. 1. A representative tracing of PEEPi,dyn measurement. From top to bottom, flow, Pdi, transdiaphragmatic pressure; Pga, gastric pressure; Poes, esophageal pressure; PEEPi,dyn, dynamic intrinsic positive end-expiratory pressure. The solid line indicates the beginning of diaphragm contraction; the dashed line indicates the zero flow; and the value of Pdi at zero flow is the PEEPi,dyn. The dotted line indicated that Pdi is measured at end inspiration.

Table 1. Demographic, anthropometric, physiological, and clinical characteristics of study patients according to the level of PEEPi,dyn (median value)

	All	PEEPi,dyn, cm H_2O		*p* value
		≤1.8	>1.8	
Patients, *n*	149	74	75	
Male, *n* (%)	81 (54.4)	33 (43.4)	35 (47.9)	0.579
Age, years	67.4±8.3	67.2±8.2	67.1±8.4	0.8434
BMI, kg/m^2	25.1±5.8	24.7±5.9	26.4±5.7	0.4740
LTOT, *n* (%)	116 (77.8)	53 (69.7)	63 (86.3)	**0.0150**
MRC score	2.5±1.3	2.4±1.3	2.7±1.2	0.1806
Exacerbations/year, *n*	1.6±0.9	1.6±0.9	1.8±0.9	0.1480
CAT score	16.4±6.1	15.0±6.2	17.1±6.0	0.1355
pH	7.41±0.04	7.41±0.03	7.40±0.04	0.2123
$PaCO_2$, mm Hg	50.4±11.5	49.30±11.34	51.55±11.59	0.2340
PaO_2, mm Hg	63.2±12.4	64.9±12.4	61.5±12.2	0.0915
FEV_1, % predicted	33.8±15.6	36.1±16.5	31.5±11.4	0.0797
FVC, % predicted	55.6±19.5	59.4±17.9	51.6±20.4	**0.0153**
FEV_1/FVC, %	43.3±14.7	45.4±15.6	41.1±13.5	0.0785
RV, % predicted	195.7±82.6	149.8±62.6	225.8±80.8	**0.0003**
f/VT, bpm × L^{-1}	50.7±25.9	48.0±25.3	53.4±26.4	0.2079
Poes, cm H_2O	5.4±12.7	4.3±11.0	6.6±14.3	0.2784
Pdi, cm H_2O	14.6±7.0	11.4±5.9	17.8±7.0	**<0.0001**
PEEPi,dyn, cm H_2O	2.4±2.0	0.9±0.4	3.9±1.8	**<0.0001**
MIP, cm H_2O	54.2±24.6	58.9±25.5	48.7±22.6	**0.0163**
MEP, cm H_2O	92.2±41.5	100.2±40.1	84.2±41.9	**0.0376**

Data are shown as *n* (%) or mean ± SD. Bold type denotes significance. CAT, COPD Assessment Test; FEV1, forced expiratory volume at 1 s; *f*, respiratory frequency; FVC, forced vital capacity; LTOT, long-term oxygen therapy; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; MRC, Medical Research Council; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PEEPi,dyn, intrinsic dynamic positive end-expiratory pressure; Pdi, transdiaphragmatic pressure; Poes, esophageal pressure; RV, residual volume; VT, tidal volume; SD, standard deviation.

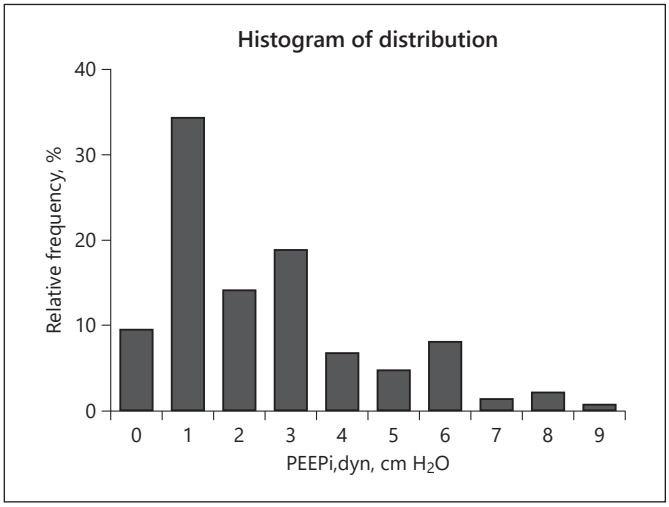

Fig. 2. Histogram of distribution of PEEPi,dyn among all patients. Peepi,dyn: mean value = 2.4 cm H_2O (95% CI 2.13–2.78 cm H_2O), median value = 1.8 cm H_2O (25–75th percentile = 0.9–3.25 cm H_2O). PEEPi,dyn, dynamic intrinsic positive end-expiratory pressure.

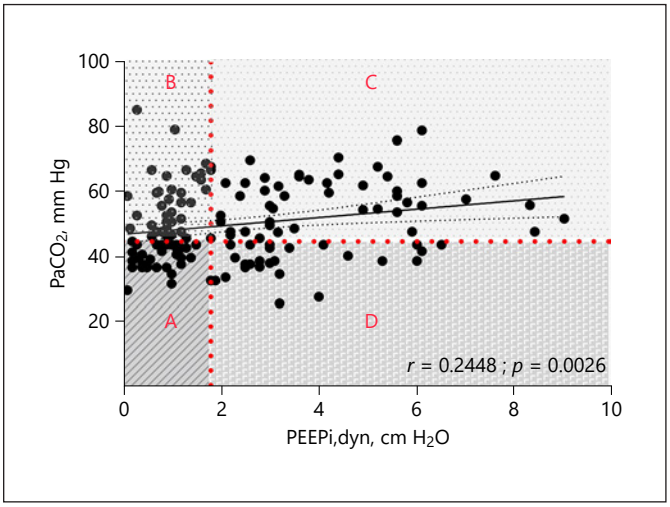

Fig. 3. Panel A: normocapnia/low PEEPi,dyn. Panel B: hypercapnia/low PEEPi,dyn. Panel C: hypercapnia/high PEEPi,dyn. Panel D: normocapnia/high PEEPi,dyn.

Results

The mean value of PEEPi,dyn was 2.4 ± 2.0 cm H_2O. Table 1 shows the demographic, anthropometric, physiological, and clinical characteristics of all patients and according to the level of PEEPi,dyn (lower and higher than the median value). As expected, patients with higher PEEPi,dyn had more severe airway obstruction and hyperinflation and lower MIP and Pdi. Figure 2 shows the individual values of PEEPi,dyn.

The distribution of patients above the median value (1.8 cm H_2O) showed a large variability, as testified by the 25–75th percentile 0.9–3.25 cm H_2O. The percentage of patients with PEEPi,dyn above 4 cm H_2O was 20.1% in the overall group and 26.4% in hypercapnic patients, while the percentage above 5 cm H_2O was 14.6% in the overall group and 19.5% in hypercapnic patients. Hypercapnic patients had a significantly higher level of PEEPi,dyn than normocapnic patients (2.8 ± 2.2 vs. 1.9 ± 1.6 cm H_2O, $p = 0.0094$, respectively). Figure 3 shows the relationship between $PaCO_2$ and PEEPi,dyn, and patients' distribution according to normocapnia/low PEEPi,dyn (24.2%, panel A), hypercapnia/low PEEPi,dyn (26.8%, panel B), hypercapnia/high PEEPi,dyn (31.5%, panel C), and normocapnia/high PEEPi,dyn (17.4%, panel D).

PEEPi,dyn did not differ among the GOLD classifications (1.5 ± 1.3, 2.2 ± 1.9, 2.7 ± 2.1, 2.4 ± 1.7 cm H_2O for classes 1–4, $p = 0.070$, and 2.0 ± 1.8, 2.4 ± 2.0, 2.7 ± 2.2, 2.5 ± 2.0 cm H_2O for stages A to D, $p = 0.868$, respectively) or among the different MRC scores (2.0 ± 1.9, 1.9 ± 1.6, 2.3 ± 2.1, 2.6 ± 1.9, 2.8 ± 2.1 cm H_2O for scores 0–4, $p = 0.422$). There was no significant difference in PEEPi,dyn between patients on LTOT or not (2.6 ± 2.0 vs. 1.9 ± 2.0 cm H_2O, $p = 0.964$), independently of the presence of hypercapnia (2.0 ± 1.7 vs. 1.8 ± 1.6 cm H_2O, $p = 0.590$ for normocapnic patients and 2.8 ± 2.1 vs. 2.2 ± 3.3 cm H_2O, $p = 0.506$ for hypercapnic patients, respectively). There was no significant difference in PEEPi,dyn between patients assessed from 1999 to 2007 and those from 2008 to 2015 (2.5 ± 2.2 vs. 2.4 ± 1.6 cm H_2O, $p = 0.791$). Table 2 shows the significant correlations between PEEPi,dyn and clinical and physiological characteristics of patients.

There were significant and moderate correlations between PEEPi,dyn and Pdi or hyperinflation. There were significant although weak correlations with indexes of airway obstruction, respiratory muscle function, $PaCO_2$, and, as expected, with *f*/VT ratio and Poes. There was also a weak correlation with the number of exacerbations/year. There was no significant correlation with MRC, CAT, or BMI; a slight, albeit significant, relationship was found only between BMI and MIP ($R = 0.1739$, $p = 0.0462$).

Table 2. Significant correlations between PEEPi,dyn and clinical and physiological characteristics of patients

	R	*p* value
Exacerbations/year, *n*	0.1868	0.0240
$PaCO_2$, mm Hg	0.2448	0.0026
FEV_1, % pred	−0.2342	0.0044
FVC, % pred	−0.2884	0.0004
RV, % pred	0.4931	0.0001
Poes, cm H_2O	−0.3297	0.0000
Pdi, cm H_2O	0.5713	0.000
f/VT, bpm × L^{-1}	0.1883	0.0219
MIP, cm H_2O	−0.2906	0.0007
MEP, cm H_2O	−0.2030	0.0295

PEEPi,dyn, dynamic intrinsic positive end-expiratory pressure; $PaCO_2$, arterial carbon dioxide tension; Pdi, transdiaphragmatic pressure; Poes, esophageal pressure; MIP, maximal inspiratory patient; MEP, maximal expiratory pressure; FVC, forced vital capacity; FEV, forced expiratory volume; RV, residual volume; VT, tidal volume; *f*, frequency.

Discussion

We found that a substantial proportion of patients with stable COPD have PEEPi,dyn levels higher than 4 cm H_2O. As compared with normocapnic, patients with chronic hypercapnia suffer from higher levels of PEEPi,dyn which is significantly, but weakly, correlated with airway obstruction, hyperinflation, respiratory muscle function, $PaCO_2$, and number of exacerbations/year.

While confirming previous reports [6, 7], our study is the first to demonstrate that there is no difference in PEEPi,dyn among the different GOLD stages, levels of dyspnoea, or health status. A second, and more important, finding of our study is that the recording of PEEPi,dyn was calculated according to the Pdi traces, rather than the Poes only, given a more accurate physiological measurement. Indeed, the correlation analysis showed that Pdi was the strongest physiological variable related to PEEPi,dyn. This result is not surprising as Pdi is directly incorporated in determination of PEEPi, therefore, is mathematically linked and, thus, correlated.

In particular, expiratory muscle activity may greatly interfere with measurements of PEEPi,dyn in patients with chronic airway obstruction. At least part of the expiratory muscle activity could be easily detected and estimated from the Pga, as shown both by Appendini et al. [18] and Lessard et al. [19]. Our results are similar to those of Haluszka et al. [6] who found a significant correlation between PEEPi,dyn and FEV_1% predicted, and $PaCO_2$. Dal Vecchio et al. [7] showed that PEEPi,dyn was present in all of the 18 COPD patients studied, and averaged 2.4 cm H_2O, a value similar to ours. Overall these results indicate that increased severity of airway obstruction promotes PEEPi,dyn and concomitant dynamic hyperinflation. This implies increased inspiratory work in the face of decreased effectiveness of the inspiratory muscles as pressure generators.

Rather interestingly, PEEPi,dyn was not correlated with measures of dyspnoea as assessed by MRC or symptom burden as assessed by CAT, confirming the multidimensional nature of symptoms which cannot be predicted by lung function [20]. The significant although weak correlation of PEEPi,dyn with number of exacerbations per year is not surprising. It has been reported that patients with frequent exacerbations have a significantly faster decline in FEV_1 than infrequent exacerbators [21]. However, we cannot exclude that the lack of correlations might be due to a sample size effect or other bias inherent to this cohort. The absence of evidence for a correlation might not represent evidence of absence of higher levels of PEEPi,dyn in more severe stages of COPD.

The aim of our study was to evaluate PEEPi,dyn during spontaneous breathing. It has been reported that the mean PEEPi,dyn in patients on home NIV for a mean duration of 31 months was 3.2 cm H_2O during spontaneous breathing [22]. Appropriate application of an EPAP can reduce end-expiratory flow limitation and alleviate the PEEPi,dyn reduce the work of breathing and inspiratory triggering asynchronies [22]. Therefore, in order to avoid a potential influence of NIV on PEEPi,dyn, we assessed only patients who were not on home mechanical ventilation. Indeed, it would have been unethical to withdraw NIV, even for a few days, to evaluate also those patients.

Clinical Implications

It has been shown that long-term NIV improves the survival of stable COPD patients with hypercapnia when the inspiratory positive airway pressure is targeted to significantly reduce hypercapnia [23, 24]. However, it has been suggested to avoid setting EPAP above the level of PEEPi,dyn as this may determine a significant rise in end-expiratory lung volume and, therefore, a greater hyperinflation. Most available home care ventilators deliver a default EPAP of 4 cm H_2O, and without direct measurement of PEEPi,dyn, there is a risk of either over assisting or under assisting the patients. Therefore, knowing the

PEEPi,dyn is important. However, an invasive assessment of PEEPi,dyn is not possible in clinical practice. Therefore, its estimation in individual patients from parameters routinely assessed may be crucial. In clinical practice, when a direct measurement is lacking, it is usually recommended not to exceed 4–6 cm H_2O unless clinical evidence suggests the presence of marked dynamic hyperinflation [25]. Considering the PEEPi,dyn mean ± SD value found in our study, the use of a default EPAP of 4 cm H_2O may appear to be reasonable. However, our results raise a warning for individual patients: actually, we do not know whether some episodes of intolerance or lack of adherence and/or adaptation to NIV in the individual patient might be due to a EPAP potentially greater than PEEPi,dyn.

Besides in acute respiratory failure [26], estimating PEEPi,dyn may also be relevant for evaluating the effects of medical therapy such as bronchodilators in patients in stable conditions. An average 56% reduction in PEEPi,dyn was reported after inhalation of salbutamol in stable patients with COPD [27]. Similar results were reported by Dal Vecchio et al. [7] with inhalation of fenoterol. In a study by Nava and Compagnoni [28] in patients in stable condition with severe COPD and chronic hypercapnia, a brief trial of inhaled steroids induced a reduction in PEEPi,dyn and in airway resistances, whereas this bronchodilator response was not detected by the usual lung function tests. Furthermore, the possible value of dynamic hyperinflation in predicting survival has been reported [29].

Limitations of the Study

There are some limitations regarding the measurements performed and the lack of sample size calculation. This is a retrospective study, and, as such, a sample size study was not possible; however, to our knowledge, this is the largest study in the field. The data were collected over a 15-year period, during which the accepted drug therapy for COPD has to some extent changed [1]. However, the findings in patients assessed at 2 different time periods were not significantly different.

Dynamic hyperinflation is a phenomenon that is most significant during periods of tachypnea such as during exercise. Assessing dynamic hyperinflation at rest may miss relevant information regarding the patient's lung mechanics when minute ventilation increases during exercise. Measurements of PEEPi,dyn during exercise would have been possible but were not part of the standard evaluation protocol for clinical use analyzed in this study.

Conclusion

Stable patients with COPD show a wide range of PEEPi,dyn levels. Chronic hypercapnia is associated with higher levels of PEEPi,dyn; PEEPi,dyn is not influenced by GOLD stage, severity of dyspnoea, or health status.

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Statement of Ethics

The protocol was approved by the Ethics Committee of the Istituti Clinici Scientifici (ICS) Maugeri, IRCCS, Pavia, Italy (2374CE, Pavia December 3, 2019). All patients admitted to the scientific institutions that took part gave their informed consent to the scientific use of their clinical and physiological data in compliance with the Helsinki Declaration.

Conflict of Interest Statement

All the authors declare to have no conflict of interest, directly or indirectly related to the manuscript. The manuscript does not report any clinical trial.

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Author Contributions

M.V. has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All the authors contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All the authors approved the final version of the manuscript and declare that questions related to the accuracy or integrity of any part of it have been appropriately investigated and resolved. M.V., as corresponding author, has been identified as guarantor of the paper, taking responsibility for the integrity of the work, from inception to published article.

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