PEEP Selection: Dynamic Elastance versus An Over-distension Measurement

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Abstract: Acute respiratory distress syndrome (ARDS) patients usually require support from ventilation in the intensive care unit (ICU). Recruitment maneuvers (RMs) with positive-end-expiratory-pressure (PEEP) are a common way to recruit alveoli and improve oxygenation. However, excessive PEEP can worsen alveoli status and thus increase the risk of ventilator-induced lung injury (VILI). To date, standards for optimal patient-specific PEEP determination remain unclear, resulting in variability and uncertainty in care and thus requiring personalized care approaches. This research examines the conventional approach, dynamic elastance (E_{dyn}), and a validated over-distension index (OD) from prior work identified from pressure-volume curves. Overall, in the studied pilot trial, the optimal PEEP selection outcome matches between E_{dyn} and OD methods within 0-2cmH$_2$O (0-1 PEEP levels) variation for 16 out of 18 patients. The variation in the rest 2 patients are 4cmH$_2$O (2 PEEP levels). While possible limitation for E_{dyn} is addressed and discussed, the over-distention index OD shows greater potential in routine care being more intuitive, general, and predictive.

Keywords: Mechanical Ventilation; Critical Care; Dynamic Elastance; Over-distension; Pressure-Volume Curve; Optimal PEEP; Ventilator-induced Lung

1. INTRODUCTION

Mechanical ventilation (MV) is an essential treatment in the intensive care (ICU) to support patients with acute respiratory distress syndrome (ARDS) (Kim et al., 2020). Recruitment maneuvers (RMs) with positive-end-expiratory-pressure (PEEP) have been applied to optimise lung conditions and minimise possible ventilator-induced lung injury (VILI) resulting from insufficient or excessive pressure support (Halter et al., 2007, Morton et al., 2018). Moreover, lung mechanics can be complex and mostly inhomogeneous, leading to simultaneous partial distension and collapse (Lu, 2012).

An optimal PEEP level is thus commonly considered as the PEEP level where reaches the best compromise between recruitment and over-distention for alveoli (Lu, 2012, Maisch et al., 2008). However, to date, standards for detecting optimal PEEP remain unestablished. Thus, new approaches are proposed and gained interests in recent decades.

Lung scans have been the 'gold' standard to distinguish alveoli being normally aerated, poorly aerated, non-aerated, and over-distended, while minor difference can exists due to scanning setting bias (Gattinoni et al., 2001, Cereda et al., 2019). Scans at end of expiratory taken at each PEEP level during titration can be effective, but radiation overdose and the inconvenience at bedside lead to a limited application (Major et al., 2018). In recent years, electrical impedance tomography (EIT) conquered above issues at bedside enabling a less harmful measurement and offered promising details for understanding lung conditions (Zhao et al., 2021, Putensen et al., 2019), but still needs to be further fully validation in clinical.

Dynamic elastance/compliance is also a popular means to study lung conditions during RM and PEEP titration by considering the maximum compliance is yielded in a best trade-off between recruitment and derecruitment (Putensen et al., 2019). As a mathematical calculation, it is easy to obtain at bedside. However, it is equally limited since the minimum E_{dyn} (maximum C_{dyn}) must still be observed via testing. Further, this value can evolve over time (Chiew et al., 2011, van Drunen et al., 2014), necessitating regular testing with associated risks.

In particular, the flattening behaviour observed at the end of inspiration in a pressure-volume (P-V) loop is considered to be strongly correlated with alveolar over-distension (Emeriaud et al., 2015, Carvalho et al., 2013, Kano et al., 1994). The features identified from the flattening behaviour, such as the lower/upper inflection point (LIP/UIP), are studied for a potential correlation with alveoli recruit ability (Koefoed-Nielsen et al., 2008). However, the correlation remains unclear with the recruited or over-distended volume in alveoli.

Some studies tend to capture the flattening behaviour itself. Fisher et al (Fisher et al., 1988) proposed to examine the ratio of the last 20% of inspiration compliance over the total compliance. However, it was tested with infant lungs and a revised calculation was suggested (Nève et al., 2001). Another elastance ratio, *%E2*, identified via a volume-dependent single compartment model (VDSCM), was suggested as more robust than Fisher et al (Kano et al., 1994). However, research suggests *%E2* is only useful in uninjured lungs (Carvalho et al., 2013) and the threshold value for over-distension remains debated (Carvalho et al., 2008, D'Antini et al., 2018).

This research examines a new over-distension index, identified from clinical measured P-V curves, as a harmless, more efficient and intuitive tool in determining optimal PEEP and compares it with a well-known and traditional approach, dynamic elastance (E_{dyn}). The analysis is fulfilled with 18 volume-controlled ventilation (VCV) patients under a stepwise RM with incremental PEEP.

2. METHODS

2.1 Examined variables

Maximum dynamic compliance (C_{dyn}), also described as minimum dynamic elastance ($E_{dyn} = 1/C_{dyn}$), is calculated:

$$E_{dyn} = \frac{1}{C_{dyn}} = \frac{(PIP - PEEP)}{V_T} \quad (1)$$

where *PIP* is the peak inspiratory pressure (cmH_2O) and V_T is the tidal volume (L).

The model-based over-distension (OD) measurement in P-V curve (Sun et al., 2022) is calculated with $k2$ and $k2end$ which are automatically identified by hysteresis loop analysis (HLA) (Zhou and Chase, 2020, Zhou et al., 2015). OD is then quantified as the pressure difference between the 'flattened' breath and a 'non-flattened' breath, as shown in Figure 1, where $k2 \approx k2end$ would yield OD $\approx$ 0cmH_2O indicating no or minimal over-distension:

$$OD = PIP - \left(V_{PIP} * k2 - k2_{intrpl}\right) \quad (2)$$

where $k2$ is the identified slope presented in Figure 1 and $k2_{intrpl}$ is the identified corresponding interpolation. V_{PIP} is the tidal volume (L) where airway pressure yields its maximum (PIP). $k2end$ is identified simultaneously with $k2$. Although it is not directly involved in the calculation but adds predictability for proposed OD method, which is presented in previous work (Sun et al., 2021).

In the previous work (Sun et al., 2022), OD is calibrated with a well-validated tool for VCV-only patients, stress index (SI) (Grasso et al., 2004). The yielded safe range is proposed to be 0-0.8cmH_2O, while OD < 0cmH_2O indicates insufficient support and OD > 0.8cmH_2O indicates over-distension risk.

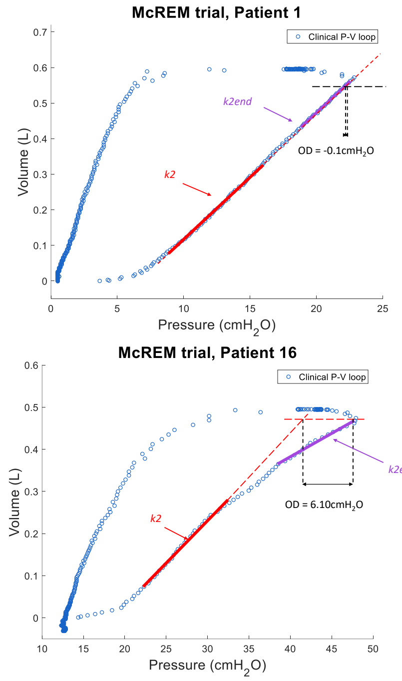

Figure 1 Examples of over-distension calculation in measured clinical P-V loops at PEEP = 0cmH_2O for Patient 1 with OD ~= 0cmH_2O (no or minimal over-distension) and at PEEP level = 12cmH_2O for Patient 16 with OD = 6.10cmH_2O (observed over-distension).

2.2 Patient data

Ventilation data from 18 ICU patients from the McREM trial (Stahl et al., 2006) is used in this approach. All 18 patients were fully sedated and intubated under invasive volume-controlled ventilation, with tidal volume set to 8 ± 2 ml/kg based on ideal body weight (Stahl et al., 2006). All 18 patients underwent one incremental staircase RM with 2cmH_2O step starting at 0cmH_2O (ZEEP). The maximum applied PEEP level for each patient is variant due to clinical setting (from 10 to 26cmH_2O), yielding 196 cases in total.

During ventilation, an end-inspiratory hold of 0.2s is applied for each breath and data were sampled at 125Hz. Patient demographics are presented in Table 1, where only the primary diagnosis is shown, but all patients have some level of ARDS, as defined by PaO_2/FiO_2 (P/F) ratio, P/F < 300mmHg (Force*, 2012).

Table 1 - Patients clinical demographics in the McREM pilot trial (Stahl et al., 2006). TBI = Traumatic Brain Injury, SAH = Subarachnoid and Subdural Hemorrhage, SDH = Subarachnoid Hemorrhage

Patient	Sex	Age (years)	P/F (mmHg)	Clinical Diagnostic
1	m	37	163	Pneumonia
2	f	50	202	Pancreatitis, pneumonia
3	f	30	162	Peritonitis, sepsis
4	f	49	289	Pneumonia
5	m	34	192	open TBI
6	m	67	234	Post reanimation
7	m	39	188	Sigma perf., peritonitis

8	m	42	235	Pneumonia, pancreatitis
9	m	51	230	TBI, pneumonia
10	m	77	225	Pneumonia
11	m	74	298	SAH, SDH
12	m	41	178	Peritonitis
13	m	62	288	SDH
14	m	39	143	TBI, pneumonia
15	m	74	271	S/P coronary artery bypass grafting, pneumonia
16	m	59	75	ARDS
17	m	45	173	Blunt abdominal trauma, pneumonia
18	m	42	260	Alcoholism, GI bleeding, sepsis

2.3 Key differences in E_{dyn} and OD

While over-distension metrics can be effective to assess lung condition and guide treatment, strong correlation with modelled physiological features and mechanics can strengthen the understanding of what is occurring with pulmonary mechanics, as well as increase its predictive power, but only if the model has predictive capability (Chase et al., 2018). Over-distension metrics with predictive power can offer further better guidance in clinical care and lower risks for patients.

E_{dyn} is available in a ventilator but does not capture the flattening of the P-V loop according to equation (1), and the nonlinear mechanics, indicating over-distension. In contrast, OD captures resulting excess pressure due to this nonlinearity, as shown in Figure 1. Furthermore, OD is a more robust calculation, and can be accurately predicted over changes in MV settings (predictive power) via a validated digital twin virtual patient model (Sun et al., 2021). Table 2 summaries the main features discussed for E_{dyn} and OD.

Table 2 - E_{dyn} and OD comparison

Metrics	Unit	Proposed safe value range (optimal PEEP)	Nonlinear behaviour captured
OD	cmH_2O	0-0.8cmH_2O	yes
E_{dyn}	cmH_2O/L	yes*	no

* A safe range within 5-10% of minimum E_{dyn} is proposed by (Chiew et al., 2015, Carvalho et al., 2008), and in clinical use from experience. However, to authors' knowledge, very little published research has considered a numerical safe E_{dyn} range instead of finding its minimum value via PEEP titration testing or similar.

3. RESULTS

3.1 Dynamic elastance, E_{dyn}

E_{dyn} is calculated for all 196 cases with equation (1). Table 3 presents the PEEP level corresponding to the minimum E_{dyn} for each patient, as well as the minimum and maximum value during RM. For 13 out of 18 patients, E_{dyn} as PEEP has a typical concave evolution which decreases from ZEEP and reaches its bottom at a specific PEEP level, assumed to be the optimal PEEP for the patient balancing benefits and detriments (Maisch et al., 2008).

However, a few patients have abnormal E_{dyn} evolution while PEEP increases. Patients 9, 12, 16, and 18 have a curve that starts increasing from ZEEP, which is normally not considered as the optimal PEEP setting. The E_{dyn} curve for Patient 13 has a small bump at first three PEEP levels and then behaves typically. The plots of E_{dyn} over PEEP for Patient 13 and 16 are also presented in Figure 2, while an example of the typical E_{dyn} evolution is also provided for Patient 17 in the upper left panel. patients), are also presented.

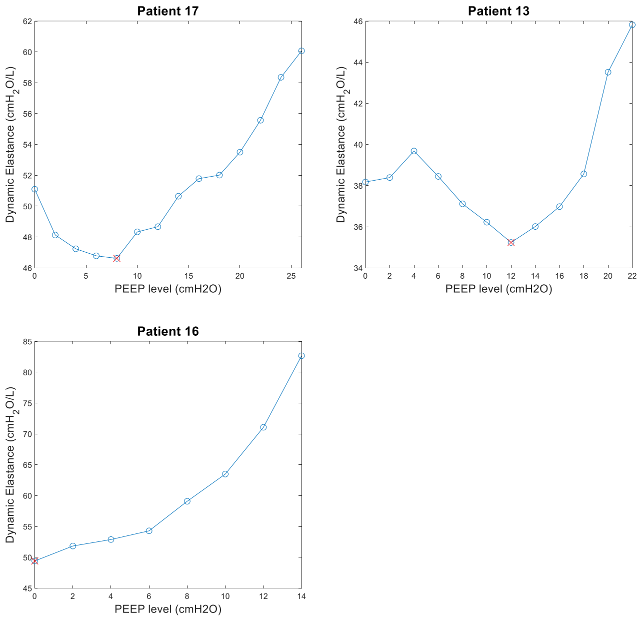

Figure 2 Examples for typical E_{dyn} evolution (cmH_2O/L) (upper left) for Patient 17, and two types of non-typical E_{dyn} evolutions (upper right and lower left) for Patients 13 and 16, respectively. Symbol 'x' indicates the yielded lowest value across PEEPs.

Table 3 - E_{dyn} (cmH_2O/L) in minimum, the PEEP level where it is reached, and maximum value for each patient

Patient	PEEP level yielded minimum E_{dyn}	minimum E_{dyn}	maximum E_{dyn}
1	4 cmH_2O	36.4	53.0
2	10 cmH_2O	51.6	64.4
3	14 cmH_2O	73.7	79.3
4	2 cmH_2O	50.4	62.2
5	8 cmH_2O	31.0	39.0
6	2 cmH_2O	35.9	45.1
7	6 cmH_2O	62.1	72.0
8	6 cmH_2O	38.0	52.4
9	ZEEP	30.3	43.6
10	6 cmH_2O	38.2	43.8
11	6 cmH_2O	24.1	33.0
12	ZEEP	73.1	99.8
13	12 cmH_2O	35.2	45.8

14	8 cmH_2O	31.3	41.9
15	10 cmH_2O	42.1	50.9
16	ZEEP	49.4	82.7
17	8 cmH_2O	46.6	60.1
18	ZEEP	55.2	67.8

3.2 OD identified by P-V curves

The corresponding OD for lowest E_{dyn} is shown in Table 4, while the minimum and maximum OD over the RM, and the highest PEEP level before OD > 0.8cmH_2O (basing on prior work (Sun et al., 2022) are also provided for each patient. For most patients, the OD is negative or near 0cmH_2O ($k2end \approx k2$) at ZEEP, indicating no or minimal over-distension, and increases with rising PEEP as expected.

The outcome, optimal PEEP selection, between E_{dyn} and OD matches (one PEEP level variation maximum, 2cmH_2O), except for 4 abnormal patients. Typical OD over PEEP evolution (14 out of 18 patients) is shown in Figure 3.

Two types of abnormal curves (4 out of 18) are also provided in Figure 3. Patient 13 acts unexpected with both E_{dyn} and OD at lower PEEPs and then behaves as expected, may indicating the unstable patient condition at the beginning. Meanwhile, Patients 10 and 11 have only 1-2 PEEP levels (at PEEP = 2-4cmH_2O) acting unexpected. If regardless of those, the optimal PEEP levels are 10cmH_2O and 6cmH_2O, respectively, where the optimal PEEP outcome matches E_{dyn} selection for Patient 11 while 2 PEEP levels variation exists for Patient 10.

Table 4 - The identified minimum and maximum OD values (cmH_2O) during RM, the correspondent OD at the minimum E_{dyn} PEEP level for each patient, and highest PEEP level before OD > 0.8cmH_2O (over-distension risk)

Patient	OD at minimum E_{dyn}	Minimum OD	Maximum OD	Highest PEEP level before OD > 0.8cmH_2O
1	0.49	-0.10	4.55	6 cmH_2O
2	0.47	-1.07	3.56	10 cmH_2O
3	1.53	-1.99	3.72	10 cmH_2O
4	-0.60	-0.60	6.24	2 cmH_2O
5	0.49	-1.33	3.65	10 cmH_2O
6	2.02	1.43	6.62	ZEEP
7	0.42	-0.24	2.56	8 cmH_2O
8	0.44	-0.57	3.66	6 cmH_2O
9	-0.16	-0.16	4.86	2 cmH_2O
10	0.46	-0.41	1.68	10 cmH_2O
11	0.79	0.57	2.10	6 cmH_2O
12	0.80	0.80	4.22	ZEEP
13	-0.22	-0.49	2.78	14 cmH_2O
14	0.29	-0.12	2.78	8 cmH_2O
15	0.80	-1.15	2.21	10 cmH_2O
16	-0.48	-0.48	10.14	2 cmH_2O
17	0.93	-0.33	2.41	6 cmH_2O
18	1.31	1.31	2.83	ZEEP

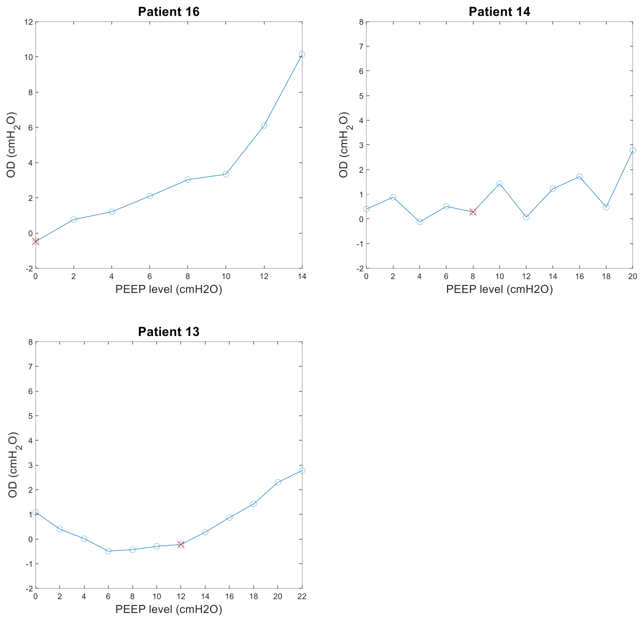

Figure 3 Examples for typical OD (cmH_2O) over PEEPs (upper left) for Patient 16, and two types of non-typical OD evolutions (upper right and lower left) for Patients 14 and 13, respectively. Symbol 'x' indicates the PEEP where yields the minimum E_{dyn}.

4. DISCUSSION

Over-distension is usually considered not existing in ZEEP or low PEEPs. However, in (Dambrosio et al., 1997), minor over-inflation is observed by CTs recognized by a range of -800 to -1000 Hounsfield units (HU). Although the quantification in HU range proposed by (Gattinoni et al., 2001) may overestimated the alveoli distension, the over-inflation is also found in (Carvalho et al., 2008) at ZEEP in -900 to -1000 HU. Thus, minor but not negligible over-distension can be assumed to exist at ZEEP, which means the optimal PEEP is possible to be ZEEP or 2cmH_2O for the patients in Table 3 and Table 4, indicating worse condition than other patients.

The equivalent efficacy of OD to identify over-distension risk is shown by the matched optimal choices of PEEP level with E_{dyn} for each patient, which are the same selection or vary with 1 PEEP level = 2cmH_2O for 16 out of 18 patients. For the two unmatched patients, Patient 3 and 10, the variation is both 4cmH_2O (2 PEEP levels). For Patient 10, E_{dyn} yields 38.2cmH_2O/L as its minimum at PEEP = 6cmH_2O and 38.4 cmH_2O/L at PEEP = 10cmH_2O of OD choice. For Patient 3, E_{dyn} difference is 0.6 cmH_2O/L.

Given above, the yielded E_{dyn} difference can be minor even with 2 PEEP levels variation (ΔPEEP = 4cmH_2O). A main problem is that the E_{dyn} varies greatly from patient to patient, as presented in Table 3, leading to a lack of understanding of calculated E_{dyn} values. Hence, it is uncertain whether this minor difference is negligible or not. More importantly, the main problem of using E_{dyn} to choose the optimum PEEP is that the overall minimum value is obtained by comparison. It requires the patient to endure the whole RM then to detect which PEEP level yields the minimum value.

Indeed, for most patients who have a concave shape of E_{dyn}

over PEEP, it is possible to stop PEEP titration by observing a reached minimum with an increased E_{dyn} at the following PEEP. However, as shown in Figure 2 and Table 3, E_{dyn} yielded its overall minimum at ZEEP for 4 out of 18 patients. Moreover, E_{dyn} values can evolve with time (Chiew et al., 2011, van Drunen et al., 2014), and thus the optimal PEEP for patients. Thus, to ensure the optimal care, a regular test is required, which can be risky and unnecessary in clinical.

Meanwhile, 1 patient has a 'false increase' at first 3 PEEP levels, as shown in Figure 2. 3 PEEP levels in the studied trial yield a ΔPEEP = 6cmH_2O, considerable large in clinical, and thus it will be dangerous for patients to take a 4th PEEP level or more steps to see whether it is a 'false increase'. Thus, it is not easy to assess the real patient condition and needs with E_{dyn} for patients in similar condition.

Given above, E_{dyn} method requires a complete RM or at least 3 or 4 PEEPs testing (in the studied trial) to ensure it is a 'real increase' instead of being a 'false increase'. This can be risky for the 4 out of 18 patients (11% probability) in this trial whose optimal PEEP is at 0-2cmH_2O, leading to a too conservative treatment or a late distinguishing in excessive PEEP application, increasing the risk of VILI (Major et al., 2018, Scohy et al., 2009). Meanwhile, the non-intuitive and patient-specific values increase the difficulty in understanding and assessing patient condition in care.

OD conquers above problems. First, it is identified by P-V loops and captures the nonlinear behaviour. The yielded values are easy to understand using the same metric of airway pressure, which is one of the most known variables in ventilation care. Moreover, OD offers a safe range (Sun et al., 2022) for clinicians to assess patient condition and is general for every patient. The prior work for accurate and robust *k2* and *k2end* predictions from one single PEEP level offers the predictability of OD at the same time (Sun et al., 2021). Hence, it is possible to predict OD from one PEEP level to multiple higher PEEP levels and then choose the optimal level before whole test procedure, which is compulsory for E_{dyn} approach, significantly lowering the risk.

The limitation of this study is the limitation of patient number and applied MV mode (only VCV patients analysed). However, OD is identified from clinical measured P-V loops which are generated by both airway pressure and tidal volume features. Thus, it has the potential to be extended with non VCV patient data. Although this study only includes the data from 18 patients, multiple PEEP levels for each patient yield 196 cases in total, which is adequate to validate the study. More patient data under more various condition and MV modes are required for further validation.

5. CONCLUSION

In conclusion, while E_{dyn} is the conventional and most known method to detect optimal PEEP where yields the best compromise between recruitment and over-distention for alveoli, it is non-intuitive and not general, and inevitable risks are taken before figuring out the optimal treatment. OD is general for every patient, more intuitive, and potential predictable, avoiding the risk for testing alternative PEEP or MV settings in care, which no existing methods can offer currently. More patients under various treatment data are required for further validation and implement for this approach.

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