Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Clinical Utilisation of Respiratory Elastance (CURE): Pilot Trials for the Optimisation of Mechanical Ventilation Settings for the Critically Ill

Shaun M. Davidson*, Daniel P. Redmond*, Hamish Laing*, Richard White*, Faizi Radzi*, Yeong Shiong Chiew*, Sarah F. Poole*, Nor Salwa Damanhuri*, Thomas Desaive, Geoffrey M Shaw***, J. Geoffrey Chase***

**Department of Mechanical Engineering, University of Canterbury, Christchurch, New Zealand (e-mail: shaun.davidson@pg.canterbury.ac.nz).*
***GIGA Cardiovascular Science, University of Liege, Liege, Belgium (email: Tdesaive@ulg.ac.be)*
**** Intensive Care Unit, Christchurch Hospital, Christchurch, New Zealand, (e-mail: Geoff.Shaw@cdhb.govt.nz)*

Abstract: Current practice in determining Mechanical Ventilation (MV) settings is highly variable with little consensus, forcing clinicians to rely on general approaches and clinical intuition. The Clinical Utilisation of Respiratory Elastance (CURE) system was developed to aid clinical determination of important MV settings by providing real-time patient-specific lung condition information at the patient bedside. The pilot clinical trials to investigate the performance and efficacy of this system are currently being carried out in the Christchurch Hospital ICU, New Zealand. This paper presents the CURE clinical trial protocol and its initial findings from the two patients recruited to date. In particular, this paper focuses on CURE's ability to determine patient-specific responses in real time to PEEP changes and recruitment manoeuvres (RM). The results from this study demonstrate the potential for CURE Soft to improve the reliability and ease with which clinicians make decisions about MV settings in the ICU.

1. INTRODUCTION

Mechanical Ventilation (MV) is a prevalent therapy, applied to an estimated 60% of patients in the Intensive Care Unit (ICU), among which there is a 28 day mortality rate of 32% (Bersten et al., 2002). MV is also expensive, costing an estimated $1800 NZ ($ 1440 USD) more per patient per day (almost doubling the daily cost of an ICU patient) (ANZICS, 2010). Despite this, current practice in determining MV settings is highly variable with little consensus (Meade et al., 2008, Sundaresan and Chase, 2011) .

One of the primary settings adjusted during MV is Positive End-Expiratory Pressure (PEEP). PEEP is an elevated pressure aimed to combat the increased tendency of injured lung to collapse (known as de-recruitment). Insufficient PEEP may lead to de-recruitment, reducing the lung area available for gas exchange and resulting in a drop in blood oxygenation. Conversely, excessively high PEEP can damage the lung by over distension (excessive stretching) of the lung tissue. Both insufficient and excessive PEEP during MV have adverse effects on patient recovery (Rouby et al., 2002, Treggiari et al., 2002).

In addition to this problem, MV patients are heterogeneous and their response to PEEP settings is highly variable. This heterogeneity further complicates the process of determining 'optimal' patient-specific PEEP. As a result, current practice involves determining ventilator PEEP based on general approaches such as the PEEP-FiO2 table (The Acute Respiratory Distress Syndrome Network, 2000, Mercat et al., 2008) and clinical experience. In addition, there is no standardization in the frequency or PEEP level of these changes. This variability in care further exposes MV patients to the risk of being ventilated on suboptimal settings that could induce further injury (Ricard et al., 2003, Carney et al., 2005) . Thus, there is a need to provide a patient-specific method to titrate PEEP in a consistent fashion.

To address this issue, a clinical trial, the Clinical Utilisation of Respiratory Elastance (CURE) has been developed and carried out at the Christchurch Hospital ICU, New Zealand. The objective of the CURE trial is to investigate the patient-specific response to different recruitment manoeuvres (RM) and the clinical feasibility of employing a minimal elastance PEEP titration method to determine 'optimal' PEEP (Chiew et al., 2011, Chiew et al., 2012, Suarez-Sipmann et al., 2007, Carvalho et al., 2007).

The CURE trial employs a software system (CURE Soft) designed to aid clinical determination of PEEP settings by providing real-time patient-specific lung condition information at the patient bedside. CURE Soft automatically estimates breath-to-breath patient-specific respiratory mechanics using a time-varying elastance model (Chiew et al., 2011). A schematic drawing of the implementation of the CURE Soft is shown in Fig. 1. CURE Soft uses the patient-ventilator's airway pressure and flow information to estimate respiratory elastance (E_{rs}), which can be used to provide information on patient lung condition, disease progression and response to MV treatment. This paper presents the CURE clinical trial and its initial findings from the patients recruited

at the Christchurch Hospital ICU. In particular, this paper focuses on the patient-specific response during a series of PEEP changes and recruitment manoeuvres (RM).

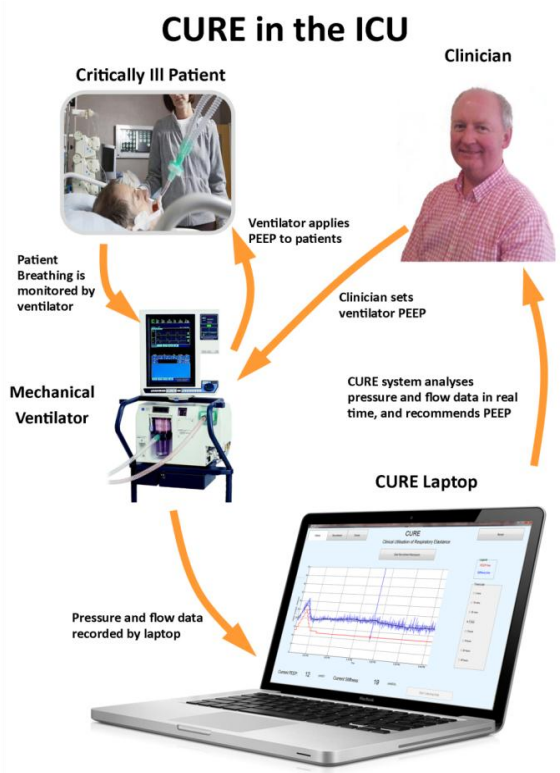

Fig. 1. Schematic drawing of the implementation of CURE

2. METHODS

2.1 Clinical Trial

2.1.1 Inclusion and Exclusion Criteria

CURE is an interventional clinical study carried out in the Christchurch Hospital ICU, New Zealand. Patients on MV due to respiratory failure who would not be negatively affected by the PEEP changes or additional use of sedatives over the course of the trial are eligible for study. The patient inclusion criteria are: 1) Patient on Mechanical Ventilation, 2) Patient diagnosed with all degrees of ARDS (Partial Pressure of arterial blood gas oxygen per Fraction of Inspired Oxygen (PF Ratio) < 300 mmHg) as per the Berlin Definition (The ARDS Definition Task Force, 2012), by intensive care clinicians 3) Arterial line in situ.

The exclusion criteria are: 1) Patients who are likely to be discontinued from MV within 24 hours, 2) Patients aged < 16, 3) Patients who are moribund and/or not expected to survive for more than 72 hours, 4) Patients whose care could be compromised if given increased sedation and/or muscle relaxants for the purpose of assessing lung recruitment and 5) Lack of clinical equipoise by ICU medical staff managing the patient. Ethics approval for this study and subsequent use of collected data was granted by the New Zealand South Regional Ethics Committee.

2.1.2 CURE Clinical Protocol

Patients who meet the inclusion criteria are consented to the CURE trial. The trial involves implementing CURE Soft in real time, providing patient-specific elastance to aid clinical decision making. In this trial, several recruitment manoeuvres (RM) are performed by the attending clinician throughout the duration of MV. A recruitment manoeuvre (RM) is a series of short term, step-wise incremental PEEP changes over a range of pressures. This brief elevated pressure serves to re-inflate or 'recruit' collapsed lung areas, portions of which typically remain open when PEEP is decreased after the manoeuvre. The magnitude, duration and frequency of these manoeuvres is standardised by the protocol, though subject to adjustment by the clinician. Whenever a RM is performed, the clinician switches CURE Soft to a mode where it will record elastance values for different PEEP levels used during the recruitment manoeuvre. CURE Soft will then output this data to aid the clinician in selecting the appropriate PEEP level to ventilate the patient at after the manoeuvre.

The clinical protocol specifies an initial RM be undertaken over a wide range of pressures specified by the attending clinician. This RM serves to recruit the patient's lung, and allows CURE to provide an elastance-PEEP profile over a wide range of pressures. This elastance-PEEP profile can then be used by the clinician to select an initial, optimum PEEP level based on a minimal lung elastance metric (Lambermont et al., 2008, Chiew et al., 2011, Sundaresan et al., 2011). Subsequent RMs take place over a smaller range, providing information that facilitates smaller shifts in PEEP as patient condition changes. The magnitude of these RMs are subject to change at the attending clinician's discretion. The detailed clinical protocol can be found online in the Australian New Zealand Clinical Trial Registry Website (http://www.anzctr.org.au/), Trial number ACTRN12613001006730.

2.2 CURE Soft

CURE Soft calculates respiratory mechanics in real-time at the patient bedside, using pressure and flow data from a Puritan Bennett 840 Ventilator (PB840) (Covidien, Boulder, CO, USA). CURE Soft is a laptop based software implemented in MATLAB. The model used is the time-varying respiratory elastance model (Equation 1) (Chiew et al., 2012).

$$P_{aw}(t) = Edrs(t) \times V(t) + R \times Q(t) + PEEP \qquad (1)$$

Where $P_{aw}(t)$ is the airway pressure over the course of the inspiration (cmH_2O), t is the time, Edrs(t) is the time-varying respiratory elastance (cmH_2O/L), V(t) is the inspired volume over the course of inspiration (L), R is the airway resistance (cmH2Os/ L) and Q(t) is the inspiratory flow over the course of the breath (L/s). An improved Multiple Linear Regression is used to determine resistance and elastance for each breath. The Edrs(t) for every breathing cycle is then normalised and the area under the curve calculated (AUCEdrs). The AUCEdrs for every breathing cycle is used as a surrogate of the patient's breath-to-breath respiratory elastance.

2.3 Analysis of Results

As the CURE trial is still on-going, the analysis of existing results is largely qualitative, and is based on current understanding of the elastance metric and observed changes in patient condition. As the trial continues and more patients are recruited, the volume of data required to employ quantitative metrics in assessing the effectiveness of the CURE protocol and system will become available.

3. RESULTS

In this pilot trial, there are two patients that have been included in the study, with CURE collecting a total of 66 hours of data to date. A summary of the data collected for these 2 patients is shown in Table 1.

Table 1. Summary of data recorded for CURE trial

	Data Recorded (Hours)	Breaths Recorded (#)	RMs	PEEP Changes
Patient 1	23.1	25,412	9	3
Patient 2	42.9	48,015	5	7
Total	66.0	73,427	14	10

3.1 Patient 1

Patient 1 had a primary diagnosis of pneumonia. Fig. 2 shows the patient's respiratory elastance and PEEP with respect to time as determined via CURE Soft. Note that there are a pair of recruitment manoeuvres that occur at approximately 320 and 430 breaths. During the first recruitment manoeuvre, there is a drop in elastance from 23.9 cmH_2O/L to 20.3 cmH_2O/L. The second recruitment manoeuvre results in only a minimal change in respiratory elastance, from 19.7 cmH_2O/L to 19.8 cmH_2O/L.

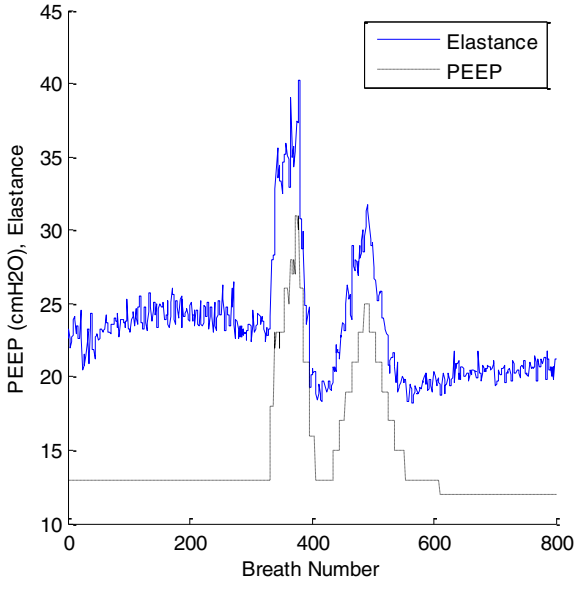

Fig. 2. The patient-specific elastance and PEEP for Patient 1 during a paired recruitment manoeuvre (RM).

During these recruitment manoeuvres, CURE Soft is switched into a mode where it displays and tracks respiratory elastance for each PEEP level. Fig. 3 shows one such plot corresponding to the first RM in Fig. 2. A drop in respiratory elastance during a RM suggests overall recruitment (Chiew et al., 2011). In this RM, the lower elastance at the end of decremental PEEP (red line) implies successful lung recruitment.

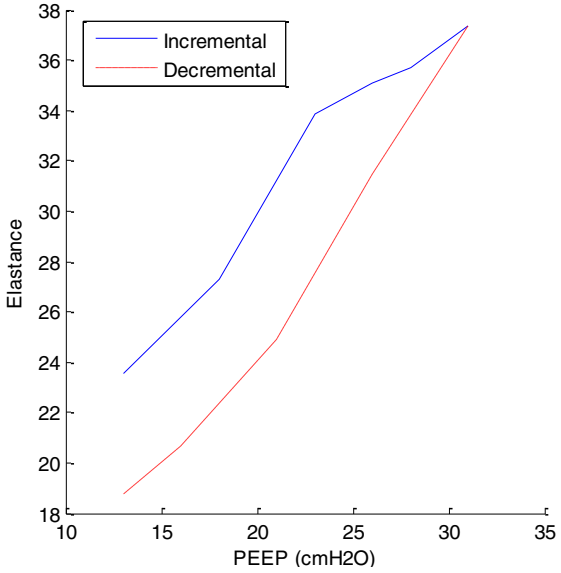

Fig. 3. CURE Elastance tracking with respect to PEEP showing a successful Recruitment Manoeuvre, Patient 1. The Blue/Red Lines indicates the elastance-PEEP relation during incremental/decremental PEEP.

Fig 4 shows an elastance vs. PEEP plot for the second RM, which occurred right after the first as shown in Fig 1. In this second RM, there is a lack of significant change in respiratory elastance, when comparing the start of the RM (blue) and end of the RM (red). This small change suggests that available lung units were already recruited during the first RM, and thus the second RM had relatively little benefit.

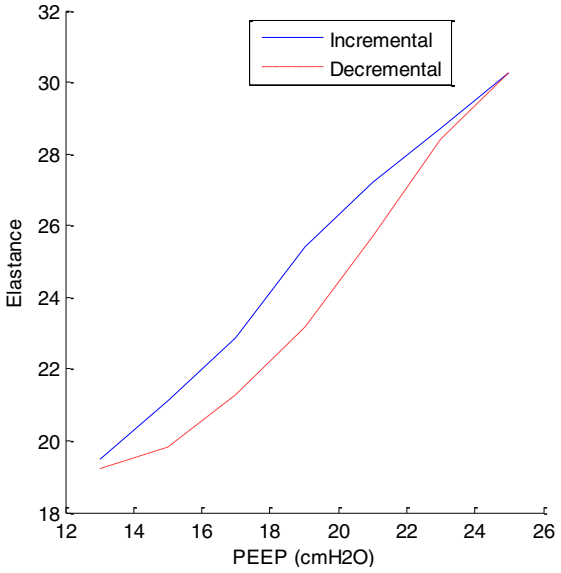

Fig. 4. CURE Elastance tracking with respect to PEEP showing an unsuccessful Recruitment Manoeuvre, Patient 1. The Blue/Red Lines indicates the elastance-PEEP relation during incremental/decremental PEEP.

3.2 Patient 2

Patient 2 had a primary diagnosis of aspiration following a cardiac arrest. Fig. 5 shows a section of the transient PEEP and elastance curves for Patient 2 as determined by CURE. Similar to the first recruitment manoeuvre shown in Figure 2, respiratory elastance has decreased from 24.2 cmH_2O/L to 22.0 cmH_2O. This drop in elastance suggests a successful recruitment manoeuvre that has recruited collapsed lung.

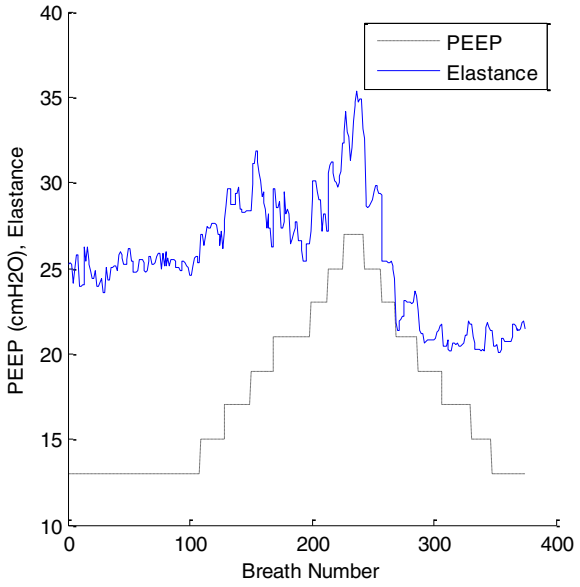

Fig. 5. Patient-specific elastance and PEEP for Patient 2 during a recruitment manoeuvre (RM).

Fig. 6 shows the CURE Soft estimated Elastance vs. PEEP plot for the RM shown in Fig. 5. The drop in elastance between the start and end of the RM suggests that lung recruitment has occurred. In Fig. 6, it is also noteworthy that there is a decrease in elastance when PEEP is increased from 19 cmH_2O to 21 cmH_2O. This sudden decrease in elastance suggests an overall alveolar recruitment that outweighs over distension. During the decremental PEEP of the RM, a relatively constant elastance is observed when PEEP is decreased from 19 to 13 cmH_2O.

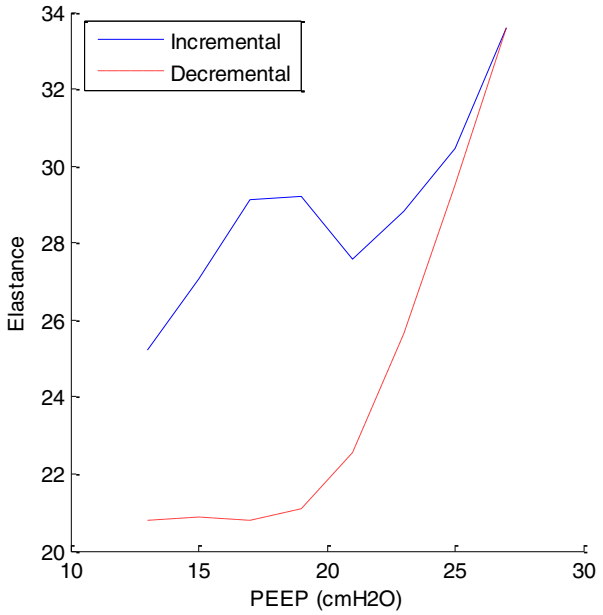

Fig. 6. CURE Soft Elastance tracking with respect to PEEP showing a successful RM, Patient 2. The Blue/Red Lines indicates the elastance-PEEP relation during incremental/decremental PEEP.

Table 2 presents summary information for all RMs recorded for the 2 patients included in the CURE trial to date. Note listed elastance values in Table 2 are the median elastance of the 20 breaths either side of the RM. The first two recruitment manoeuvres for Patient 1 were combined due to their proximity (see Figure 2). A recruitment manoeuvre was deemed successful if it resulted in a greater than 10% decrease in elastance.

Table 2. Patient-specific respiratory elastance before and after each recruitment manoeuvre

Patient 1	**RM1-2**		**RM3**		**RM4**		**RM5**		**RM6**		**RM7**		**RM8**		**RM9**	
	B*	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
Elastance	24.2	19.7	17.2	16.2	21.2	22.6	17.9	18.6	19.7	20.7	19.2	21.0	18.8	20.3	22.5	21.0
PEEP	13 +18	12	12 +6	11	11+6	11	11 +6	11	11 +6	10	10 +6	10	10 +6	10	10 +6	10
Successful	Yes		No		No		No		No		No		No		No	
Patient 2	**RM1**		**RM2**		**RM3**		**RM4**		**RM5**							
	B	A	B	A	B	A	B	A	B	A						
Elastance	24.4	21.8	22.7	23.5	21.7	23.3	25.7	21.3	23.6	22.2						
PEEP	13 +14	13	13+6	15	15+6	13	13+14	19	19+6	19						
Successful	Yes		No		No		Yes		No							

Note*
RM - Recruitment manoeuvre
B - Before the recruitment manoeuvre (+maximum increase in PEEP during RM)
A - After the recruitment manoeuvre

4. DISCUSSION

4.1 Clinical Implications (Patient 1)

The clear contrast between Figs. 3 and 4 highlights the capacity of the CURE system to distinguish between successful and unsuccessful RMs. The successful recruitment manoeuvre in Fig. 3 shows a decrease in elastance for all PEEPs between the incremental PEEP (blue) and the decremental, PEEP (red). This change in respiratory elastance signifies that the incremental stage has resulted in recruitment of collapsed lung, and thus has the potential to improve overall oxygenation (Suarez-Sipmann et al., 2007). Compare this to the subsequent RM shown in Fig 4, where respiratory

elastance during the incremental phase and decremental phases are relatively similar, implying minimal change in overall lung recruitment resulted from the manoeuvre. The minimal elastance change during the second manoeuvre also implies that significant de-recruitment after the initial manoeuvre has not occurred. De-recruited lung would be re-recruited during a second manoeuvre occurring over a similar pressure range, and this re-recruitment did not occur.

4.2 Clinical Implications (Patient 2)

Fig. 6 shows a successful recruitment manoeuvre, with similar characteristics to Fig 3, for Patient 2. This RM was performed when the patient was aspirated and at the risk of lung collapse. During this RM, a sudden decrease in elastance was observed when PEEP was increased from 19 cmH_2O to 21 cmH_2O. This sharp, noticeable drop in respiratory elastance suggested that a sudden recruitment of a large collapsed area of lung occurred at this PEEP. Alveolar recruitment is both time and pressure dependant (Albert et al., 2009) thus the result shown here, detected in real time by CURE Soft, matches clinical behaviour described in literature. Studies on capturing PEEP induced recruitment are currently limited to radiographic imaging methods. These methods are costly, not clinically feasible and expose the patient to radiation and further risks of lung injury (Brenner and Hall, 2007). This result further shows the potential of CURE Soft to capture clinically useful information (lung recruitment) that was previously unavailable in real-time.

In Fig 6, it is also interesting to note that the patient-specific elastance becomes approximately constant when PEEP is decreased from 19 to 13 cmH_2O. At the end of the RM, the patient was ventilated at PEEP 13 cmH2O. However, at this PEEP level, it was observed that the patient experienced a drop in oxygenation and thus, an additional recruitment manoeuvre was performed on the patient shortly after this desaturation event. It is hypothesised that de-recruitment occurred. This de-recruitment implies that the patient was not ventilated at a sufficient PEEP to maintain the recruited lung. It has been suggested that the appropriate PEEP to maintain recruited lung for this patient would have been PEEP 19 cmH_2O, at the inflection point in the decremental curve. The constant elastance during decreasing PEEP may signify oncoming de-recruitment and thus the patient should be ventilated at higher PEEP to maintain recruitment (Briel M and et al., 2010). The implications of these observations will be further investigated over the course of the on-going trial.

4.3 Clinical Implications (Overall RMs)

Table 2 presents summary statistics for all 14 recruitment manoeuvres captured by CURE Soft. This serves to emphasize the ability of CURE Soft to detect the difference between a successful and unsuccessful RM. Here a threshold of a 10% reduction in respiratory elastance was set as the requirement for a successful recruitment manoeuvre. Using this threshold, 3 of the 14 RM performed were successful. In both cases the initial RM recorded was successful, and in both cases this initial RM occurred over a large range of PEEPs per the clinical trial, while subsequent RMs typically occurred over a smaller PEEP range. This behaviour is intuitively expected, as a larger RM is more likely to cause recruitment due to the larger pressure range than a smaller RM.

Overall, the CURE trial investigation using CURE Soft was able to provide clinicians with unique, real time information on patient-specific disease states and response to changing MV settings (PEEP). This information is provided with no additional burden to the patients (such as use of an invasive or specialised protocol). Such information has the potential to make clinical decision making with regards to MV settings more reliable, leading to potential improvement in MV care, patient outcomes, shorter duration of stay in the ICU and thus a decrease in the economic burden placed on health-care by MV therapy.

4.4 Limitations and Future Work

This trial is an ongoing pilot trial, and as such, the information presented here has some limitations. Firstly, there is the limited volume of information provided, covering only 2 patients. This limitation will be addressed as the trial proceeds, with the pilot trial intended to include up to 30 patients. Secondly, the analysis provided here is primarily qualitative and based on clinical observations. More rigorous quantitative analysis will be conducted using a matched retrospective cohort once sufficient patients are recruited into the pilot trial.

There is also potential to develop the system such that it is able to directly recommend optimal PEEP. The system currently is able provide information that allows an informed clinician to better select PEEP, but is not internally able to interpret this data and directly produce a recommendation. Prior to implementation of such a system, further investigation into the correlation between elastance and optimal PEEP will need to be conducted, possibly through employment of image based techniques such as Electric Impedance Tomography (Victorino et al., 2004).

5. CONCLUSIONS

Initial results from the CURE pilot trial, collected from 2 MV patients, showed that the system is able to provide detailed, previously unavailable information about the internal response of these patients to MV in real-time. The real time elastance data offered by CURE has allowed clinicians to distinguish between successful and unsuccessful recruitment manoeuvres, identify significant recruitment events and capture transient changes in patient lung condition. This information has the potential to improve the reliability and ease with which clinicians make decisions about MV settings in the ICU, improving patient outcomes and reducing associated costs. The pilot trial and analysis of accompanying results is ongoing, with up to 30 patients intended to be included by the trial conclusion.

6. ACKNOWLEDGEMENTS

The authors wish to thank Erwin J van Drunen, Christopher Pretty, Paul Docherty, ICU nurses and member of the mechanical ventilation team for their support in this research.

7. CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFRENCES

Albert, S. P., Dirocco, J., Allen, G. B., Bates, J. H., Lafollette, R., Kubiak, B. D., Fischer, J., Maroney, S. and Nieman, G. F. (2009). The role of time and pressure on alveolar recruitment. *Journal of Applied Physiology,* volume 106**,** 757-765.

Anzics 2010. Centre for Outcome and Resource Evaluation (CORE) Annual Report. Victoria, Australia.

Bersten, A. D., Edibam, C., Hunt, T., Moran, J., Group, T. A. and New Zealand Intensive Care Society Clinical, T. (2002). Incidence and Mortality of Acute Lung Injury and the Acute Respiratory Distress Syndrome in Three Australian States. *Am. J. Respir. Crit. Care Med.,* volume 165**,** 443-448.

Brenner, D. J. and Hall, E. J. (2007). Computed Tomography -- An Increasing Source of Radiation Exposure. *N Engl J Med,* volume 357**,** 2277-2284.

Briel M, M. M. M. A. and Et Al. (2010). Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: Systematic review and meta-analysis. *JAMA: The Journal of the American Medical Association,* volume 303**,** 865-873.

Carney, D., Dirocco, J. and Nieman, G. (2005). Dynamic alveolar mechanics and ventilator-induced lung injury. *Crit Care Med,* volume 33**,** S122-S128.

Carvalho, A., Jandre, F., Pino, A., Bozza, F., Salluh, J., Rodrigues, R., Ascoli, F. and Giannella-Neto, A. (2007). Positive end-expiratory pressure at minimal respiratory elastance represents the best compromise between mechanical stress and lung aeration in oleic acid induced lung injury. *Critical Care,* volume 11**,** R86.

Chiew, Y. S., Chase, J. G., Shaw, G., Sundaresan, A. and Desaive, T. (2011). Model-based PEEP Optimisation in Mechanical Ventilation. *BioMedical Engineering OnLine,* volume 10**,** 111.

Chiew, Y. S., Chase, J. G., Shaw, G. M. and Desaive, T. (2012). Respiratory system elastance monitoring during PEEP titration. *Critical Care,* volume 16**,** P103.

Lambermont, B., Ghuysen, A., Janssen, N., Morimont, P., Hartstein, G., Gerard, P. and D'orio, V. (2008). Comparison of functional residual capacity and static compliance of the respiratory system during a positive end-expiratory pressure (PEEP) ramp procedure in an experimental model of acute respiratory distress syndrome. *Critical Care,* volume 12**,** R91.

Meade, M. O., Cook, D. J., Guyatt, G. H., Slutsky, A. S., Arabi, Y. M., Cooper, D. J., Davies, A. R., Hand, L. E., Zhou, Q., Thabane, L., Austin, P., Lapinsky, S., Baxter, A., Russell, J., Skrobik, Y., Ronco, J. J., Stewart, T. E. and For the Lung Open Ventilation Study, I. (2008). Ventilation Strategy Using Low Tidal Volumes, Recruitment Maneuvers, and High Positive End-Expiratory Pressure for Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA,* volume 299**,** 637-645.

Mercat, A., Richard, J.-C. M., Vielle, B., Jaber, S., Osman, D., Diehl, J.-L., Lefrant, J.-Y., Prat, G., Richecoeur, J., Nieszkowska, A., Gervais, C., Baudot, J., Bouadma, L., Brochard, L. and For the Expiratory Pressure Study, G. (2008). Positive End-Expiratory Pressure Setting in Adults With Acute Lung Injury and Acute Respiratory Distress Syndrome: A Randomized Controlled Trial. *JAMA,* volume 299**,** 646-655.

Ricard, J. D., Dreyfuss, D. and Saumon, G. (2003). Ventilator-induced lung injury. *Eur Respir J,* volume 22**,** 2s-9.

Rouby, J. J., Lu, Q. and Goldstein, I. (2002). Selecting the Right Level of Positive End-Expiratory Pressure in Patients with Acute Respiratory Distress Syndrome. *Am J Respir Crit Care Med,* volume 165**,** 1182-1186.

Suarez-Sipmann, F., Bohm, S. H., Tusman, G., Pesch, T., Thamm, O., Reissmann, H., Reske, A., Magnusson, A. and Hedenstierna, G. (2007). Use of dynamic compliance for open lung positive end-expiratory pressure titration in an experimental study. *Crit Care Med,* volume 35**,** 214 - 221.

Sundaresan, A., Chase, J., Shaw, G., Chiew, Y. S. and Desaive, T. (2011). Model-based optimal PEEP in mechanically ventilated ARDS patients in the Intensive Care Unit. *BioMedical Engineering OnLine,* volume 10**,** 64.

Sundaresan, A. and Chase, J. G. (2011). Positive end expiratory pressure in patients with acute respiratory distress syndrome - The past, present and future. *Biomedical Signal Processing and Control,* volume 7**,** 93-103.

The Acute Respiratory Distress Syndrome Network (2000). Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. *N Engl J Med,* volume 342**,** 1301-1308.

The Ards Definition Task Force, A. (2012). Acute respiratory distress syndrome: The berlin definition. *JAMA: The Journal of the American Medical Association,* volume 307**,** 2526-2533.

Treggiari, M., Romand, J., Martin, J. and Suter, P. (2002). Air cysts and bronchiectasis prevail in nondependent areas in severe acute respiratory distress syndrome: a computed tomographic study of ventilator-associated changes. *Crit Care Med,* volume 30**,** 1747 - 1752.

Victorino, J. A., Borges, J. B., Okamoto, V. N., Matos, G. F., Tucci, M. R., Caramez, M. P., Tanaka, H., Sipmann, F. S., Santos, D. C. and Barbas, C. S. (2004). Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *American Journal of Respiratory and Critical Care Medicine,* volume 169**,** 791-800.