Clinical and experimental validation of a capnodynamic method for end-expiratory lung volume assessment

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1 INTRODUCTION

It is estimated that 15-20 million surgical cases requiring general anaesthesia and mechanical ventilation (MV) are performed annually in Europe. Among patients undergoing non-thoracic surgery, approximately 10% will develop post-operative pulmonary complications (PPC) potentially increasing morbidity, mortality and length of admission.1 Post-operative atelectasis, a common PPC, may impair gas
exchange and reduce end-expiratory lung volume (EELV). If detected, atelectasis may be attenuated by recruitment manoeuvres. In the clinical setting, respiratory system compliance (CRS) is commonly used as a tool for recruitment manoeuvres and PEEP titration. CRS consists of two components; lung (CL) and chest wall (CCW) compliance. Since both CCW and CL, and thus CRS, may change during surgical procedures, EELV may provide valuable complementary information to lung mechanics and gas exchange being helpful to optimize ventilator settings and better detect and characterize relevant pathophysiological processes such as lung strain, overdistension, collapse and lung recruitment. Our research group has developed a non-invasive, breath-by-breath continuous method based on expired carbon dioxide dynamics for calculation of effective lung volume (ELV). ELV is a new entity that could be assumed to measure a functional lung volume, the lung volume where the gas exchange takes place. In a recent experimental study ELV was found to closely correlate with EELV in healthy lungs, showing good trending ability over a range of moderate PEEP levels.

The primary aim of this study was to evaluate the ELV method in healthy subjects and anaesthetized patients employing two different reference methods. A secondary aim was to challenge the method at higher levels of PEEP in an experimental porcine model using a third reference method.

2 | MATERIALS AND METHODS

In this study we have used four different methods for lung volume measurements. All volumes presented are corrected for temperature, pressure and saturation to body temperature pressure saturated and include airway dead space. For better readability we have chosen to use the term EELV also at zero PEEP, instead of functional residual capacity (FRC).

2.1 | The capnodynamic ELV method

The capnodynamic method for calculating ELV is based on the differential Fick’s principle. Assuming a steady state in mixed venous carbon dioxide, induced variations in expired alveolar carbon dioxide are used for analyses in mechanically ventilated subjects. These variations are induced by alterations of ventilatory pattern. Normal ventilatory cycles are followed by cycles with an end-inspiratory pause added. This cycle consisting of 3-4 out of 9-10 breaths is consistently repeated and results in a transient short variation in end-tidal carbon dioxide concentration. The respiratory rate is adjusted to compensate for imposed inspiratory pauses so that minute ventilation remains unchanged. Data from each cycle are inserted into an overdetermined set of equations describing a mole balance of carbon dioxide transported to and from the lungs. From these equations ELV can be calculated by optimizing the fit between measured data and a lung model by means of a least-square error procedure. With each new breath, a new equation replaces the oldest providing breath-by-breath continuous calculation of ELV representing the average value of the 9-10 preceding breaths. ELV reported in this study is the carbon dioxide-based EELV, including airway dead space up to the main-stream capnometer. We used a modified SERVO-i ventilator (Maquet Critical Care) with a mainstream capnometer for the ELV measurements.

The studies on human subjects were performed at Karolinska University Hospital in Solna. The study was approved by the local ethical committee for human research (reference 2014/1393-31/2).

2.2 | Anaesthetized patients: ELV vs EELV (partial N2 wash-out and wash-in)

Patients scheduled for different types of head and neck surgery (thyroidectomy, parathyroidectomy and mandibular surgery) were included in the study after informed consent. Exclusion criteria were an American Society of Anesthesiology classification III or higher, history of smoking and respiratory or cardiovascular disease.

Patients were pre-oxygenated with fraction of inspired O (FiO) 0.8 and anaesthetized using target-controlled infusion with propofol and remifentanil. Mivacurium chloride (0.2 mg/kg) was injected to facilitate endotracheal intubation. Patients were ventilated in a volume-controlled mode with 7 mL/kg, predicted body weight (PBW), and FiO 0.4. The study design required two ventilators; CareScape r860 (General Electric) and a SERVO-i.

2.3 | Study protocol

Initially patients were ventilated with the CareScape r860 at zero PEEP to measure EELV during a nitrogen multiple breath wash-out/wash-in (EELV NMBW). Thereafter ventilation was changed to SERVO-i, providing the specified breathing pattern. After approximately 3 minutes of stabilization, ELV was recorded during the following 3 minutes and a mean value registered. ELV measurements were repeated at both PEEP 10 and 5 cm H2O. The endotracheal tube was then clamped to maintain PEEP and ventilation was switched back to the CareScape r860. The protocol was completed with an EELV NMBW measurement at PEEP 5 cm H2O. Due to time constraints, EELV NMBW was not measured at PEEP 10 cm H2O.

The Nitrogen Multiple Breath Wash-out (NMBW) integrated to the CareScape 680r ventilator exploits small changes (10%-20%) in FiO2
to produce a partial nitrogen wash-out/wash-in. A breath-by-breath summation of exchanged nitrogen provides an estimate of EELV<sub>NMBW</sub>. If the difference in nitrogen exchange exceeded 10% between the wash-out and wash-in, no value was shown. The NMBW method has been validated with good accuracy and precision at low PEEP levels.⁷

### 2.4 Healthy subjects: ELV vs EELV

In two consecutive sessions, estimated ELV in 10 awake healthy subjects was compared to EELV measurements using a body-box plethysmography (Carestream v-max 62).

During the body-box plethysmography, the subjects were put in a hermetically closed body-box at FiO<sub>2</sub> 0.21 and instructed to breathe through a spirometry system in a sitting position. At the end of expiration, a valve in the breathing circuit was closed and subjects were instructed to breathe against the obstruction in a sequence of breathing attempts. The pressure oscillations created in the body-box allow determination of EELV (EELV<sub>BP</sub>) with good accuracy.⁶,⁸

Effective lung volume was measured by passively ventilating subjects with the capnodynamic breathing pattern through a tight mouthpiece, with the SERVO-I ventilator at FiO<sub>2</sub> 0.4, PEEP zero and VT to 7 mL/kg PBW,⁵ in the same body position as the body-box plethysmography. The respiratory rate was adjusted to match the individual ventilation requirement. ELV was recorded every minute during a minimum of 3 consecutive minutes until the subjects showed signs of discomfort or a total of 10 measurements were obtained. An average of three consecutive measurements of ELV awake (ELV<sub>aw</sub>) with an observed good fit between measured and modelled carbon dioxide dynamics were compared to the mean value of three baseline (BL) body-box plethysmography measurements of EELV<sub>BP</sub>.

### 2.5 Porcine model: ELV and EELV

The study was approved by the Uppsala animal research ethical committee (reference C 47/15) and performed at the Hedenstierna laboratory, Uppsala University, Sweden.

Surgical preparation and anaesthesia have previously been described in detail.¹⁰ Summarily, eight pigs with a mean weight of 34 kg (range 32-37 kg) were anaesthetized and mechanically ventilated (SERVO-I, Maquet Critical Care) in a volume-controlled mode (ELV<sub>aw</sub>) to produce a partial nitrogen wash-out/wash-in. A breath-by-breath summation of exchanged nitrogen provides an estimate of EELV<sub>NMBW</sub>. If the difference in nitrogen exchange exceeded 10% between the wash-out and wash-in, no value was shown. The NMBW method has been validated with good accuracy and precision at low PEEP levels.⁷

### 2.6 Statistics

Human data were tested for normality by the D’Agostino K2 test and animal data with Shapiro-Wilks test. Results are presented as mean (SD) if not stated otherwise. Inherent precision of the methods was defined as twice the coefficient of variation (CV = SD/mean), calculated from multiple BL measurements for ELV and EELV<sub>SF6</sub>. Bias was calculated as the mean difference, and precision as limits of agreements (LoA); bias ±1.96 SD. Percentage error (PE) was calculated as T-value × SD, (T-value calculated using freedom T-table with respect to few subjects), divided by the average of the two means of the compared methods, except in the healthy subjects as EELV<sub>BP</sub> is considered gold standard. The trending ability was evaluated with a four-quadrant plot where concordance was calculated as the percentage of paired delta ELV and EELV values having the same direction of change, with increments in PEEP.

### Results

Data in the anaesthetized patient study were collected between 1 December 2014 and 21 October 2015, from the porcine model in November 2015 and from healthy subjects in January 2016.

#### TABLE 1 Demographics of study subjects

|                  | Patients N 14 | Subjects N 7 |
|------------------|---------------|--------------|
| **Age (y)**      | 49 (21-77)    | 42 (32-55)   |
| **Length (cm)**  | 167 (152-188) | 178 (168-189)|
| Female/male      | 11/3          | 2/5          |
| **PBW (kg)**     | 60 (45-82)    | 72 (59-83)   |
| **Weight (kg)**  | 72 (53-108)   | 78 (59-85)   |

Note: Expressed as mean (range). All patients are classified as ASA I or II. Abbreviations: ASA, American Society of Anesthesiology; PBW, predicted body weight.
Demographic data for the healthy subject population are presented in Table 1. Lung volume measurements from all three experimental protocols are presented in Table 2.

### 3.1 ELV and EELV in anaesthetized patients

Twenty-two patients were included in the study. Eight patients were excluded from the data analysis; seven patients because EELV\textsubscript{NMBW} data could not be obtained and one patient due to technical problems with the ELV-method. See Table 1 for demography of included patients.

Effective lung volume had an inherent precision of ±14%. Bland-Altman analysis of ELV vs EELV\textsubscript{NMBW} showed in mL; bias (LoA) 147 (−930 to 1224) and PE 63% at PEEP 0 cm H\textsubscript{2}O and 161 (−1043 to 1635) and PE 71% at PEEP 5 cm H\textsubscript{2}O respectively (Figure 1A and Table 2). During PEEP alterations ELV and EELV\textsubscript{NMBW} had a 100% concordance from 0 to 5 cm H\textsubscript{2}O, (Figure 2A,B).

### 3.2 ELV and EELV in healthy subjects

Seven of the ten healthy participating subjects met the predefined criteria of acceptable stability and were included in the data analysis. See Table 1 for demography of included subjects. Bland-Altman analysis comparing ELV to EELV\textsubscript{BP} at PEEP 0 cm H\textsubscript{2}O showed in mL; bias (LoA) 73 (−866 to 1007) and PE 26% (Figure 1B and Table 2).

### 3.3 ELV and EELV in a porcine model

One animal was excluded due to technical problems with the reference EELV\textsubscript{SF6} method. The inherent precisions for ELV and EELV\textsubscript{SF6} were ±11 and ±16% respectively. Bland-Altman analysis at PEEP 5, 10, 15 and 20 cm H\textsubscript{2}O showed in mL bias (LoA) and PE (%): 223

### TABLE 2 Complete results for all experiments

|        | Patients | Subjects | Pigs |
|--------|----------|----------|------|
| PEEP   | 0        | 10       | 5    |
| N      | 14       | 14       | 14   |
| ELV (mL BTPS (SD)) | 1530 (740) | 2240 (900) | 2040 (870) |
| EELV (mL BTPS (SD)) | 1470 (460) | 1949 (530) | 3543 (605) |
| Bias   | 147      | 161      | 71   |
| SD of Bias (mL) | 550      | 614      | 396  |
| 95% LoA (mL) | −930 to 1224 | −1043 to 1635 | −866 to 1007 |
| PE (%) | 73       | 61       | 26   |
| VDaw (mL BTPS) | 60-150   | 60-150   | 100-300 |
| Venous admixture (%) | 7 (5-10) | 7 (5-10) | 5 (4-7) |

Note: Expressed All lung volumes are presented as mean as Body Temperature Pressure Saturated (BTPS) and include airway dead space. VDaw is derived from calculations based on expired CO\textsubscript{2}.

Abbreviations: EELV, end-expiratory lung volume; ELV, effective lung volume; LoA, limits of agreement; PE, percentage error; VDaw, airway dead space.
At higher PEEP levels bias decreased, whereas LoA as well as PE increased (Figure 1C and Table 2). Mean values for ELV and EELVSF6 increased in a stepwise-fashion during PEEP elevation (Figure 3A). The concordance rate was 100% throughout the PEEP changes (Figure 3B).

4 | DISCUSSION

In this study we present the first evaluation in humans of a continuous carbon dioxide-based method for lung volume measurement with added confirmatory experimental data. We evaluated the trending capability in anaesthetized mechanically ventilated patients. Trending was reliable, although scattered, with a 100% concordance rate between ELV and EELV when PEEP was changed from 0 to 5 cm H$_2$O, in line with results from our previous animal experiments.$^3,15$ Although bias was low, agreement between EELV and ELV was poor, as indicated by wide LoA and high PE.

In the evaluation of healthy subjects, we used body-box plethysmography as the reference; the gold standard for lung volume measurement in spontaneously breathing subjects. After simple instructions to passively follow the ventilator pattern, adequate measurements could be obtained in 7 of 10 subjects. The EELV$_{BP}$ was larger in healthy subjects than in patients which could be explained by difference in position (sitting vs supine) and effects of anaesthesia. Despite the methodological differences and experimental challenges between ELV$_{aw}$ and EELV$_{BP}$, we found a low bias and PE which indicates that ELV is a reliable method for measuring FRC (EELV$_{BP}$) in awake humans with healthy lungs.

For ethical reasons, we investigated the method during high PEEP conditions in the animal laboratory, allowing us to use a fast and reliable reference EELV-method, EELV$_{SF6}$. We found reliable trending capabilities, whereas agreement was PEEP dependent. ELV presented with good agreement and low PE at clinically used PEEP-levels but deteriorated when challenged with higher PEEP-levels. As in our previous animal studies, exploring lower levels of PEEP,$^3$ ELV values were slightly higher than EELV$_{SF6}$ but this overestimation decreased at higher PEEP.

Although EELV measurement is perceived as clinically important,$^16$ it is seldom used in clinical decision-making. Available methods in general require additional equipment, only provide intermittent measurements, or require changes in either inspiratory

\begin{figure}
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\caption{Trending capacities for ELV in anaesthetized patients (n = 14). A, Individual changes in ELV during PEEP changes. B, Four quadrant plot showing ELV trending ability during PEEP increase from 0 to 5 cm H$_2$O. ∆ ELV (mL) compared to ∆ EELV$_{NMBW}$ (mL). Concordance rate 100%. Dotted line represents line of equality. EELV, end-expiratory lung volume; ELV, effective lung volume.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Trending capacities for ELV in anaesthetized pigs (n = 7): A, Relationship between ELV and EELV expressed as mean and SD during stepwise increase in PEEP. B, Trending capacities for ELV in relation to EELV described by a four quadrant plot during PEEP increase. ∆ ELV compared to ∆ EELV$_{SF6}$ shows a concordance rate of 100% (n = 21). Dotted line represents line of equality. EELV, end-expiratory lung volume; ELV, effective lung volume [Colour figure can be viewed at wileyonlinelibrary.com]}
\end{figure}
gas composition or concentration. The capnodynamic method relies on periodically repeated short inspiratory pauses delivered by the ventilator, which cyclically changes the carbon dioxide concentration allowing continuous, breath by breath, calculation of the ELV.

4.1 Study limitations

Effective lung volume was originally defined by Gedeon et al as the lung volume participating in gas exchange. The proposed method is more correctly designated as the lung volume which gives the best fit between measured and calculated carbon dioxide variations, according to the capnodynamic equation. The use of carbon dioxide as a tracer wash-out gas has advantages such as continuous endogenous production, but also disadvantages due to complex kinetics affected by ventilation and perfusion, biological activity and high blood and tissue solubility. It could be argued that end-inspiratory pauses are a less favourable pattern for the lung compared to end-expiratory pauses. The resulting intrathoracic pressure could impair lung perfusion, transiently impairing CO2 transfer to the alveoli which in turn could affect the method. Increased intrathoracic pressure also impairs venous return to the heart resulting in variations in cardiac output. We used inspiratory pauses to induce the needed alterations in carbon dioxide since our unpublished data from animal experiments showed better agreement with the reference method using inspiratory rather than expiratory pauses.

The EELVnMBW technique, the only available clinical method in mechanically ventilated patients for measuring EELV, is mainly intended for use in the intensive care unit. The method requires approximately 40 breaths in total, an equilibration time between the wash-out and wash-in phase and for these values to be within 10% of each other. In eight patients the wash-out/wash-in manoeuvre did not produce any EELV-value and could not be repeated due to strict time constraint of the protocol during elective surgery and were excluded from the final analyses. Possible reasons include unstable oxygen consumption and carbon dioxide production in the early phase of anaesthesia as well as entities measured being unidentical, not being performed simultaneously or having uncorrelated sources of errors.

To optimize EELVnMBW performance, longer stabilization periods would probably have been needed which was not possible due to the aforementioned time constraints.

Our previous experimental validation studies found that ELV resulted in larger values than EELV at lower PEEP levels in pigs and rabbits. Higher levels of PEEP impair lung perfusion and could potentially decrease ELV relative to EELV, but this was not observed in this study, possibly because PEEP was not increased enough to compromise lung perfusion. However, with this in mind, ELV cannot strictly be considered the same entity as EELV. In research regarding validation of haemodynamic monitoring devices, there is controversy about statistical methods and cut-off values for defining interchangeability between two methods when the reference method is unprecise. However, lung monitoring during MV is a largely unexplored field making the a priori stated criteria highly arbitrary. For practical reasons we have applied the same methodology and limits used in haemodynamic research. In line with CO monitoring, it may be argued that detecting volume changes of 10%-15% would be beneficial to the attending anaesthesiologist. Furthermore, trending capability is probably more reliable than absolute lung volumes per se when titrating PEEP or monitoring changes in lung volume.

4.2 Clinical implications

Measuring lung volume is an essential component in the assessment of lung function and receives growing attention as it provides a better understanding of the mechanisms involved in ventilation-induced lung injury. Many conditions, besides anaesthesia and the supine position, requiring MV are associated with a decrease in EELV and are frequently related to the development of atelectasis. Altered chest wall compliance and positional changes further reduce functional lung volume, and not only impairs gas exchange, but render lungs more vulnerable to the mechanical stress imposed by positive pressure ventilation. Strain, in particular dynamic strain (tidal volume/EELV), the resulting deformation of lung tissue to an overdistended lung unit, has been suggested to closely associate with ventilation-induced lung injury and is not possible to determine without measuring lung volumes. Atelectasis, them self defined as a PPC, may increase the risk of pneumonia or other PPCs which are associated with increased morbidity and mortality. The use of PEEP and lung recruitment can preserve and restore functional lung volume. The proposed ELV method has the possibility to continuously monitor changes in EELV in response to PEEP and surgical manipulation. ELV has thus the potential to become a useful tool to indicate the need for recruiting the lung and help individualize the level of PEEP to better implement a lung protective ventilation strategy.

In conclusion, this study presents the first evaluation of a continuous carbon dioxide-based end-expiratory lung volume measurement method in humans, combined with an experimental porcine model. The capnodynamic method showed low bias and good trending capacities when compared with EELV in awake humans and animals and promising trending results in anaesthetized patients. This method may become a useful trending tool for monitoring lung function during MV, if these results can be confirmed in the context of a wider clinical setting.

CONFLICT OF INTEREST

Tomas Öhman, Thorir Sigmundsson, Anders Oldner and Caroline Hällsjö Sander declare no conflict of interest. Magnus Hallbäck is employed at Maquet Critical Care AB (MCC). Fernando Suarez Sipmann performs consultant activities for MCC. Mats Wallin is employed at MCC. Håkan Björne has received grants for research from MCC.

AUTHORS’ CONTRIBUTIONS

T.O, T.S, C.H.S., F.S.S., M.H, M.W, A.O. and H.B. were involved in study design, data collection and analysis. T.O, T.S, C.H.S., H.B. A.O., M.H., M.W. and F.S.S. were involved in drafting and revision of the manuscript.
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